
Adaptive trials: Some general considerations

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Regulatory guidelines

- EMA (2007) Reflection paper on methodological issues in confirmatory clinical trials planned with an adaptive design
- FDA (2016) Adaptive designs for medical device clinical studies
- FDA (2019) Adaptive design clinical trials for drugs and biologics
- NMPA (2020) Guideline on adaptive designs for clinical trials

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- A new guideline on adaptive clinical trials that provides a transparent and harmonized set of principles for the regulatory review of these studies
- Points to consider:
 - Common terminology
 - Potential benefits and areas of meaningful applications
 - Principles for the design, conduct, analysis, and proper interpretation of adaptive clinical trials
 - Documentation that is important for the planning and implementation of adaptive clinical trials, and the interactions between sponsors and agencies

What are adaptive designs?

For the purpose of this talk, an adaptive design is a clinical trial design that allows for prospectively planned modifications to one or more aspects of the trial based on interim analysis of accumulating data from participants in the trial.

Advantages and challenges

- Possible advantages
 - Ethical advantages
 - Efficiency increases
 - Improved understanding of drug effects
- Possible challenges
 - Add complexities and uncertainties related to key principles below
 - Appropriate planning can be more challenging and lead to longer lead times before starting the trial than with a non-adaptive design

Regulatory acceptability of additional uncertainty attributable to proposed adaptations will depend on the trade-offs relative to the advantages of a proposed adaptive design

Five principles

The following principles are intended to help sponsors and regulators to navigate through the planning, implementation and interpretation of adaptive designs:

- Adequacy within the development program
- Adequacy of trial planning
- Limiting the chances of erroneous conclusions
- Reliability of estimation
- Maintenance of trial integrity

Principles are relevant to all phases of clinical development, although the practical considerations and implementation can be different

Special topics and considerations

- Data monitoring models
- Role of simulations
- Adaptive designs using Bayesian methods
- Adaptive designs in master protocols

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

Questions?