# Adaptive Methods in Clinical Research

*Lecture 1: Single arm binary outcome designs*

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# A dose of reality

Ben Goldacre, Guardian 1-09-08:

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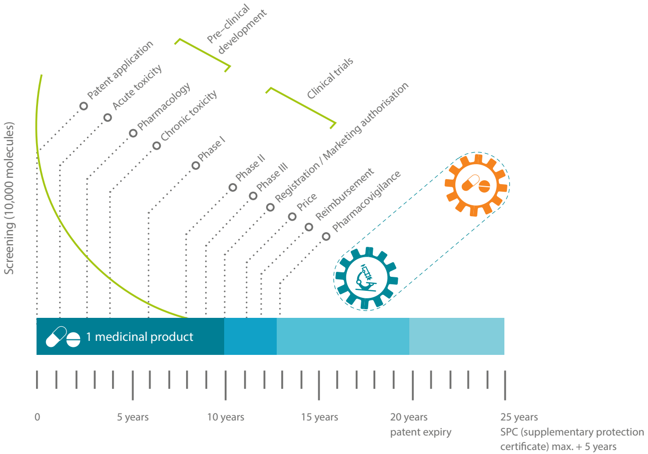
- **Before 1935**: doctors were basically useless
- **1935-1995**: antibiotics, dialysis, transplants, intensive-care units, heart surgery, every drug you've ever heard of
- **1995-now**: the low-hanging fruit of medical research has all been harvested, and the industry is rapidly running out of new drugs

# The development process

PHASES OF THE RESEARCH AND DEVELOPMENT PROCESS



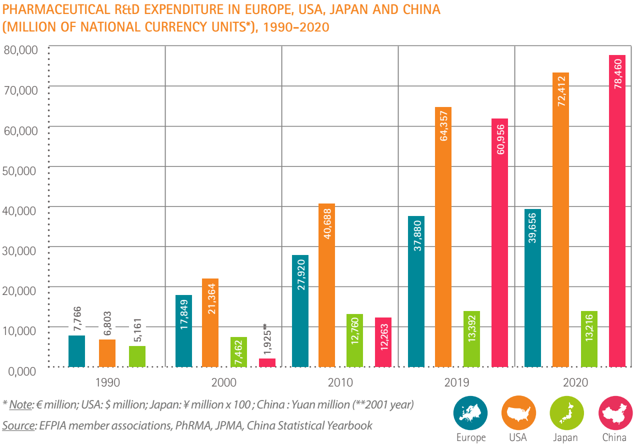

Source: European Federation of Pharmaceutical Industries and Associations (2022)

# Drug development

Development of a novel medicinal product

- takes 10-15 years
- costs several hundred million euros on average
  - largest contributors are confirmatory (phase III) trials
  - often involve thousands of patients with follow-up period frequently lasting years

# Cost on R&D in Pharmaceutical industry




Source: European Federation of Pharmaceutical Industries and Associations (2022)

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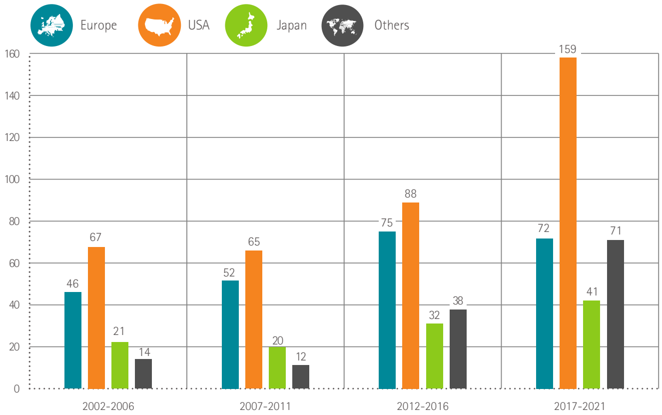
# New molecular entities

