MEDIZINISCHE UNIVERSITÄT WIEN

Adaptive Clinical Trials

Martin Posch

Center for Medical Statistics, Informatics and Complex Systems
Medical University of Vienna, Austria

Group Sequential Designs

Designs with one or more interim analyses

> Advantages

- Trial can be stopped early for efficacy or futility
- On average less patients are needed compared to fixed sample design.

> Limitations

- Suitable mainly for short term endpoints

Response Adaptive Designs

Patients are randomized to multiple treatment arms and the allocation ratio is continuously re-adjusted based on the observed responses

> Advantages

- Efficient for dose finding (smaller number of patients needed)
- Less patients are treated with toxic or non-efficacious doses
- Allocation may employ Bayesian decision making.

> Limitations

- Estimates and hypothesis tests may be biased
- Requires short term endpoints

Confirmatory Adaptive Designs

Integrate studies with a learning objective (e.g. dose finding, population selection, sample size planning) into confirmatory hypothesis testing

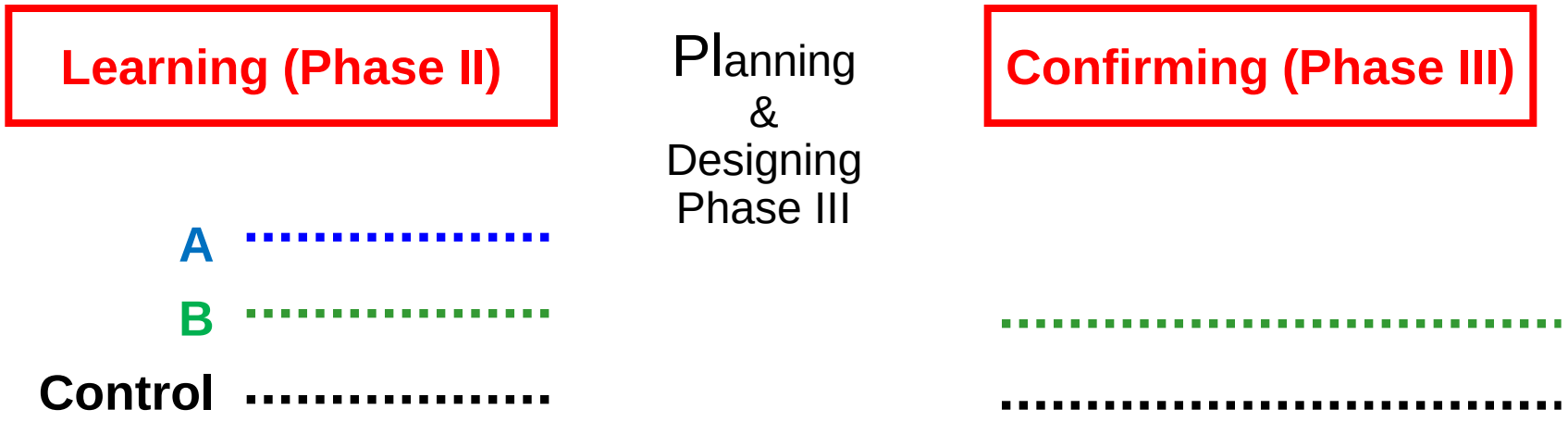
> Advantages

- Allows a range of adaptations in ongonig trials
  - Sample size reassessment, treatment selection, endpoint modification, enrichment….,
- All data are used for decision making
- On average smaller total number of patients needed

> Limitations

- Additional complexity in the conduct and analysis of the trial
- More resources for the planning phase required

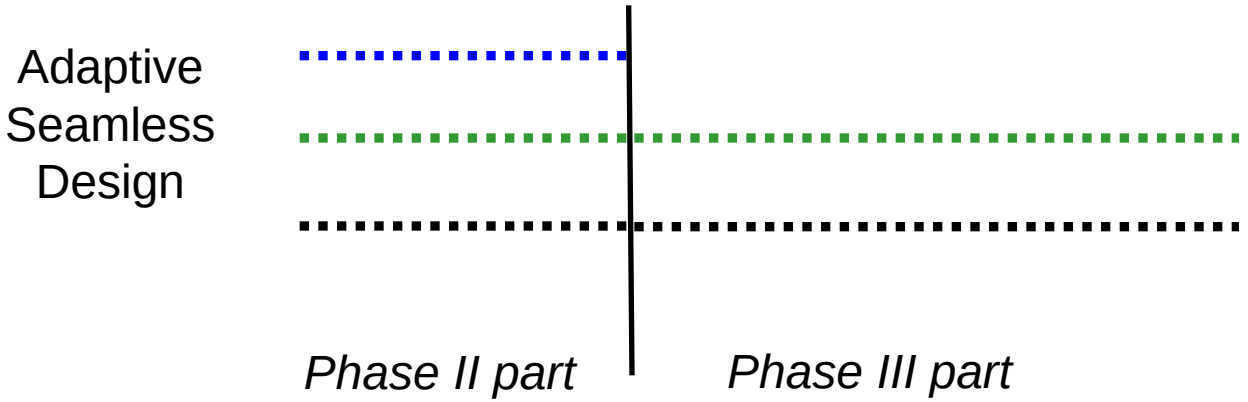
Classical Two Study Approach



- Conduct phase II trial.
- Plan phase III trial based on the information from phase II trial (which treatment, which number of patients, etc.).
- Conduct confirmatory phase III trial. Demonstrate efficacy using ONLY phase III trial data.

Adaptive Treatment Selection

Learning, Selecting and Confirming (Phase II & III)



- Conduct phase II trial as internal part of a combined trial.
- Plan phase III trial based on data from phase II part.
- Conduct phase III trial as internal part of the same trial.
- Demonstrate efficacy with data from phase III + II part.

Summary

- Adaptive designs allow to optimize the trial design based on interim data
- They can be applied in the exploratory and confirmatory setting.
- For rare diseases, academic led, joint multi-company multi-armed adaptive designs are discussed to address limited patient resources.

Selected References

- C. Jennison and B.W. Turnbull. Group sequential methods with applications to clinical trials. CRC Press, 2000.
- F. Bretz, F. Koenig, W. Brannath, E. Glimm, and M. Posch.
  Adaptive designs for confirmatory clinical trials.
  Statistics in Medicine, 28:1181–1217, 2009.
- D. Berry, P. Müller, A. Grieve, M. Smith, T. Parke , R. Blazek, N. Mitchard, M. Krams
  Adaptive bayesian designs for dose-ranging drug trials . In: Case Studies in Bayesian Statistics V . New York : Springer , pp. 99 – 181, 2001.
- EMA. CHMP Guideline on Clinical Trials in Small Populations, 2005
- EMA. Reflection paper on methodological issues in confirmatory clinical trials planned with an adaptive design, 2007.
- US FDA. Draft Guidance for Industry: Adaptive design clinical trials for drugs and biologics, 2010.
- US FDA. Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products, 2012