Principles for adaptive clinical trials – a personal view

Adaptive Designs & Multiple Testing Procedures
Basel
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Overview

- Introduction
- Essential elements for studies with an adaptive design
  - Justification of an adaptive design: fit for purpose
  - 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
  - Planning, conducting, and reporting simulation studies
  - Adaptive designs using Bayesian methods
  - Early versus late drug development
- Discussion

Introduction

- What are adaptive designs?
  Definition as it is not so clear. Here is one 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”

- Simple versus complex adaptive designs?
  Adaptive designs can be very different, from operationally seamless designs up to complex designs like enrichment designs. Different types of adaptive designs need to be handled differently

- Why do we want to use adaptive designs?
  - Adaptive designs are usually alternatives to classical standard designs. There use is not always obvious and needs to be benchmarked against standard designs
  - The advantages of an adaptive designs should be clearly understood such that they outweigh the inherent risks (benefit risk assessment)

Justification of an adaptive design – Fit for purpose

- Clinical trials should be properly designed, conducted, and analyzed to address the clinical question(s) of interest within the context of the overall development program

- Careful evaluation of completed trials allows thoughtful use of the knowledge obtained from those trials to best inform the goals and design choices for subsequent trials

- Careful use of adaptive design methods in confirmatory settings should maintain the orderly, thoughtful accumulation of data needed to establish and adequately describe a drug's usefulness

Justification of an adaptive design – Fit for purpose

- The number and complexity of adaptations should be carefully considered when planning an adaptive design. The more adaptations or the more complex they are, the higher are the risks for the study

- When considering an adaptive design, the totality of information on the safety and effectiveness of the drug under development needs to remain adequate to inform regulatory decision-making

- The tradeoffs of an adaptive versus non-adaptive designs 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

- It is important that there is adequate clinical trial planning to ensure the design, conduct, and analysis are appropriate, and results are reliable and interpretable
  - Includes following the general estimand framework from ICH E9(R1)

- Aspects that should be pre-specified 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

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

Planning an adaptive design

- Adequate planning is essential to provide confidence in the trial's conclusions
  - Facilitates the evaluation of the appropriateness of statistical methods for many types of adaptations
  - Help assure that adaptations are based on accumulating data in a valid manner
  - Enables informed discussion with independent committees (if involved in the adaptations) at the trial design stage
  - Ensures trial integrity

Limiting the chances of erroneous conclusions

- For given trial results (and further evidence), conclusions will be drawn which inform subsequent development decisions, regulatory decision-making, or medical practice
  - It is therefore important that the chance of erroneous conclusions is limited
  - In confirmatory trials, limiting the chance about erroneous conclusions of safety or effectiveness is particularly critical for appropriate regulatory decision-making
- The probability of erroneous conclusions of effectiveness depends on
  - The proportion of evaluated drugs that are ineffective (may require discussion…)
  - The probability of rejecting null hypotheses when they are true (Type I error probability)
- The standard approach in confirmatory trials to limit erroneous conclusions of effectiveness is to select the design and analysis approach such that the Type I error probability is controlled at a pre-specified threshold

Limiting the chances of erroneous conclusions

- Using conventional statistical methods that would apply in non-adaptive trials, and that ignore the adaptive nature of the design, may cause inflation of the Type I error rate

- Adaptive designs for confirmatory trials should address the possibility of Type I error probability inflation
  - In some cases, such as blinded sample size adaptation based on a nuisance parameter, conventional methods for analysis in non-adaptive trials may be used
  - In other cases, such as group sequential designs, it is necessary to use specialized methodology for adaptive designs which have been shown analytically to ensure Type I error probability control
  - In certain cases, where there is no known formal analytical proof of Type I error probability control, it may be necessary to use simulations to support control of the Type I error probability

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 trial end

- In confirmatory trial settings, reliable estimates of treatment effects are critical to facilitate benefit-risk evaluations for regulatory decision-making and labeling
  - Expectation is generally for limited to no bias in estimates and related quantities
  - Assumptions of a chosen analysis method should be minimal and plausible, with potential departures being assessed through an estimand-aligned sensitivity analysis

Reliability of estimation

- Using conventional statistical methods that would apply in non-adaptive trials, and that ignore the adaptive nature of the design, may cause bias in estimates and incorrect estimates of uncertainty