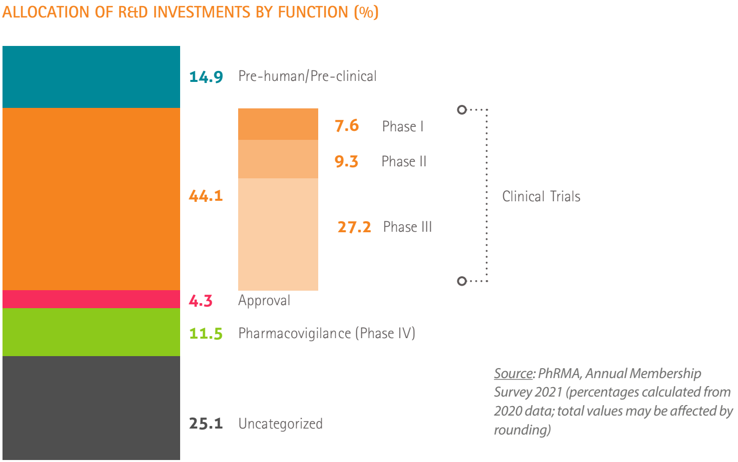
NUMBER OF NEW CHEMICAL AND BIOLOGICAL ENTITIES (2002-2021)




*Source: SCRIP – EFPIA calculations (according to nationality of mother company)*

Source: European Federation of Pharmaceutical Industries and Associations (2022)

# Cost on R&D in Pharmaceutical industry

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# Success rates

According to a recent review (Wong, Siah & Lo, Biostatistics, 2019), between 2000 and 2015

- **41.0%** of confirmatory clinical trials overall and
- **64.5%** of confirmatory clinical trials in oncology

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have been unsuccessful.

- **13.4%** of treatments entering Phase I receive approval
- In oncology only **3.4%** of treatments entering Phase I receive approval

# Consequences

- Avoid going straight into large and expensive phase III trials
- Take more care during phases I and II
- Explore the potential of “new” statistical methods:
  - Sequential designs
  - Adaptive designs
  - Bayesian methods

What is an adaptive design?

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Possible adaptations:

- Stop the trial early when we observe a very strong (or weak) treatment effect;
- Re-estimate the required sample size;
- Stop recruitment to a poorly-performing treatment.

# Why consider adaptive designs?

Different benefits for different forms of adaptation, including:

- Stopping early: fewer participants required on average
- Sample size re-estimation: more likely to reach required power
- Drop “loser” treatment: decrease the proportion of participants receiving poorly-performing treatment

In clinical trials, data accumulates steadily over time $\rightarrow$ natural to sequentially monitor results and perform interim analyses, for a number of reasons:

- **Ethical**: Minimise participants exposure to unsafe/ineffective treatments
- **Economic**: Allow *early stopping* $\rightarrow$ fewer patients needed on average.
- **Administrative**: Ensure trial is being run as planned.

# Interim analysis

In clinical trials, data accumulates steadily over time $\rightarrow$ natural to sequentially monitor results and perform interim analyses, for a number of reasons:

- **Ethical**: Minimise participants exposure to unsafe/ineffective treatments
- **Economic**: Allow *early stopping* $\rightarrow$ fewer patients needed on average.
- **Administrative**: Ensure trial is being run as planned.

Continuous monitoring is often impractical $\rightarrow$ examine the data at periodic intervals.

# Single-arm binary outcome trials

In oncology, a single-arm binary outcome trial (response/no response) often takes place after dose finding (Phase I).

Research question: Is the response rate $p$ of the selected dose large enough to continue development?

We test $H_0 : p \leq p_0$ against $H_1 : p > p_0$. In general:

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**Type-I error-rate**: $P(\text{reject } H_0 | H_0 \text{ is true})$

**Power**: $P(\text{reject } H_0 | H_1 \text{ is true})$

We wish to control the type-I error-rate to be $\alpha$ when $p = p_0$ and power our trial to a level $1 - \beta$ under $p = p_1$.

$p_0$: the greatest response rate that we deem typical for standard of care.

$p_1$: the smallest response rate that is large enough to warrant further study.

