# Introduction to Adaptive Experimental Design

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# Outline

1. Motivational example
2. Overview of adaptive designs
3. Examples of adaptive designs
   - Blinded sample size re-estimation
   - Simon's two-stage design
   - Bayesian phase 2 trial with stopping for efficacy and futility

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- Suppose you want to test the effect of a new treatment on a yes/no patient response
- success rate of current treatment is 20%
- minimum clinically important increase is 20%, for a response rate is 40%
- Based on 90% power, you design a study with 47 patients.

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- during the study, you get nervous.
- after 25 patients collected, you look at the data
- 9 patients had response. $\frac{9}{25} = 36\%$
- $p$-value based on current data is 0.08.

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- you decide to continue the trial and see what happens
- by the end of the trial, 16 out of 47 had responses
- the $p$-value based on $\frac{16}{47}$ responses is 0.026
- you publish your results

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- What's the problem?

- What's the problem?
- the p-value of 0.026 is not correct

# $p$-values and adaptive design

- $p$-values are calculated based on the specific design
- If the design changes, the $p$-value calculation changes
- $p$-value calculation is impossible if the changes were not prespecified

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# $p$-values and adaptive design

- almost always must pre-define interim analyses and decision rules at design stage
- helpful to involve statistician in design

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# Adaptive designs

What are they?

**adaptive** some aspect of the study design may change during the study depending on observed values after trial has begun

- changes can be based on patient clinical characteristics or patient responses

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# Types of adaptive features

- sample size
  - based on accruing outomes
  - early stopping
  - interim sample size re-estimation
- treatment group randomization weights (adaptive randomization)
  - pick the winner
  - arm dropping
  - increases the chance that each patient gets the most effective treatment
- dose (in phase one dose escalation)

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# Example of an adaptive design with early stopping and outcome-adaptive group allocation

