

$\{ \text{(Some) Bayesian Clinical Trial, Group Sequential} \} \subset \{ \text{Adaptive Designs} \}$

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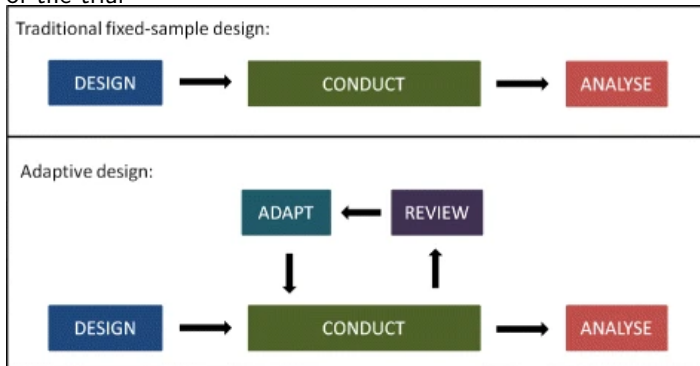
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# Outline

- ▶ Intro to *Adaptive Design (AD)*
- ▶ Intro to *Group Sequential Design*
  - ▶ Same 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

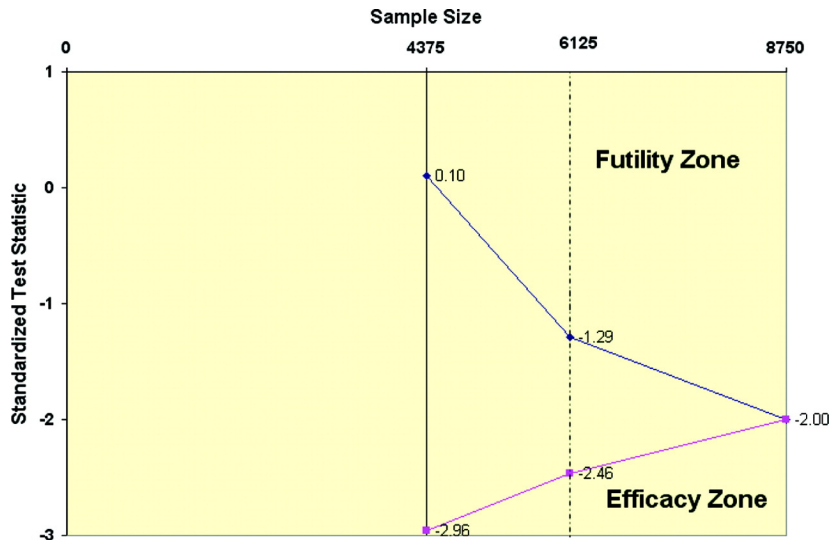
# Adaptive Design

- ▶ 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 trial 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

