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

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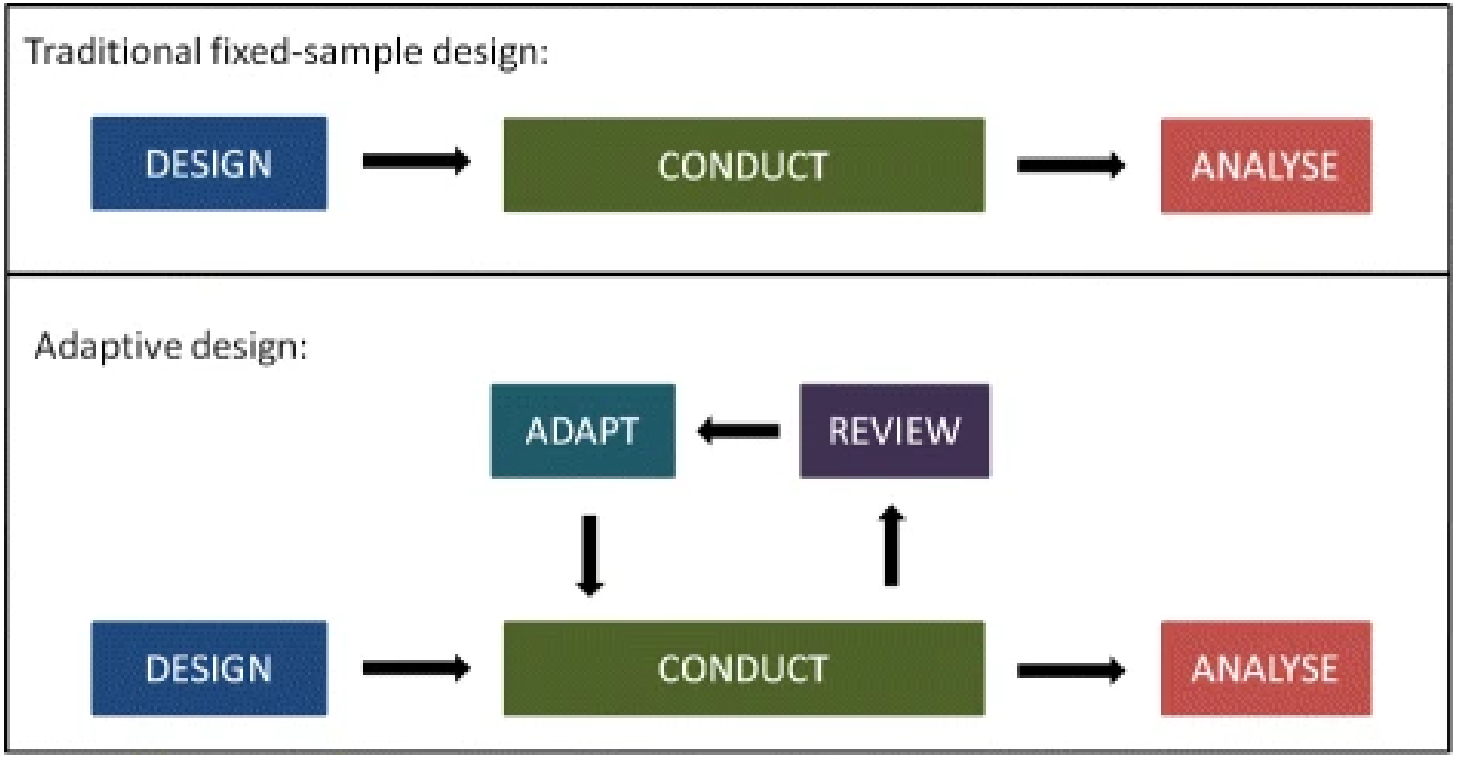
Outline

- Intro to *Adaptive Design (AD)*
- Intro to *Group Sequential Design*
  - Sample 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