# Single-stage design (A'Hern 2001)

The most simple single-arm binary outcome design is the single-stage design:

Recruit $n_{max}$ participants. A go decision is made (i.e. the trial is deemed a success) if the final number of responses $S_{n_{max}}$ exceeds a specified boundary $r$ (i.e. $S_{n_{max}} > r$).

We choose a set of design parameters that satisfy specified type-I error-rate and power requirements for $p_0$ and $p_1$.

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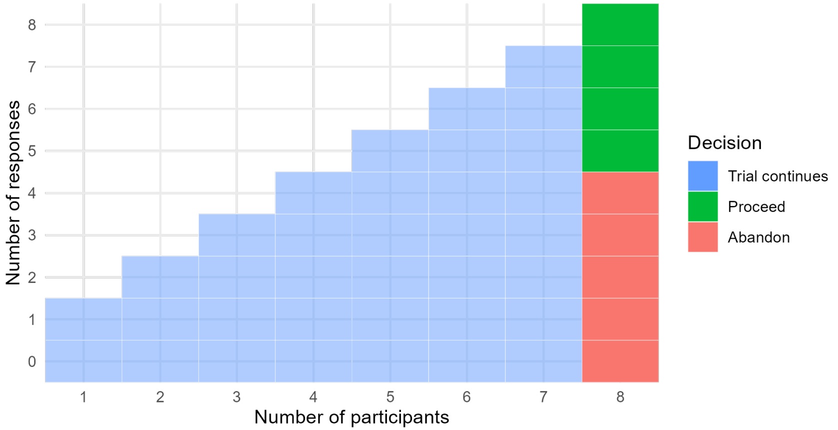
# Single-stage design (A'Hern 2001)

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## Simon design (Simon 1989)

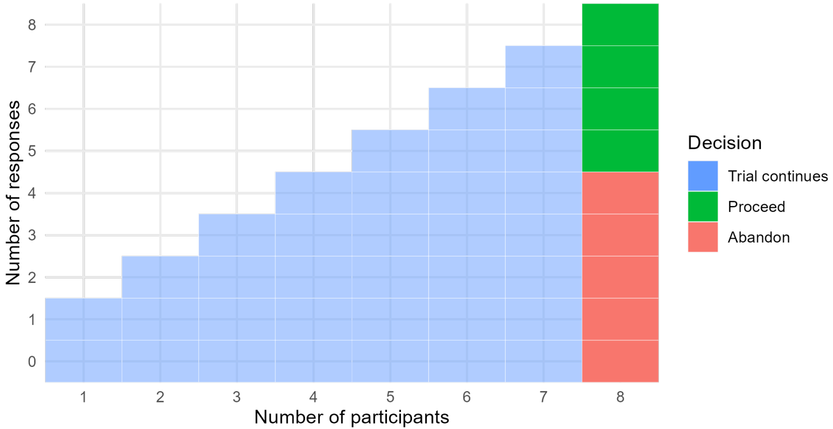
Simon design is a simple adaptation to the single-stage design:

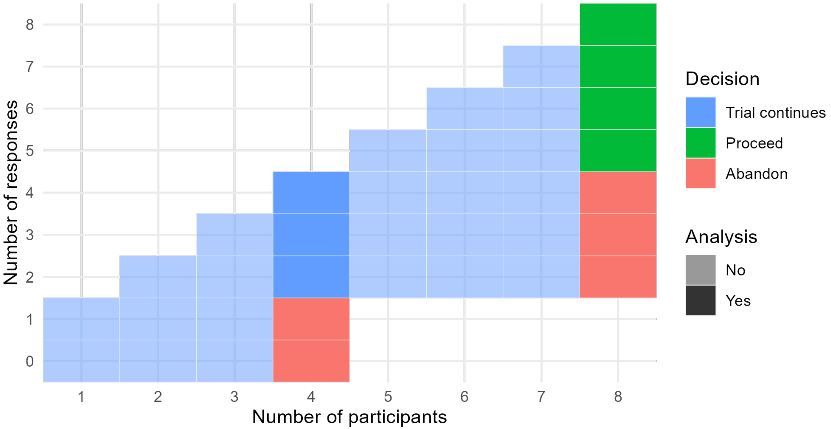
Include single interim analysis after $n_1$ participants.