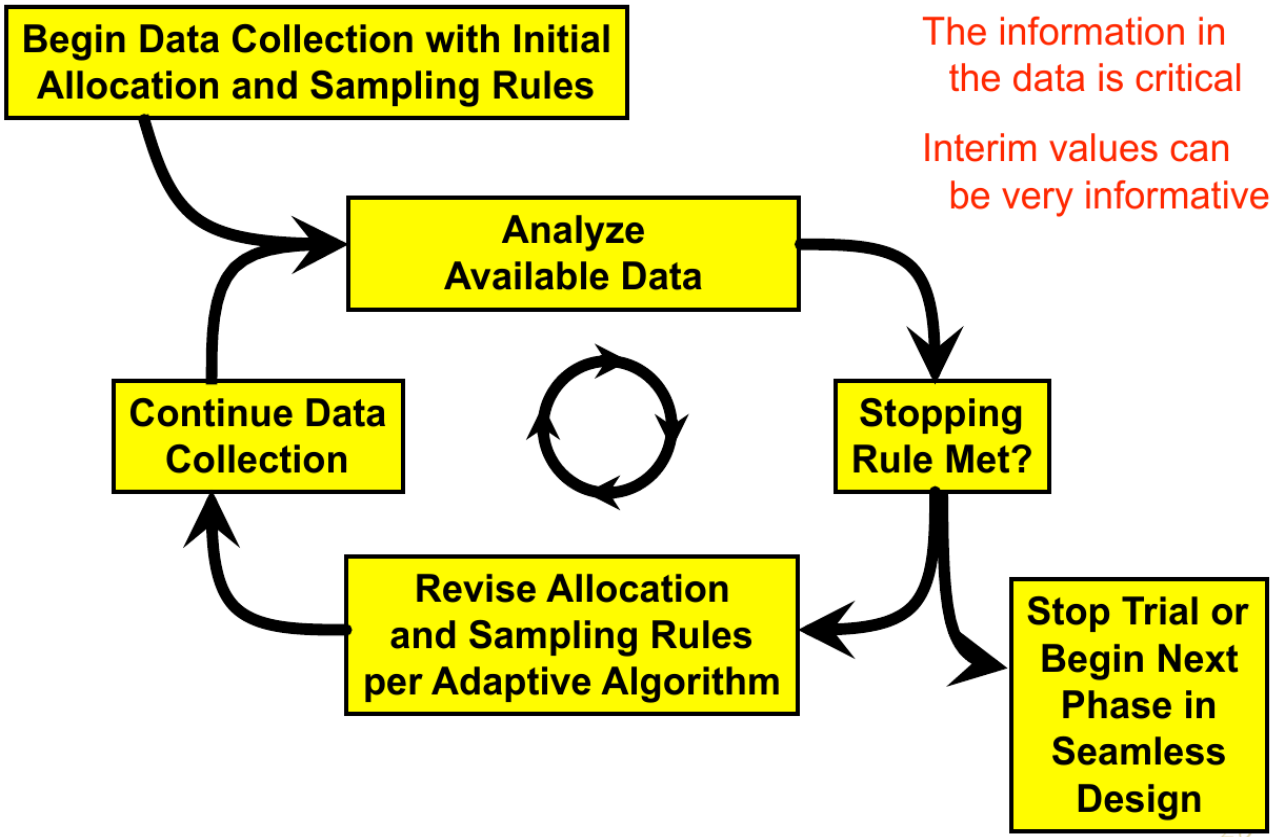


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*Image from Jason Connor*

# Purpose of adaptive designs

- more efficient designs
  - decrease number of patients
  - decrease patient exposure time
  - faster
  - cheaper
  - better use of resources

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# When to use adaptive designs

- patient response is observed fast relative to patient accrual rate
- large cost associated with each patient or with duration of study
- uncertainty in computing power

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# Challenges of adaptive designs

- require specialized statistical expertise and large time investment
- need more time in planning and development phase
- can require very prompt or real time data entry
- can require very good coordination between study sites
- regulatory approval
- can yield biased estimates

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# How to compare different designs

- power
- probability of type one error
- expected sample size (E(N)), maximum sample size
- probability of early termination (PET) for futility
- practicality (including number of looks)

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# Study design parameters

Statisticians can help identify the effects of different:

- timing of interim analyses
- accrual rates
- decision rules/ cut offs
- effect sizes
- maximum sample sizes

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- Allows for **blinded** sample size re-estimation mid-study in a two-arm experiment

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# Sample size reestimation [Gould, 1995]

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- This can be done without unblinding the treatment groups

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# Sample size reestimation [Gould, 1995]

- Allows for **blinded** sample size re-estimation mid-study in a two-arm experiment
- Sample size is re-estimated with an updated estimate of the **variance** based on the data collected so far.
- This can be done without unblinding the treatment groups
- No $p$-values are calculated in the interim analysis

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- Suppose you want to compare a treatment's effect to placebo on a binary patient response

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- The event rate for the placebo is usually estimated from prior studies.

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# Sample size reestimation [Gould, 1995]

- Suppose you want to compare a treatment's effect to placebo on a binary patient response
- To calculate the appropriate sample size, you need to know the overall event rate
- The event rate for the placebo is usually estimated from prior studies.
- It would be useful to re-calculate the sample size midway through the study based on an updated estimate

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# Sample size reestimation

- allows for computing the sample size needed at an interim point
  - with a new variance estimate based on the data

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  - **interim analysis is blinded**

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# Sample size reestimation

- allows for computing the sample size needed at an interim point
  - with a new variance estimate based on the data
  - **interim analysis is blinded**
  - then have option of increasing the sample size

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# Example of sample size reestimation

- Suppose you want have a new treatment that is hoped to reduce progression of diabetic retinopathy

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# Example of sample size reestimation

- Suppose you want have a new treatment that is hoped to reduce progression of diabetic retinopathy
- You want to test the treatment in a controlled trial
- How many patients do you need?

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# Example of sample size reestimation

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# Example of sample size reestimation

- How many patients do you need?
- Untreated, $\approx 22\%$ of diabetics have progression within 2 years
- This figure is estimated from a very small study
- A 50% reduction is considered the minimum clinically relevant effect
- The estimated overall event rate is $\frac{22\%+11\%}{2} = 16.5\%$
- Sample size calculation says for 90% in a two-sided test, you need **240** patients in each group.

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- You decide to re-estimate the sample size after you collect half the data.
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# Example of sample size reestimation

- You decide to re-estimate the sample size after you collect half the data.
- You collect blinded data on 120 patients in each group.
- The study statistician finds that the overall event rate on the current data is 20%, not 16.5%
- Based on this updated number, you only really needed **190** patients in each group, not 240.