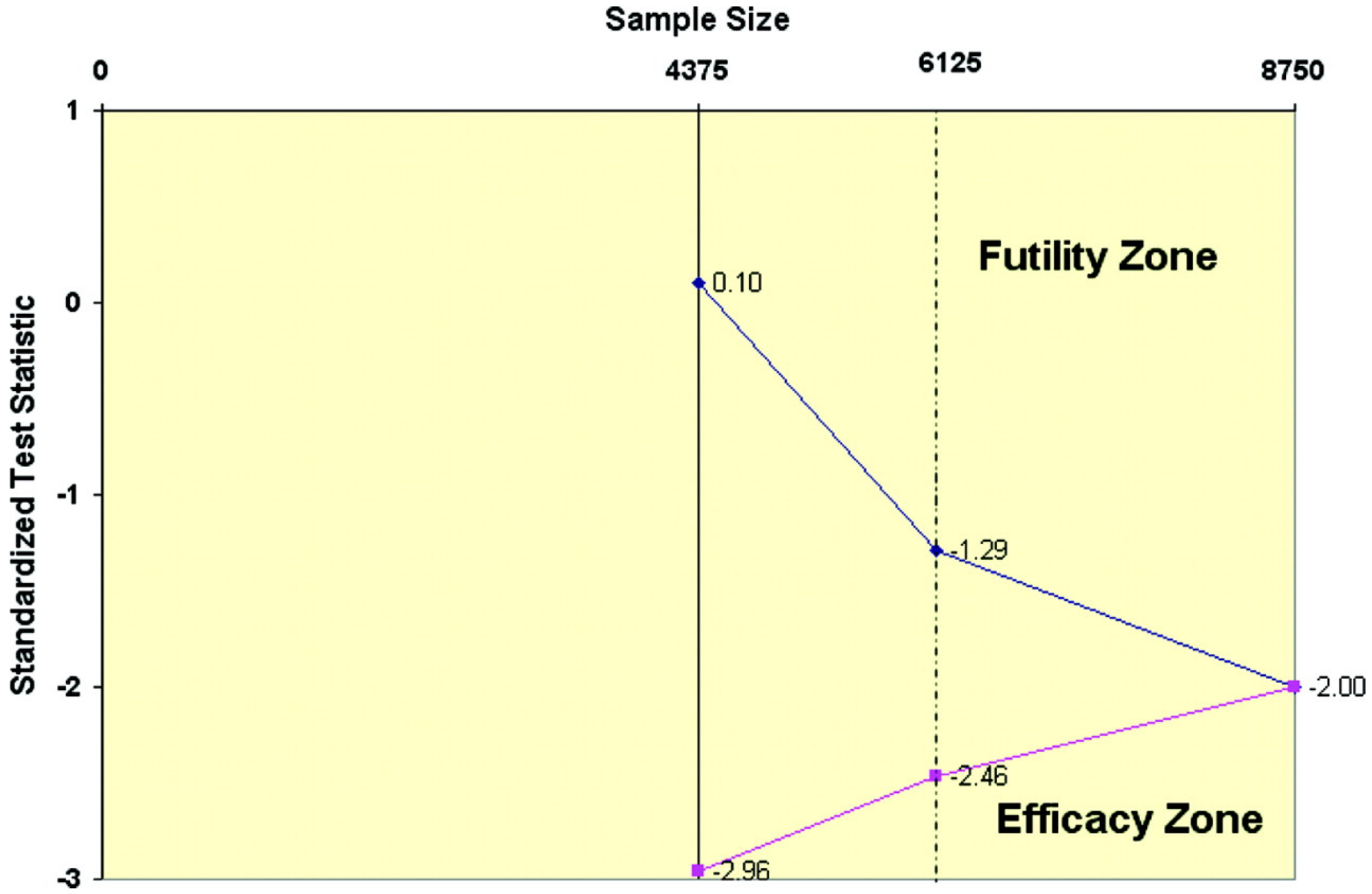
Adaptive Design

- 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

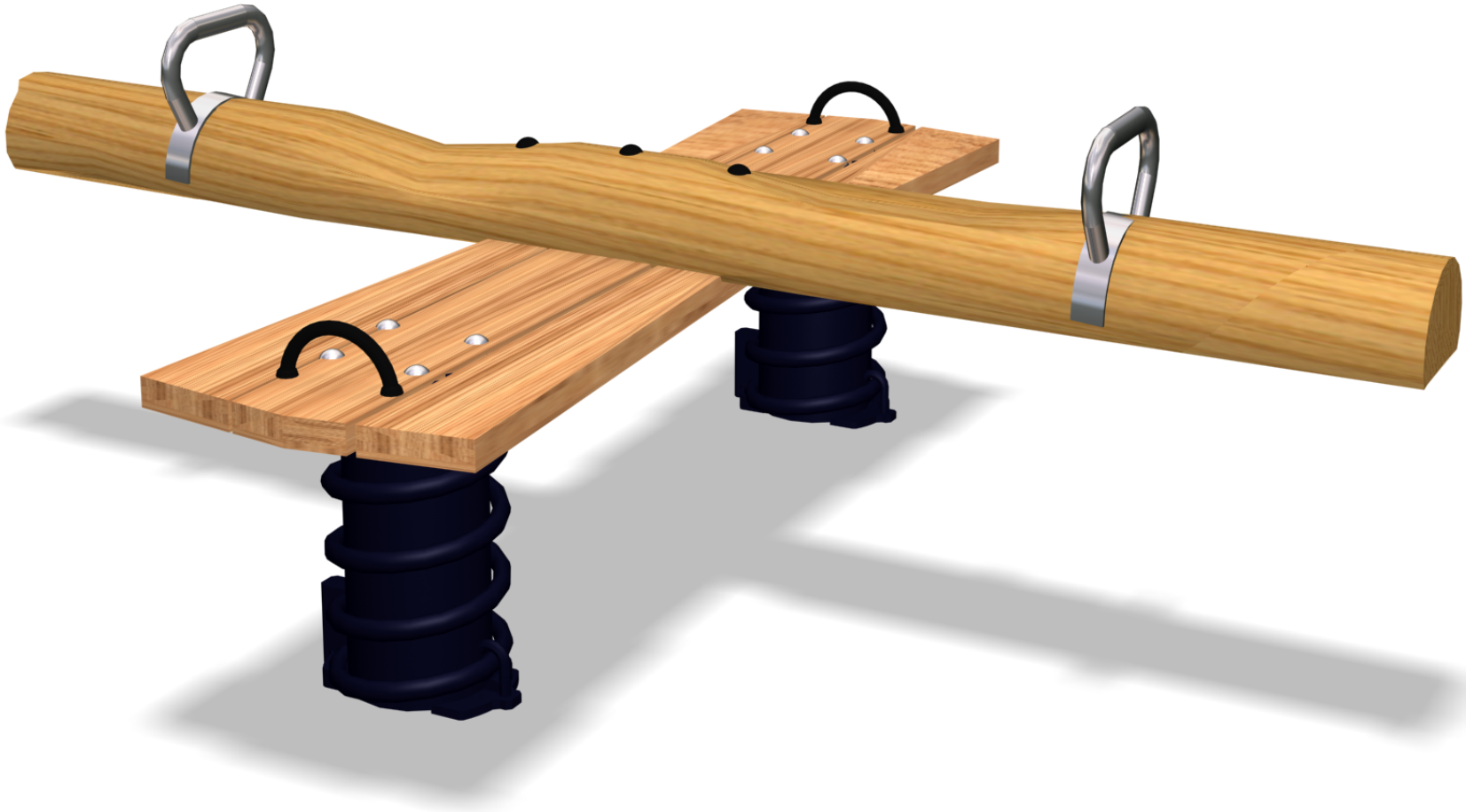
Group Sequential Design



Rationale

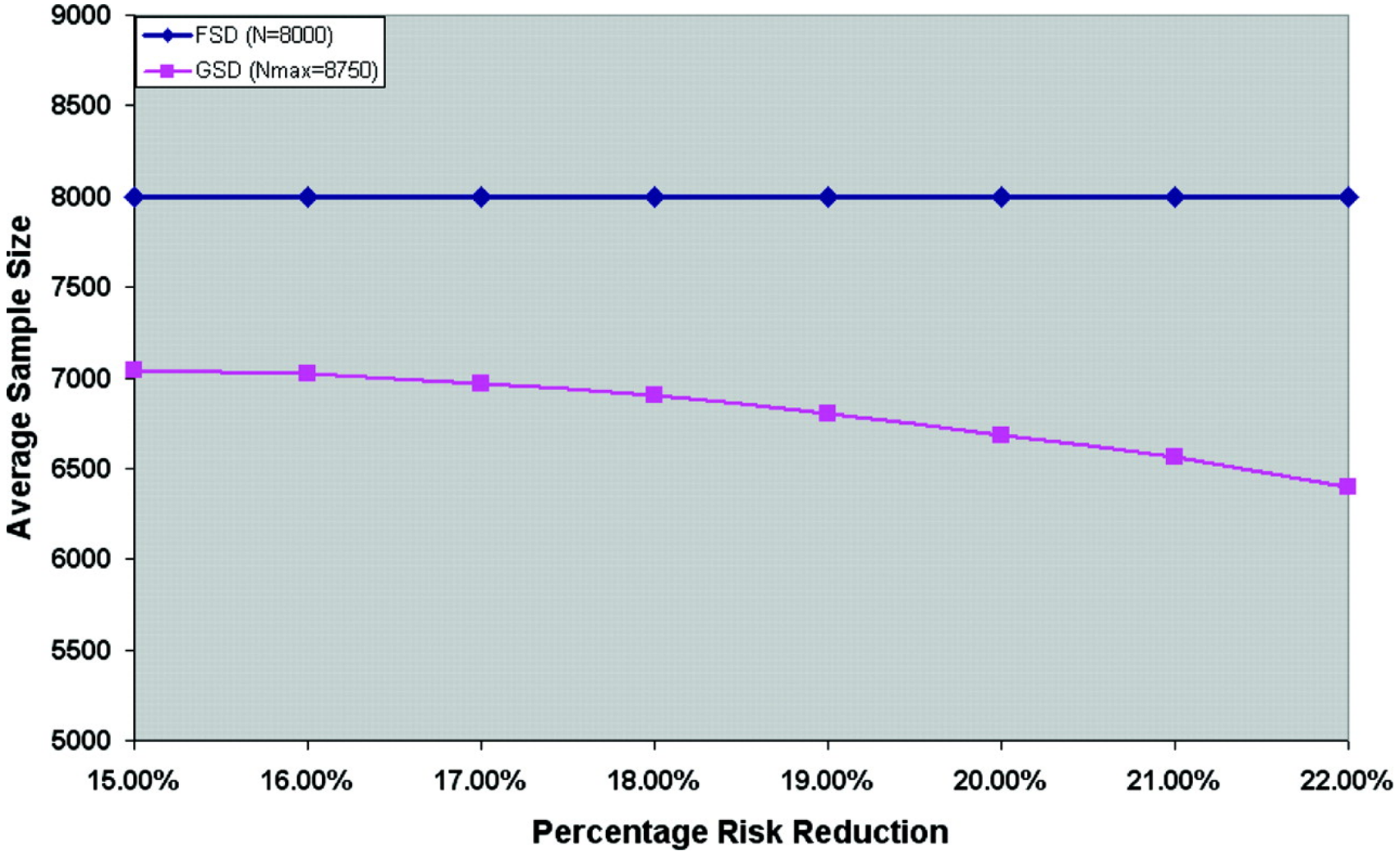
- Investigation of the trend
  - "Lowering the risk of ignoring trends and the risk of responding too quickly to trends observed in comparisons of treatment groups during the course of an ongoing trial."
- Review of Power/Sample Size Calculation
  - statistical test (fixed)
  - anticipated effect size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