If $S_{n_1} \leq r_1$, stop for lack of benefit.

Otherwise, recruit another $n_{max} - n_1$ participants and make a go/no-go (success/failure) decision at $n_{max}$.

# Single-stage design




Number of responses
8
7
6
5
4
3
2
1
0
1
2
3
4
5
6
7
8
Number of participants
Decision
Trial continues
Proceed
Abandon
Analysis
No
Yes

# Simon design

Simon designs can be obtained using the command `ph2simon` in the `clinfun` package. The command will return at least two designs:

- Minimax, which minimises the maximum sample size
- Optimal, which minimises the expected sample size under the null hypothesis ($ESS(H_0)$).

```
##
##  Simon 2-stage Phase II design
##
## Unacceptable response rate:  0.2
## Desirable response rate:  0.4
## Error rates: alpha =  0.05 ; beta =  0.1
##
##             r1 n1  r  n EN(p0) PET(p0)    qLo   qHi
## Minimax      5 24 13 45  31.23  0.6559 0.108 1.000
## Admissible   4 20 14 49  30.74  0.6296 0.058 0.108
## Optimal      4 19 15 54  30.43  0.6733 0.000 0.058
```

$PET(p_0)$: Probability of Early Termination

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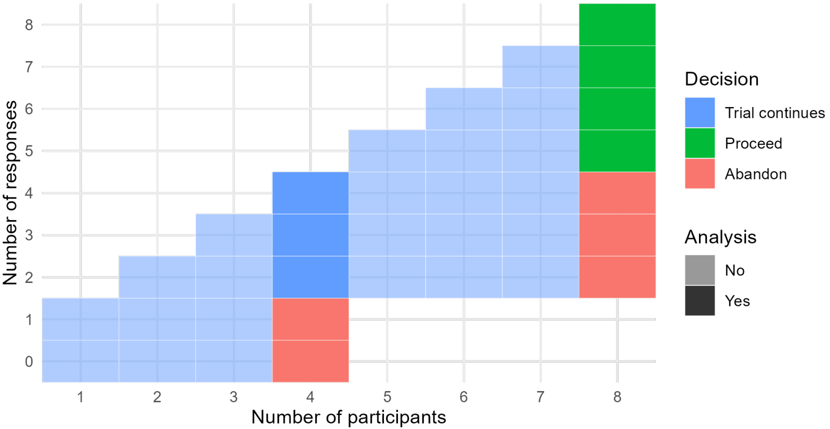
# Mander and Thompson design (2010)

An extension to the Simon design, where the trial may additionally end early for a go decision after $n_1$ participants if $S_{n_1} \geq e_1$.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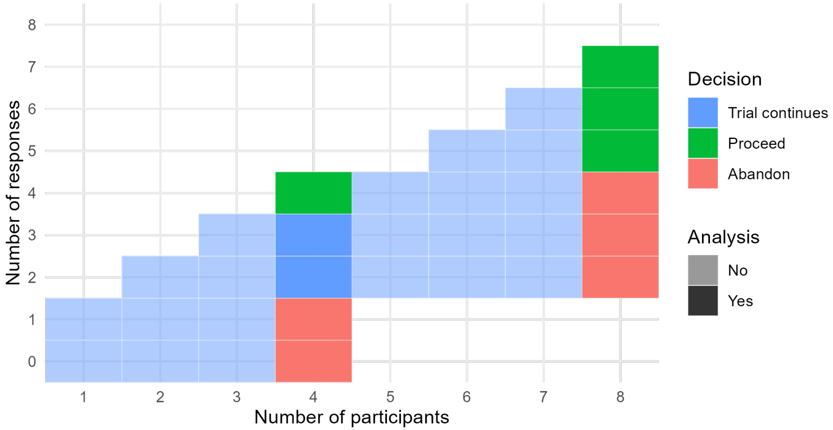
# Mander and Thompson design

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# Obtaining design parameters

For these binary outcome designs, it is possible to calculate the probability of rejecting $H_0$ using the set of design parameters, e.g. $\{n_1, n_{max}, r_1, r\}$, conditional on a response rate.