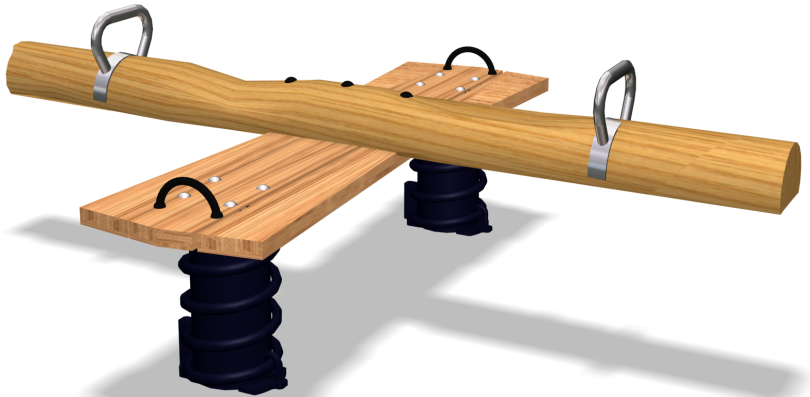


# Rationale

- ▶ 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

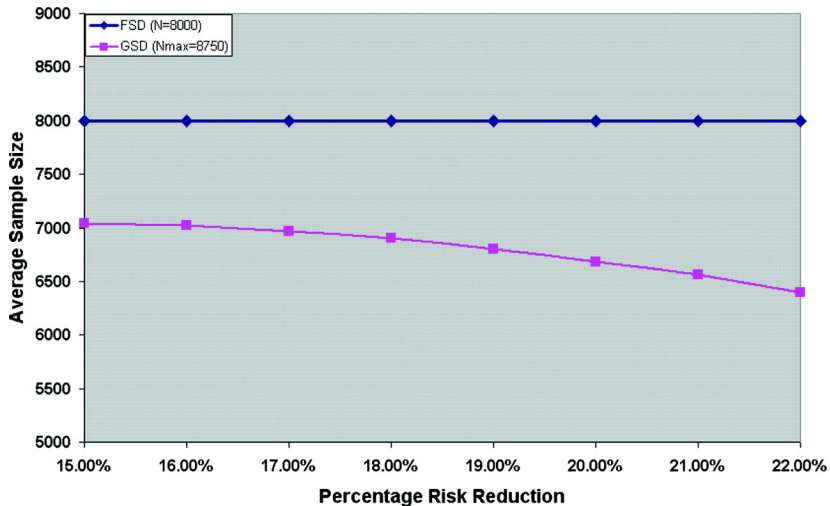


# Rationale



# Group Sequential Design

► Why do we want to use it

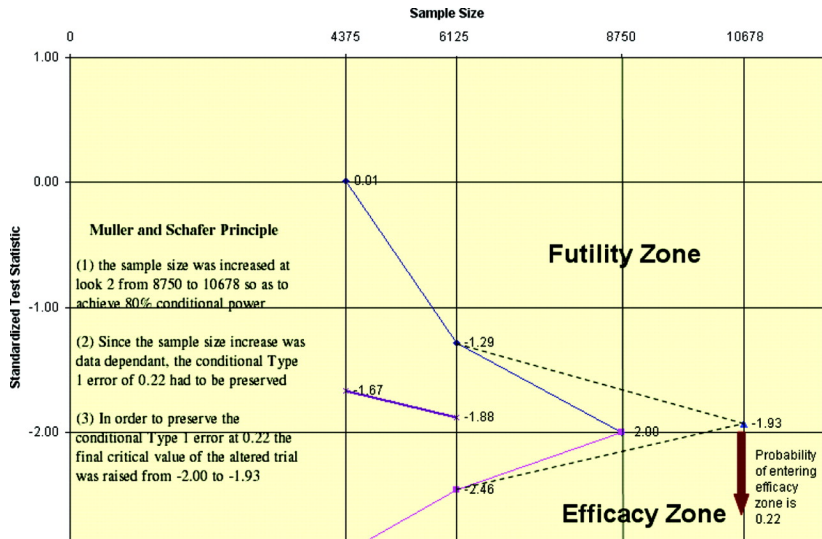


# Group Sequential Design

- ▶ 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  
controlling 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

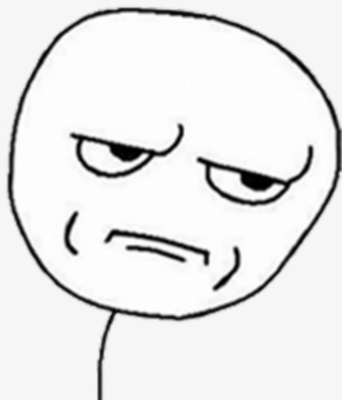
- ▶ Non-statistical issues
  - ▶ the possibly of introducing optional bias
  - ▶ explaining the heterogeneity between the stages of an AD trial
- ▶ Statistical issues
  - ▶ biased estimation for effect size
  - ▶ incorrect coverage for confidence interval
  - ▶ p-value
  - ▶ type I error rate
  - ▶ multiple hypothesis testing

# 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

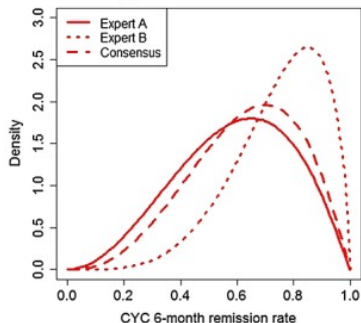
# Procedure

- ▶ 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

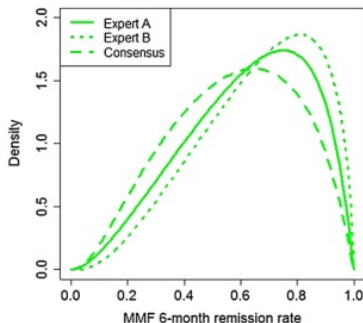
# Determine a prior distribution on the bases of expert opinion