- Adaptive design 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

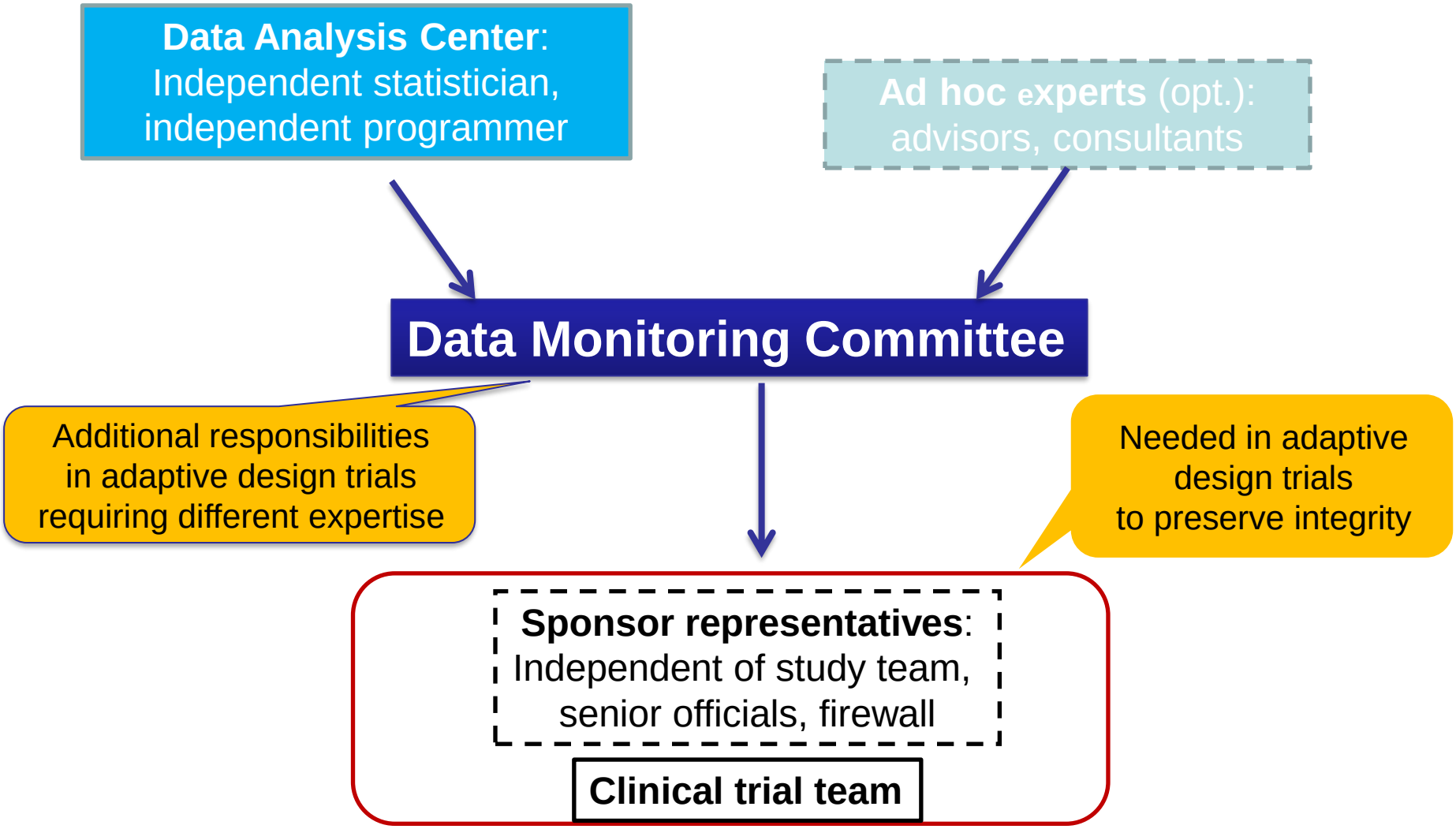
- Integrity of a trial should be maintained such that it achieves its objectives in a timely, reliable, and ethical manner

- Knowledge about accumulating data and/or certain types of design changes by the sponsor, investigators or patients can impact trial integrity by affecting their behavior in ways that are difficult to predict and impossible to adjust for
  - Such knowledge can introduce subtle, maybe unobserved, changes in trial conduct, such as changes in the pace and characteristics of subjects recruited, specific details of the administration of the study treatment or other medications or endpoint assessments
  - For example, knowledge of interim results by sponsor personnel could diminish their ability to perform their trial management functions (e.g., implementing protocol amendments or updating the final analysis plan) in a manner that is objective and avoids bias

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
- Independent experts covering, as a group, relevant expertise needed to monitor the trial
- 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
- Adaptations informed by non-comparative data (e.g., blinded sample size re-estimation) typically does not require a DMC
- In confirmatory trial 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



Planning, conducting, and reporting simulation studies

- Major use of simulations is to estimate operating characteristics of a trial design (e.g., Type I error rate, reliability of estimates) or a development approach
- Applications include, but are not limited to:
  - Comparing candidate designs (potentially including non-adaptive ones)
  - Choosing adaptive design elements, e.g., number and timing of interim analyses, adaptation and stopping rules
  - Demonstrating that certain important operating characteristics meet appropriate levels, especially when it may not be feasible to analytically calculate those operating characteristics
  - Assessing potential impact of certain assumptions for a planned design/analysis
  - Comparing different drug development approaches to assess fitness-for purpose, e.g., dose-ranging trial and two phase 3 trials vs. adaptive dose selection trial and single phase 3 trial

Planning, conducting, and reporting simulation studies

- Simulation studies need to be rigorously planned, conducted, and documented
- Points to consider 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

Adaptive designs using Bayesian methods

Above principles remain applicable when using Bayesian methods to ensure the trial is appropriately designed, conducted, analyzed, and interpreted.

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
  - When 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
- Operating characteristics
  - Operating characteristics needs to be given careful consideration and simulations will often be necessary for their evaluation
  - For example, 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

Early versus late drug development

- Alpha control, minimization of bias, maintenance of trial integrity is in early development for decision making as important as in late development

- Nevertheless, implementation of adaptive designs appear easier in early development than in late as responsibility of adequate trial conduct and decision making is with the sponsor
  - Hypothesis 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

- The decision to use an adaptive design will often depend on many factors
- Principles discussed above apply to both exploratory and confirmatory trials and ensure that an adaptive design produces reliable and interpretable trial results
- It is critical to understand how much the adaptive elements being considered add uncertainty about the ability of the trial to adhere to these principles
- Different weighting of advantages and disadvantages may apply in different phases of drug development and should be considered in the context of the overall program
- Some topics (e.g., use of Bayesian methods) need more discussion

Questions?