As such, we do not directly calculate stopping boundaries. Instead, we can calculate type-I error-rate as $P(\text{reject } H_0 | p = p_0)$ and power as $P(\text{reject } H_0 | p = p_1)$.

With this in mind, we can calculate $\alpha$ and $1 - \beta$ for all possible combinations of $\{n_1, n_{max}, r_1, r\}$ to obtain a suitable set of design parameters for our choice of $p_0, p_1, \alpha$ and $1 - \beta$.

# Curtailment in trial design

## Non-stochastic curtailment

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Stop when either success or failure is *certain*.

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Stop when either success or failure is *certain*.

### Stochastic curtailment

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# Curtailment in trial design

## Non-stochastic curtailment

Stop when either success or failure is *certain*.

## Stochastic curtailment

Stop when either success or failure is *very likely*.

# “Very likely”?

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How do we define “very likely”?

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By using conditional power:

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- $P(\text{reject } H_0 \text{ at } n_{max} | p = p_1)$
- $P(\text{reject } H_0 \text{ at } n_{max} | p = \hat{p})$
- $P(\text{reject } H_0 \text{ at any point} | p = p_1)$

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Stop if success is certain: CP=1 (NSC)

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Stop if failure is certain: CP=0 (NSC)

Stop if success is very likely: $CP > \theta_E$ (SC)

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Stop if success is certain: CP=1 (NSC)

Stop if failure is certain: CP=0 (NSC)

Stop if success is very likely: $CP > \theta_E$ (SC)

Stop if failure is very likely: $CP < \theta_F$ (SC)

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By planning to end a trial early due to a high or low CP, we can reduce that trial's expected sample size.

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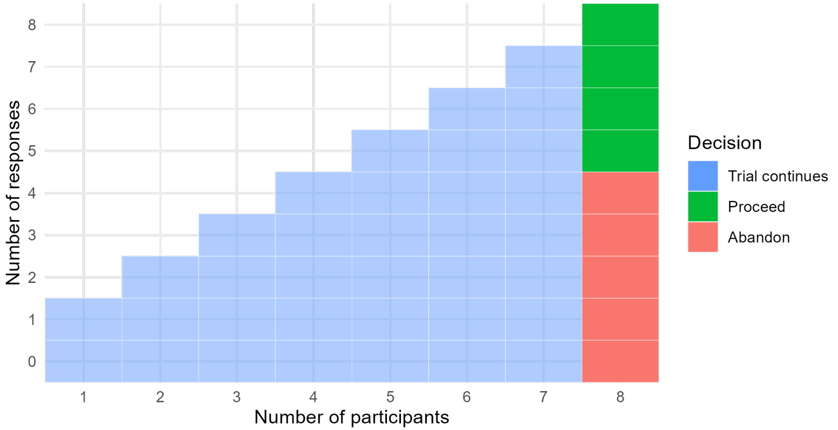
R package for Mander and Thompson design, non-stochastic curtailment and non-stochastic curtailment designs: `curtailment`. Latest version on github (though also on CRAN), link in References.