Rationale



Group Seuqential Design

- Why do we want to use it

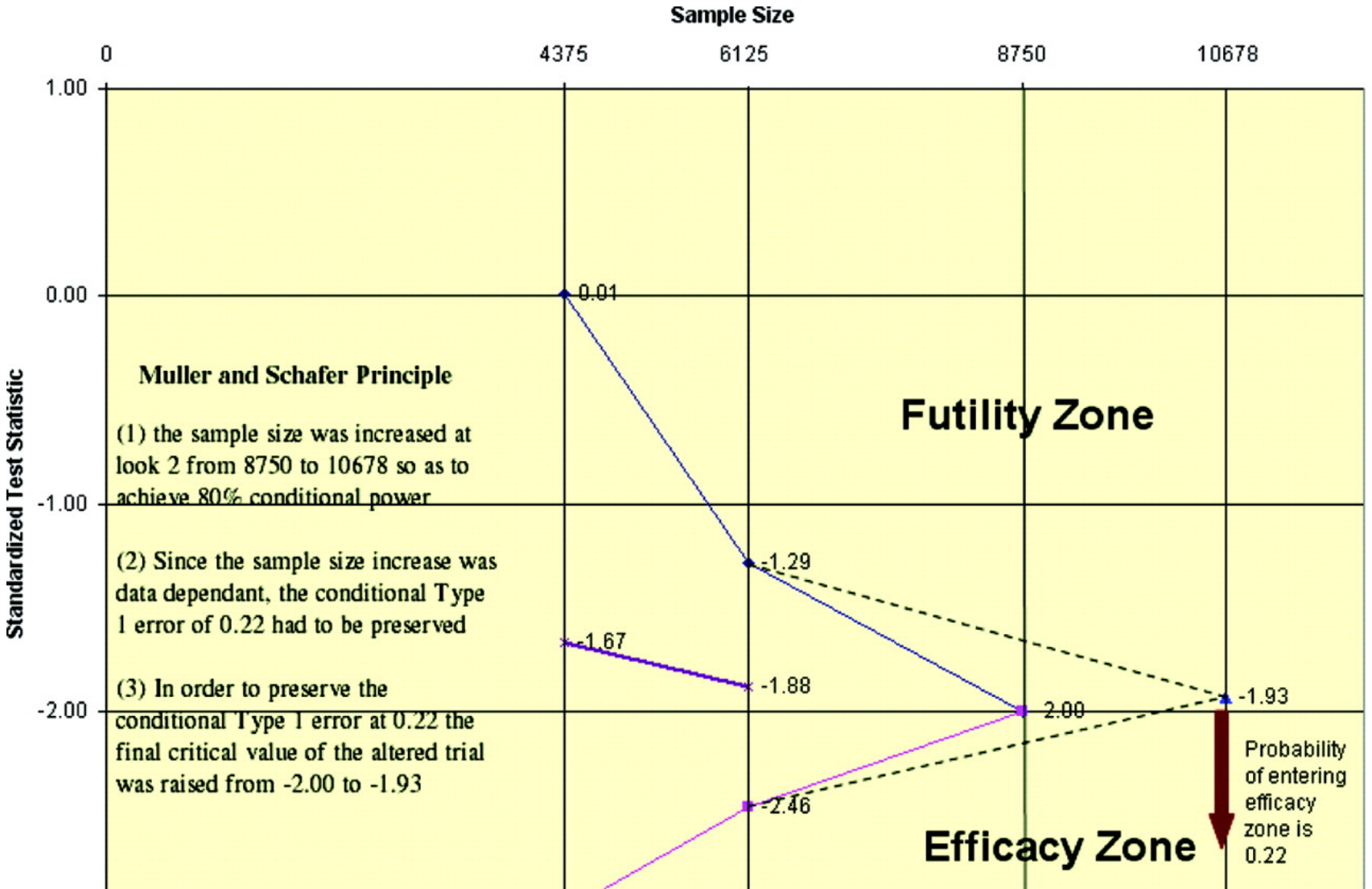


Group Sequential Design

- 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

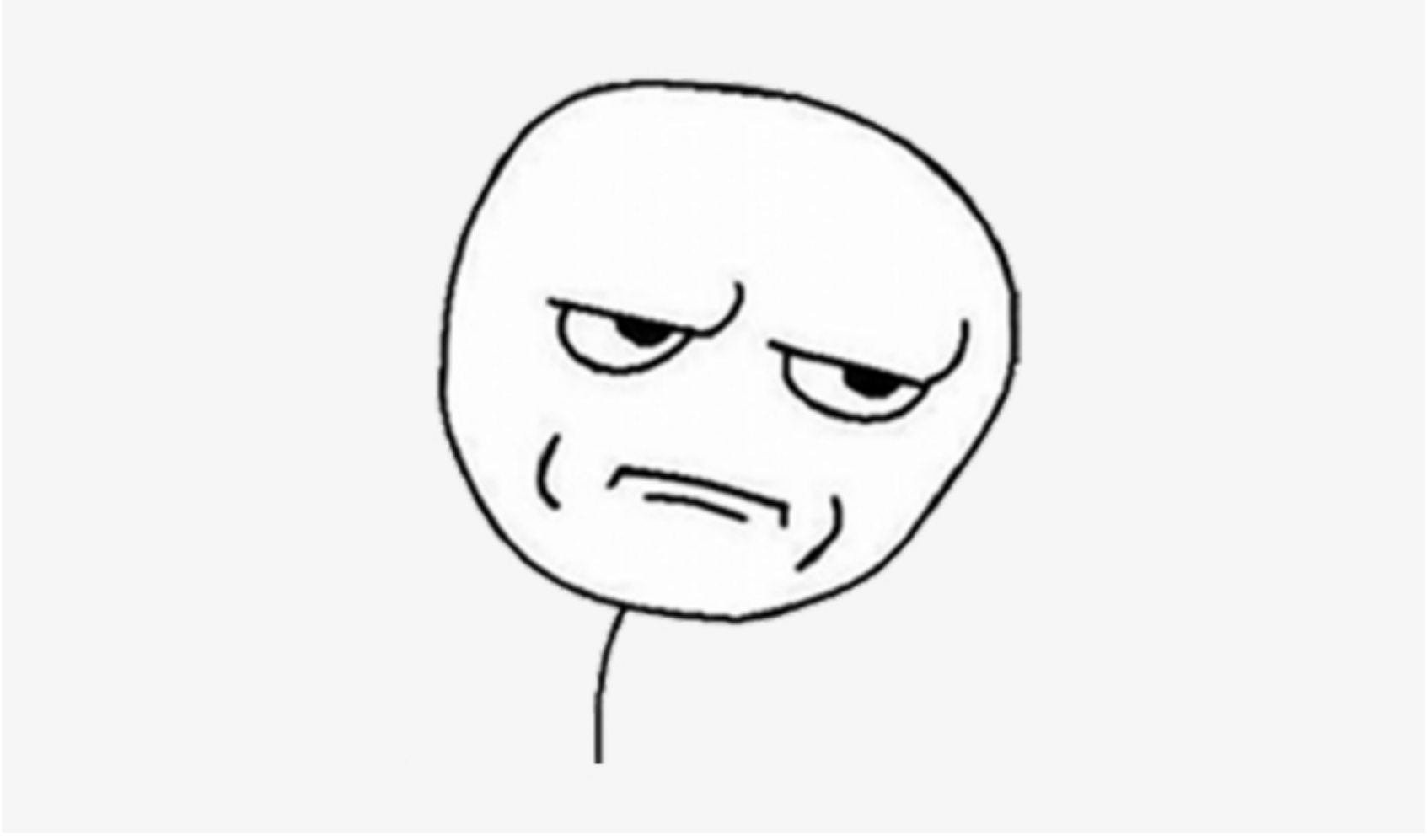
- Non-statistical issues
  - the possibly of introducing optional bias
  - explaining the heterogeneity between the stages of an AD trial
- Statistical issues
  - biased estimation for effect size
  - incorrect coverage for confidence interval
  - p-value
  - type I error rate
  - multiple hypothesis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