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- The study statistician finds that the overall event rate on the current data is 20%, not 16.5%
- Based on this updated number, you only really needed **190** patients in each group, not 240.
- Since you already collected 120 per group, you decide to only collect the needed 70 remaining patients in each group.

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- Based on this updated number, you only really needed **190** patients in each group, not 240.
- Since you already collected 120 per group, you decide to only collect the needed 70 remaining patients in each group.
- You saved 50 patients per group, 100 total!!

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# Simon's two-stage design

- Simon's Optimal two-stage designs [Simon, 1989]
  - two planned stages
  - after the first stage, have option to stop for futility based on the data

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  - at the end of stage one, have option to end for futility
  - minimizes expected sample size in the case of $H_0$
  - They have published cut-offs in their article, and also a software program. Available in sample size software PASS

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# Example of Simon's design

- Suppose you have a drug and want to assess its antitumor activity to see if worth further development

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# Example of Simon's design

- Suppose you have a drug and want to assess its antitumor activity to see if worth further development
- primary endpoint: proportion of patients whose tumors shrink at least 50%
- plan to test it in an uncontrolled trial
- test $H_0 : p \leq 20\%$, existing drug has 20% response rate
- clinicians agree that minimum clinically significant effect would be an increase of 20%.

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# Example of Simon's design

- For 90% power, need 47 patients for a traditional, one-stage design

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- For 90% power, need 47 patients for a traditional, one-stage design
- You are hesitant to devote 47 patients to a drug that may not work

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# Example of Simon's design

- For 90% power, need 47 patients for a traditional, one-stage design
- You are hesitant to devote 47 patients to a drug that may not work
- Decide to consider Simon's optimal two-stage design

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# Example of Simon's design

- Input parameters: $\alpha = 0.05$, power$= 90\%$, $p_0 = 0.20$, $p_1 = 0.40$

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# Example of Simon's design

- Input parameters: $\alpha = 0.05$, power$= 90\%$, $p_0 = 0.20$, $p_1 = 0.40$
- Output:

| | |
|---|---|
| stage 1 $n_1$ | 19 |
| total $n$ | 54 |
| end trial after stage 1 and reject drug if | $\leq \frac{4}{19}$ responses |
| reject drug after stage 2 if | $\leq \frac{15}{54}$ responses |
| expected sample size under $H_0$ | 30.4 |
| probability of stopping early under $H_0$ | 0.67 |

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- decide to use Simon's optimal two-stage design

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- observe first 19 patients

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- 7 patients had greater than 50% reduction in tumor sizes

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- observe first 19 patients
- 7 patients had greater than 50% reduction in tumor sizes
- Continue to stage 2
- observe 35 more patients and 11 more patient responses

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- observe first 19 patients
- 7 patients had greater than 50% reduction in tumor sizes
- Continue to stage 2
- observe 35 more patients and 11 more patient responses
- total of $\frac{18}{54}$ responses

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- observe first 19 patients
- 7 patients had greater than 50% reduction in tumor sizes
- Continue to stage 2
- observe 35 more patients and 11 more patient responses
- total of $\frac{18}{54}$ responses
- reject $H_0$ and decide to pursue the drug in further study!

# Simon's design

- Advantages
  - very simple
  - allow you to hedge against an ineffective treatment
- Disadvantages
  - only provides for futility stopping (not stopping for efficacy)

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# Bayesian adaptive studies

Bayesian adaptive design early stopping can be based on predictive probability of trial success

predicted probability of success $P(\text{success at final analysis}|\underline{X})$

- flexible
- customizable
- can stop early for efficacy, futility

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# Scenario

Suppose . . .

- We have a treatment and want to evaluate its effect on a binary outcome.

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Suppose . . .

- We have a treatment and want to evaluate its effect on a binary outcome.
- On the current standard therapy, 15% of patients have the response.
- We hope that with the new treatment, the response rate will be higher, like 35% or 45%.

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# Scenario

Suppose . . .

- We have a treatment and want to evaluate its effect on a binary outcome.
- On the current standard therapy, 15% of patients have the response.
- We hope that with the new treatment, the response rate will be higher, like 35% or 45%.
- We want to test this drug in one-arm experiment to see if it warrants further study.