# Add NSC to single-stage design

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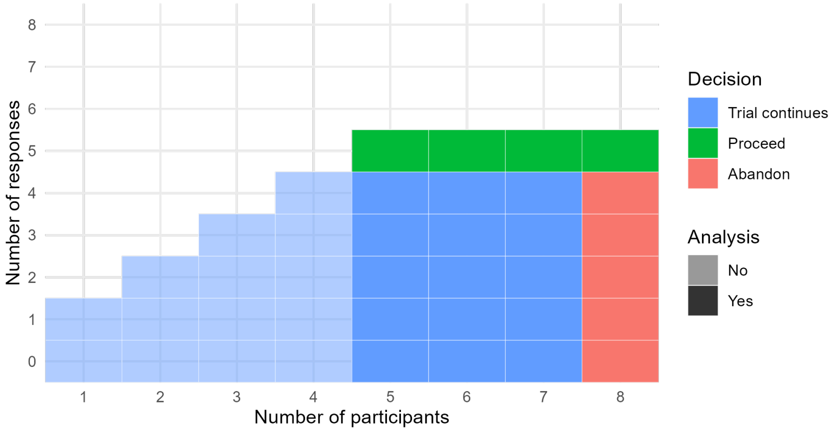

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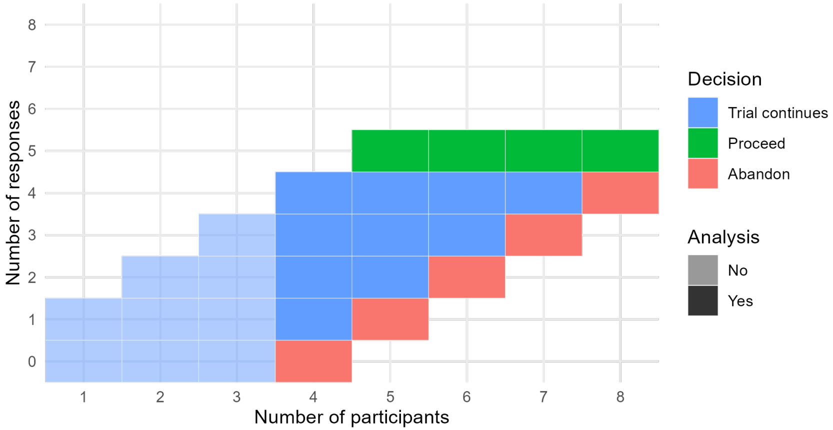

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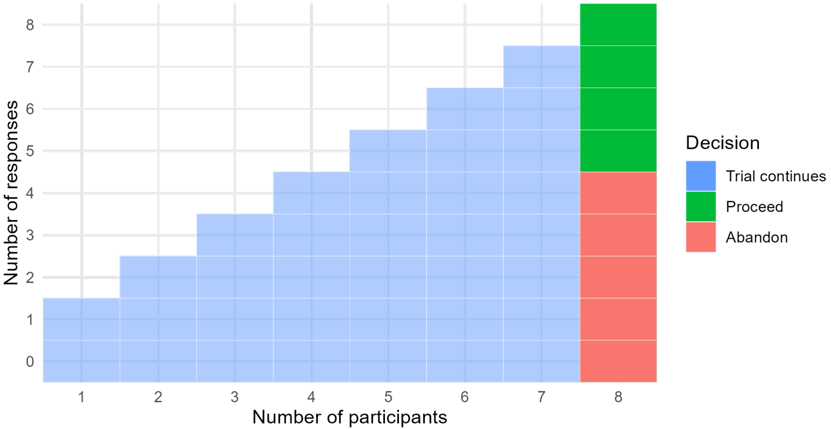

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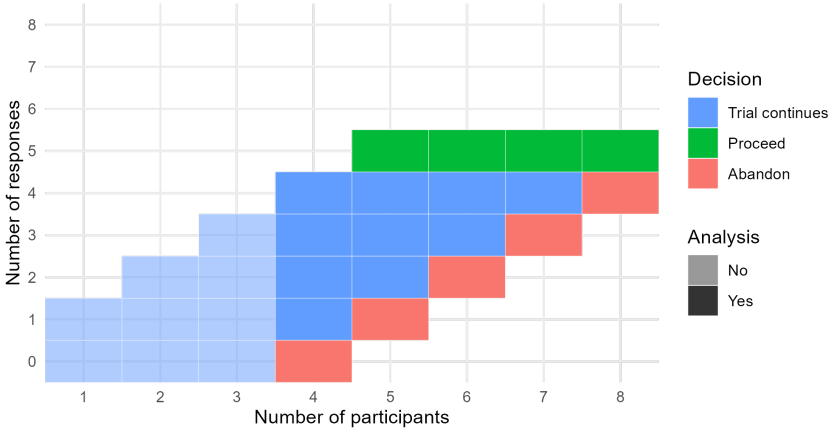