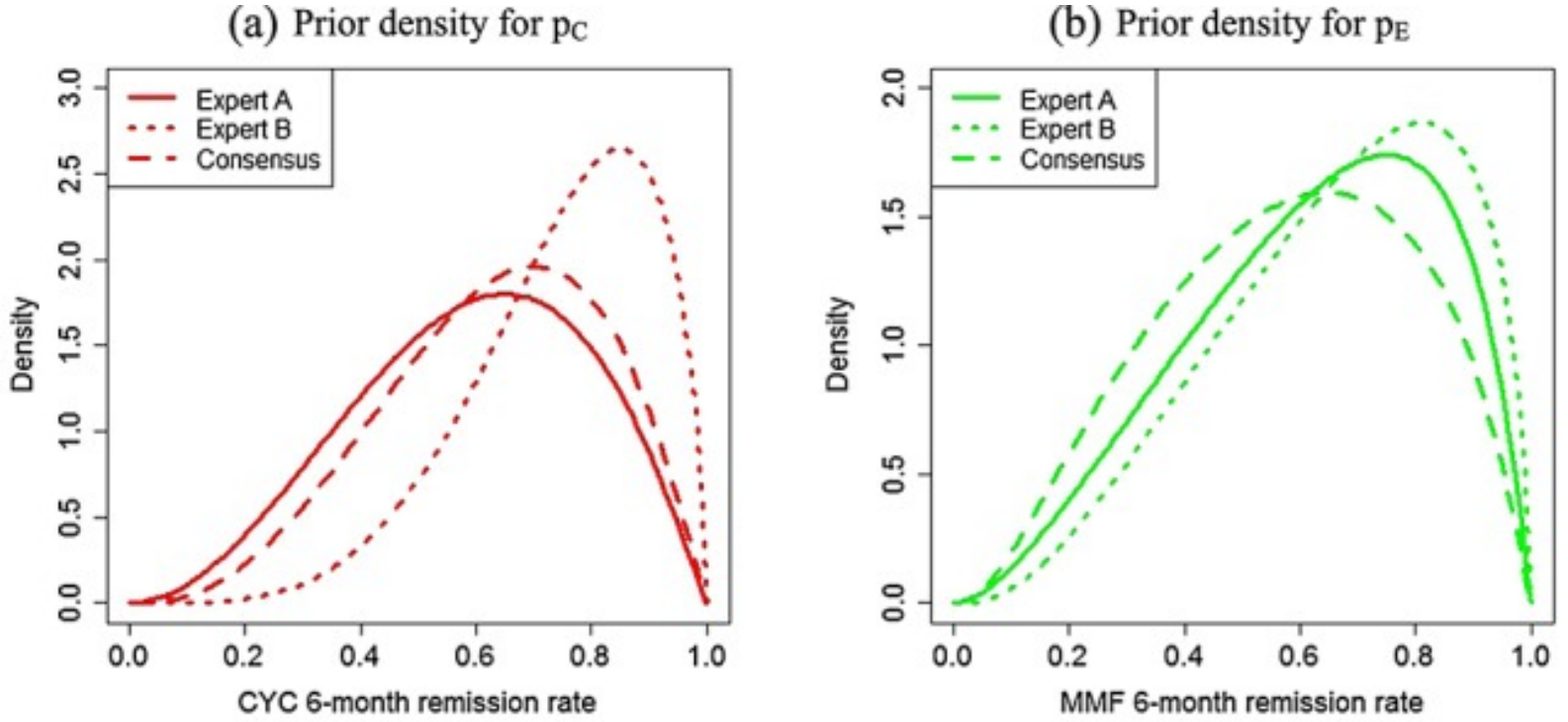
- Motivation:
  - incident rate is low
  - no trial to reference with
  - impossible to recruit enough people based on power & sample size calculation