# Example of Bayesian adaptive design

- Decide on a Bayesian adaptive design with a maximum sample size of 19.
- Opportunity to stop the trial early for futility or efficacy at fixed interim point(s): after observing 10, 13, and 16 outcomes.
- **Time of looks** and **criteria for stopping** need to be specified in advance

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# Example of Bayesian adaptive design

- Final analysis based on Bayesian posterior probability: $P(p > 15\%|\textit{data})$.
- If $P(p > 15\%|\textit{data}) > 0.97$ (success), investigate the treatment further with randomized study comparing with standard treatment.

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# Example of Bayesian adaptive design: efficacy stopping rule

- Criteria for stopping early for **efficacy** based on **probability of superiority**.
- Will stop and declare success if

$$P(p > 15\% | \textit{current data}) > 0.97$$

at any interim look.

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# Example of Bayesian adaptive design: futility stopping rule

- Criteria for stopping early for **futility** based on **predicted probability of success**, based on the number of successes observed so far.
- Will stop and draw no conclusion if

$$P(\text{success at final analysis}|\textit{current data}) < 0.05$$

at any interim look.

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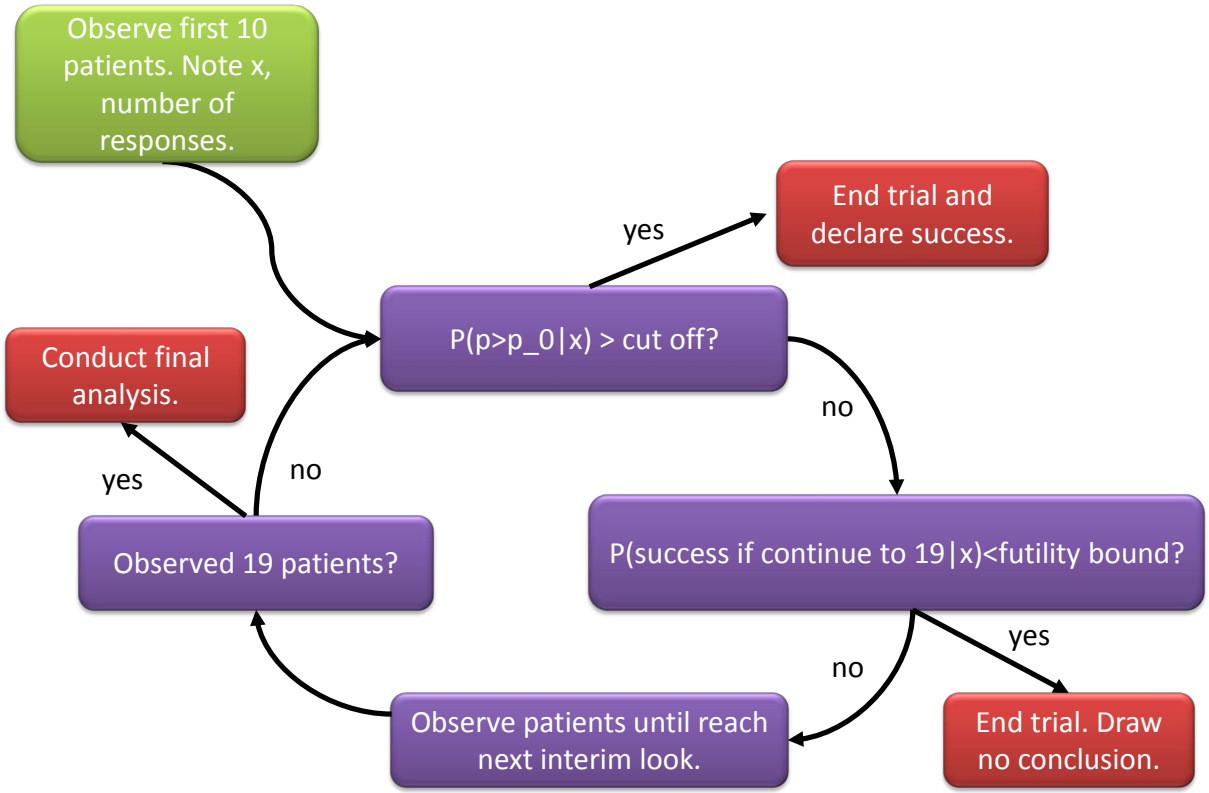
# How the actual trial would work

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# How the design performs

efficacy cut-off $= 0.97$, futility bound $= 0.05$

| $p_{\text{true}}$ | Pr(win) | E(N) | PET Futility | PET Efficacy |
|---|---|---|---|---|
| 0.15 | 0.054 | 12.2 | 0.92 | 0.04 |
| 0.35 | 0.678 | 13.5 | 0.31 | 0.57 |
| 0.45 | 0.904 | 12.3 | 0.09 | 0.83 |

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# Example of Bayesian adaptive design

- Will do futility and efficacy analysis after observing 10, 13, and 16 outcomes. Maximum is 19.
- Will stop and declare success if

$$P(p > 15\% | \textit{current data}) > 0.97$$

at any interim look.