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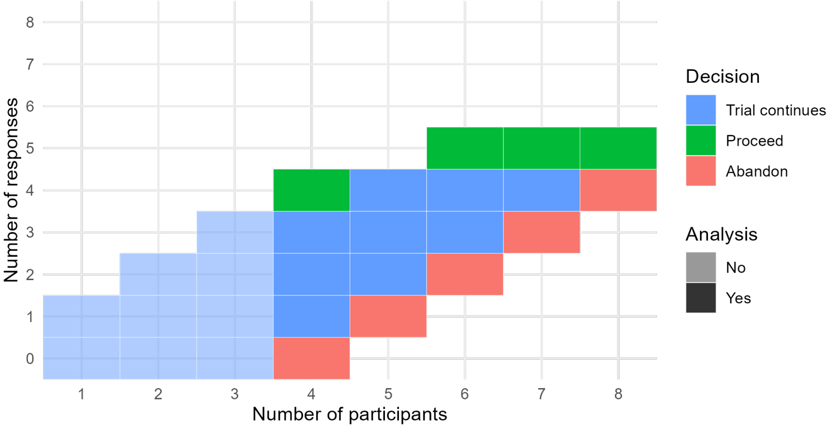


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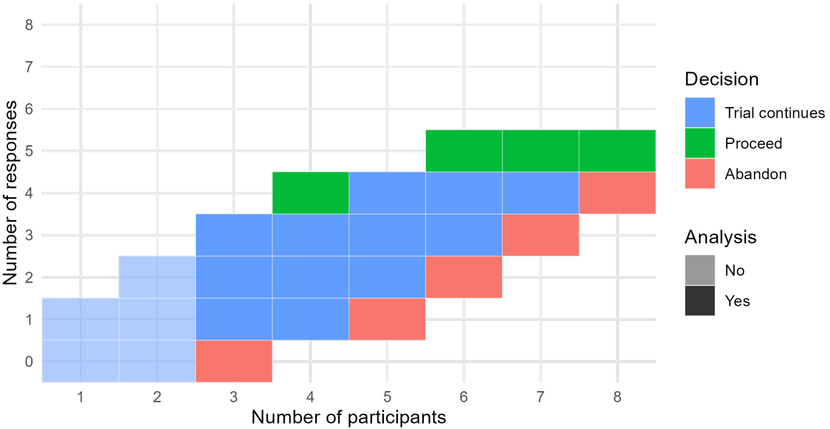


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# Advantages, disadvantages: Simon design

Advantages:

- Simple, well-known to regulators
- Decreases number of participants receiving poorly-performing treatment

Disadvantages:

- When treatment works, trial will not end early (exception: you make a type II error!)
- At the points where early stopping takes place, what would be the probability of trial success if there was no stopping boundary? Not (typically) considered when choosing design parameters.

# Advantages, disadvantages: Mander and Thompson

Advantages:

- Simple
- Allows early stopping for promising treatment

Disadvantages:

- May want more information if trial going well

# Advantages, disadvantages: two-stage designs

Disadvantages:

- Final decision may be known with certainty between interim analyses
- Discrete data: may result in design with lower type-I error-rate or higher power than required.

# Advantages, disadvantages: curtailment

Advantage:

- Decreased expected sample size under both $p = p_0$ and $p = p_1$.

Disadvantages:

- More frequent monitoring required:
  - More work (both analysis and logistics)
  - Difficult if responses come quickly

- Curtailment can also be used in the two-arm setting
- Next lecture: multiple arms and multiple stages

# References


- R.P. A'Hern. Sample size tables for exact single-stage phase II designs. Statistics in Medicine, 20(6):859–866, 2001
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