# (Some) Bayesian Clinical Trial, Group Sequential Adaptive Designs

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# Outline

- Intro to *Adaptive Design (AD)*
- Intro to *Group Sequential Design*
- Sampe Size Re-estimation
- Intro to *Bayesian Clinical Trial*
- Bayesian Clinical Trial for Very Rare Disease
- Reporting AD
- Practical Advice for ADs
- Quiz

# Adaptive Design

- What is adaptive design?
- *pre-specified* changes can be made based on analyses of accumulating data whilst maintaining the *validity* and *integrity* of the trial

# Adaptive Design

- Why we want to use adaptive design?
- *flexibility* $\Rightarrow$ efficient trials
- When to use adaptive design?
  - used in Phase I - Phase III

# Adaptive Design

- What adaptive design can do?
  - abandoning treatments or doses ( *CRM*, *E-WOC*, *multi-arm multi-stage*, *adaptive dose-ranging* )
  - changing the allocation ratio of patients to trail arms ( *adaptive randomization*)
  - rapid transitioning between phases ( *seamless phase I/II*, *seamless phase II/III* )
  - stopping the whole trial at an early stage for success or lack of efficacy ( **group sequential** )
  - refining the sample size ( *sample size re-estimation* )
  - identifying patients most likely to benefit and focusing recruitment efforts on them ( *population enrichment* )

# Group Sequential Design

- What is group sequential design
  - recruit participants by pre-planned stages (groups)
  - cumulative assessment after each stage finished using pre-planned significance levels/ critical values
  - possible early stop due to efficacy or futility
  - if not stop early, guaranteed overall type I error and power

# Group Sequential Design

# Rationale

- Investigation of the trend
  - "Lowering the risk of ignoring trends and the risk of responding too quickly to trends observed in comparisons of treatment groups during the course of an ongoing trial."
- Review of Power/Sample Size Calculation
  - statistical test (fixed)
  - anticipated effect size
  - significance level
  - power
  - sample size

# Rationale

# Group Seuqential Design

- Why do we want to use it

# Group Sequential Design

- When to use
- often used in Phase III, when you need a lot of participants/ money
- focus on studying efficacy
- Where is the catch
  - Overall sample size is larger than that of a fixed design controling effect size, type I error and power
  - Useless when observed effect size is smaller than that assumed in the initial study design

# Adaptive Sample Size Re-estimation

- Modifying the design without inflating type I error or losing power, when if the observed effect size is smaller than anticipated effect size

# Adaptive Sample Size Re-estimation

- Pandora's Box
- possibly results a substantially larger trial to pursue effect sizes of limited clinical interest.
- Make sure the new effect size you are powering for is still clinically important
- Really know what you are asking for!

## Issues of Adaptive Design

  - Non-statistical issues
- the possibly of introducing optional bias
- explaining the heterogeneity between the stages of an AD trial
- Statistical issues

# Bayesian Clinical Trial

- What is Bayesian Clinical Trial -Personally, it is any clinical trial that relies on Bayesian methods for either the design or the analysis or both
- What about Bayesian statistics
- parameter of interest is a random variable instead of an unknown constant
- How Bayesian statistics is helping
- answer more questions: what is the probability of the parameter is within a interval?
  - sample size is a less restrictive factor in the design
- easier to analyze accumulated data without worrying about inflating type I error
- easier to incorporate prior information
- incorporate decision theory

# Bayesian Clinical Trial

- What is the catch?
- justification and documentation, specifically the choice of prior

# Bayesian Clinical Trial for Rare Disease

- Motivation:
- incident rate is low
- no trial to reference with
- impossible to recruit enough people based on power & sample size calculation

# Procedure

- Decide statistical model
- Determine a prior distribution on the bases of expert opinion
- Determine prior distributions combining expert opinion with historical data
- Choice of an allocation ratio and Bayesian decision criterion

# Determine a prior distribution on the bases of expert opinion

- Define the criteria for an "expert" and find some experts (more than 1)
- Elicit expert opinion
- Characterize expert prior opinion
- Reach the consensus

# Determine prior distributions combining expert opinion with historical data

- Find relevant data, and decide whether to use
- Elicit opinion on the relevance of the data
- Statistically update prior distributions with the relevant data
- Assess the impact of alternative priors

# Choice of an allocation ratio and Bayesian decision criterion

- Deciding the decision criterion in terms of probability
- Lots of integrations

# Reporting Adaptive Design

# Practical Aspects of ADs

- Obtain funding: convince the design is appropriate
- non-technical terms
- show advantages over non-adaptive designs
- recommending reviewer
- Communicating the design to trail stakeholders/participants:
- independent statistical expert to confirm (stakeholders)
- prepare a good information sheet(participants)
- Independent Data Monitoring Committee: Integrity
- keep people with a vested interest strictly blinded to alleviate the possibility of ad hoc decisions

# Practical Aspects of ADs

- Run the trial: trials are more “variable”
- robust central system,
- budget more time and resource for quality control and validation

# Conclusion

# Quiz

- What is this?

# Supplementary

Definitions:

- *Integrity*: "Integrity means ensuring that trial data and processes have not been compromised, e.g. minimising information leakage at the interim analyses."
- *Validity*: "Validity implies there is an assurance that the trial answers the original research questions appropriately, e.g. by using methods that provide accurate estimates of treatment effects and correct p values and confidence intervals (CIs) for the treatment comparisons."