- Will stop and draw no conclusion if

$$P(\text{success at final analysis} | \textit{current data}) < 0.05$$

at any interim look.

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# Example of Bayesian adaptive design

- Begin trial!

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- Begin trial!
- Observe first 10 patients.

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- There were 2 responses

# Example of Bayesian adaptive design

- Begin trial!
- Observe first 10 patients.
- There were 2 responses
- Calculate probability of superiority and predicted probability of success.

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# Example of Bayesian adaptive design

- Begin trial!
- Observe first 10 patients.
- There were 2 responses
- Calculate probability of superiority and predicted probability of success.
- $P(p > 15\% | \textit{current data}) = 0.594$

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# Example of Bayesian adaptive design

- Begin trial!
- Observe first 10 patients.
- There were 2 responses
- Calculate probability of superiority and predicted probability of success.
- $P(p > 15\% | \textit{current data}) = 0.594$
- $P(\text{success at final analysis} | \textit{current data}) = 0.059$

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# Example of Bayesian adaptive design

- Begin trial!
- Observe first 10 patients.
- There were 2 responses
- Calculate probability of superiority and predicted probability of success.
- $P(p > 15\% | \textit{current data}) = 0.594$
- $P(\text{success at final analysis} | \textit{current data}) = 0.059$
- Continue to 13 patients.

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# Example of Bayesian adaptive design

- Begin trial!
- Observe first 10 patients.
- There were 2 responses
- Calculate probability of superiority and predicted probability of success.
- $P(p > 15\% | \textit{current data}) = 0.594$
- $P(\text{success at final analysis} | \textit{current data}) = 0.059$
- Continue to 13 patients.
- There were no more responses!

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# Example of Bayesian adaptive design

- Begin trial!
- Observe first 10 patients.
- There were 2 responses
- Calculate probability of superiority and predicted probability of success.
- $P(p > 15\% | \textit{current data}) = 0.594$
- $P(\text{success at final analysis} | \textit{current data}) = 0.059$
- Continue to 13 patients.
- There were no more responses!
- $P(p > 15\% | \textit{current data}) = 0.445$

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# Example of Bayesian adaptive design

- Begin trial!
- Observe first 10 patients.
- There were 2 responses
- Calculate probability of superiority and predicted probability of success.
- $P(p > 15\% | \textit{current data}) = 0.594$
- $P(\text{success at final analysis} | \textit{current data}) = 0.059$
- Continue to 13 patients.
- There were no more responses!
- $P(p > 15\% | \textit{current data}) = 0.445$
- $P(\text{success at final analysis} | \textit{current data}) = 0.004$

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# Example of Bayesian adaptive design

- Begin trial!
- Observe first 10 patients.
- There were 2 responses
- Calculate probability of superiority and predicted probability of success.
- $P(p > 15\% | \textit{current data}) = 0.594$
- $P(\text{success at final analysis} | \textit{current data}) = 0.059$
- Continue to 13 patients.
- There were no more responses!
- $P(p > 15\% | \textit{current data}) = 0.445$
- $P(\text{success at final analysis} | \textit{current data}) = 0.004$
- Stop for futility! No conclusion is drawn.

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# Bayesian trial with early stopping for futility and efficacy

- Advantages
  - very flexible
  - can be modified for time to event
- Disadvantages
  - requires very specialized statistical expertise

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# Summary

- Designs with adaptive sample size
  - usually require planning at design stage
  - can optimize the number of patients and duration of study to the given situation

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Gould, A. (1995).
Planning and revising the sample size for a trial.
*Statistics in Medicine*, 14:1039–1051.


Simon, R. (1989).
Optimal two-stage designs for phase ii clinical trials.
*Controlled Clinical Trials*, 10:1–10.

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Adaptive trail design group
Tuesdays 10:30 am
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