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

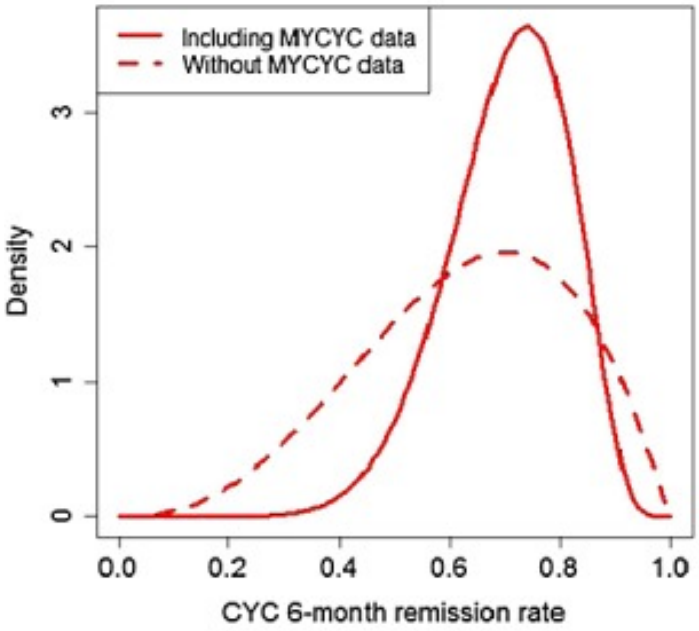
- Define the criteria for an "expert" and find some experts (more than 1)
- Elicit expert opinion
- Characterize expert prior opinion
- Reach the consensus



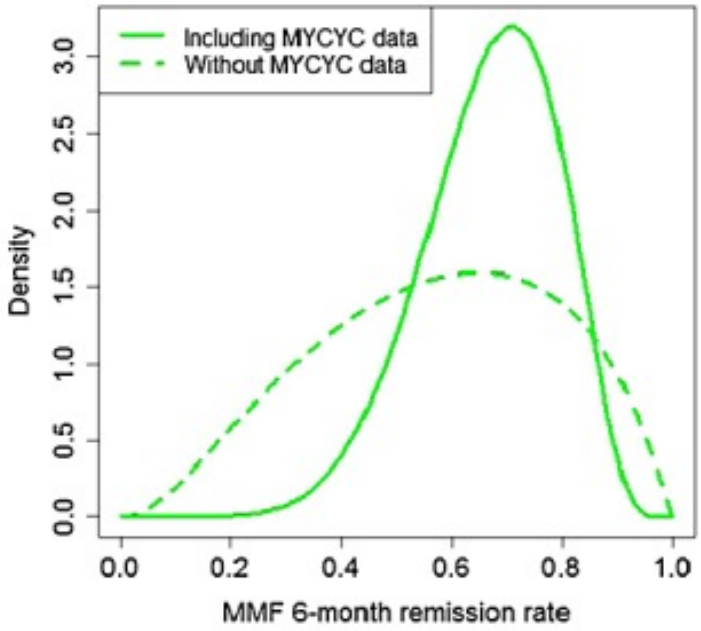
Determine prior distributions combining expert opinion with historical data