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

(a) Prior density for  $p_C$



(b) Prior density for  $p_E$



(c) Comparison of prior densities for  $p_C$  and  $p_E$



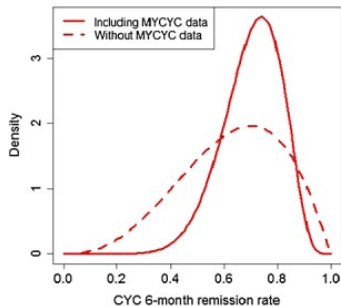
(d) Prior density for  $\theta$



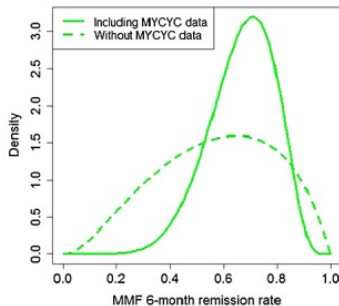
# Determine prior distributions combining expert opinion with historical data

- ▶ 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

(a) Prior density for  $p_C$



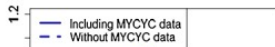
(b) Prior density for  $p_E$



(c) Comparison of prior densities for  $p_C$  and  $p_E$



(d) Prior density for  $\theta$



## Choice of an allocation ratio and Bayesian decision criterion

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

# Reporting Adaptive Design

Guideline | [Open Access](#) | Published: 16 November 2018

## Development process of a consensus-driven CONSORT extension for randomised trials using an adaptive design

[Munyaradzi Dimairo](#) , [Elizabeth Coates](#), [Philip Pallmann](#), [Susan Todd](#), [Steven A. Julious](#), [Thomas Jaki](#), [James Wason](#), [Adrian P. Mander](#), [Christopher J. Weir](#), [Franz Koenig](#), [Marc K. Walton](#), [Katie Biggs](#), [Jon Nicholl](#), [Toshimitsu Hamasaki](#), [Michael A. Proschan](#), [John A. Scott](#), [Yuki Ando](#), [Daniel Hind](#) & [Douglas G. Altman](#)

[BMC Medicine](#) **16**, Article number: 210 (2018) | [Cite this article](#)

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# 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 trial 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

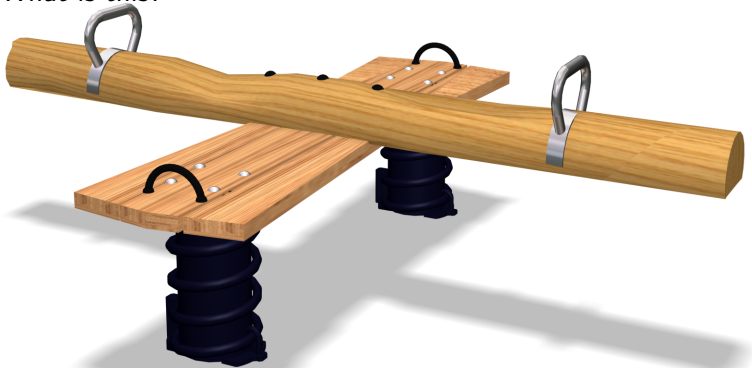


# Conclusion

- ▶ Adaptive designs are more flexible design compared to traditional fixed-sample design
- ▶ On average, group sequential designs require less participants when used properly
- ▶ Sample size re-estimation is theoretically possible if you have pre-specified
- ▶ Bayesian clinical trial can be a solution when studying very rare design
- ▶ Reporting adaptive designs is hard
- ▶ Talk to somebody experienced when designing adaptive studies.

# Quiz

► What is this?



# Supplementary

## Definitions:

- ▶ *Integrity*: “Integrity means ensuring that trial data and processes have not been compromised, e.g. minimizing 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.”