- 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

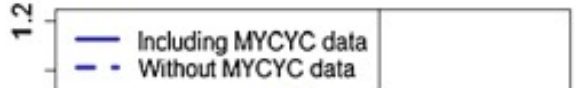


(b) Prior density for p_E



(c) Comparison of prior densities for p_C and p_E

(d) Prior density for θ



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

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

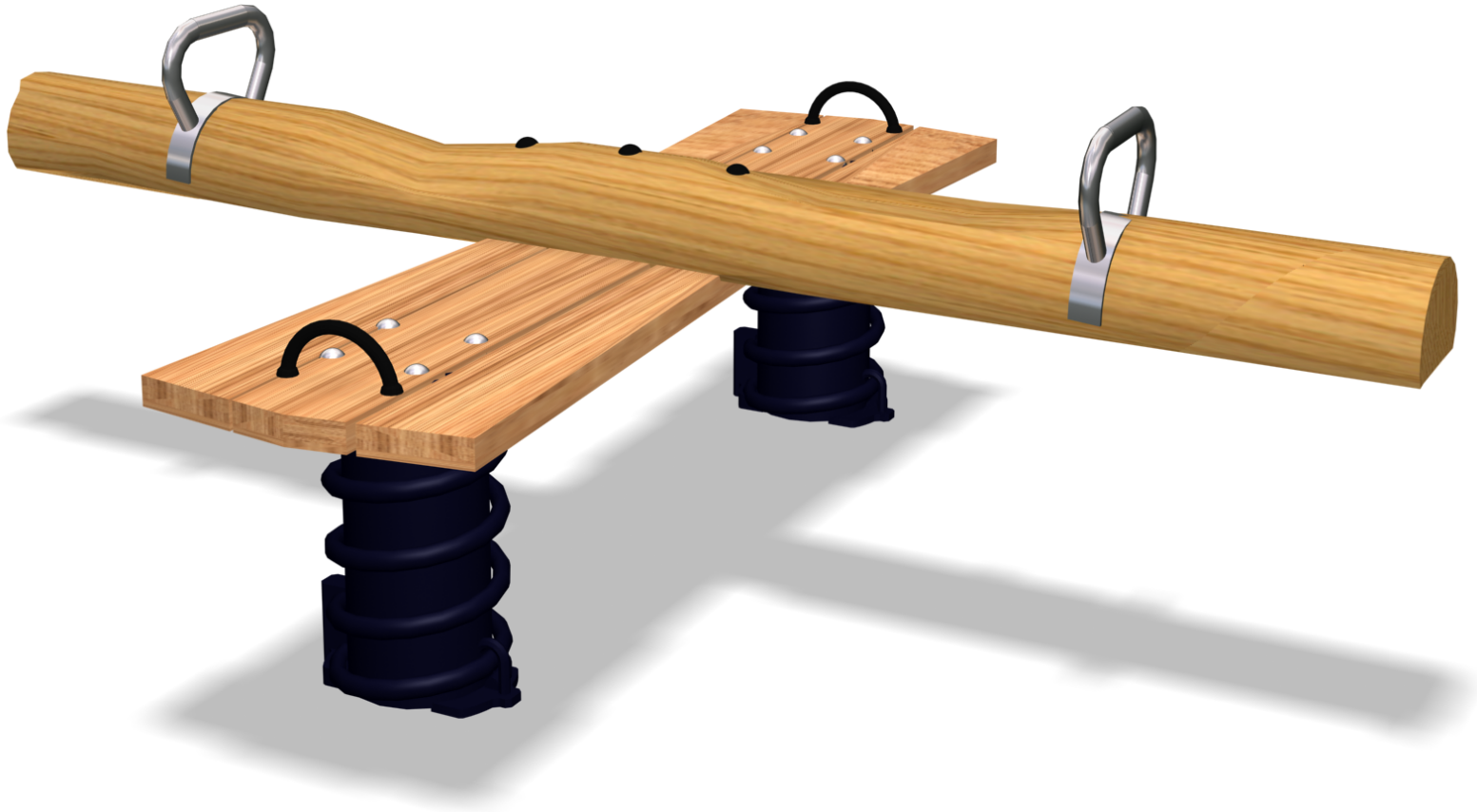
- Run the trial: trials are more "variable"
  - robust central system,
  - budget more time and resource for quality control and validation

Conclusion

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

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."