MRC Biostatistics Unit

UNIVERSITY OF CAMBRIDGE

Adaptive Methods in Clinical Research

Lecture 1: Single arm binary outcome designs

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Link to material

https://github.com/adaptive-designs/course-24

A dose of reality

Ben Goldacre, Guardian[1]:

- **Before 1935**: doctors were basically useless

[1] https://www.theguardian.com/business/2008/sep/01/pharmaceuticals.drugs

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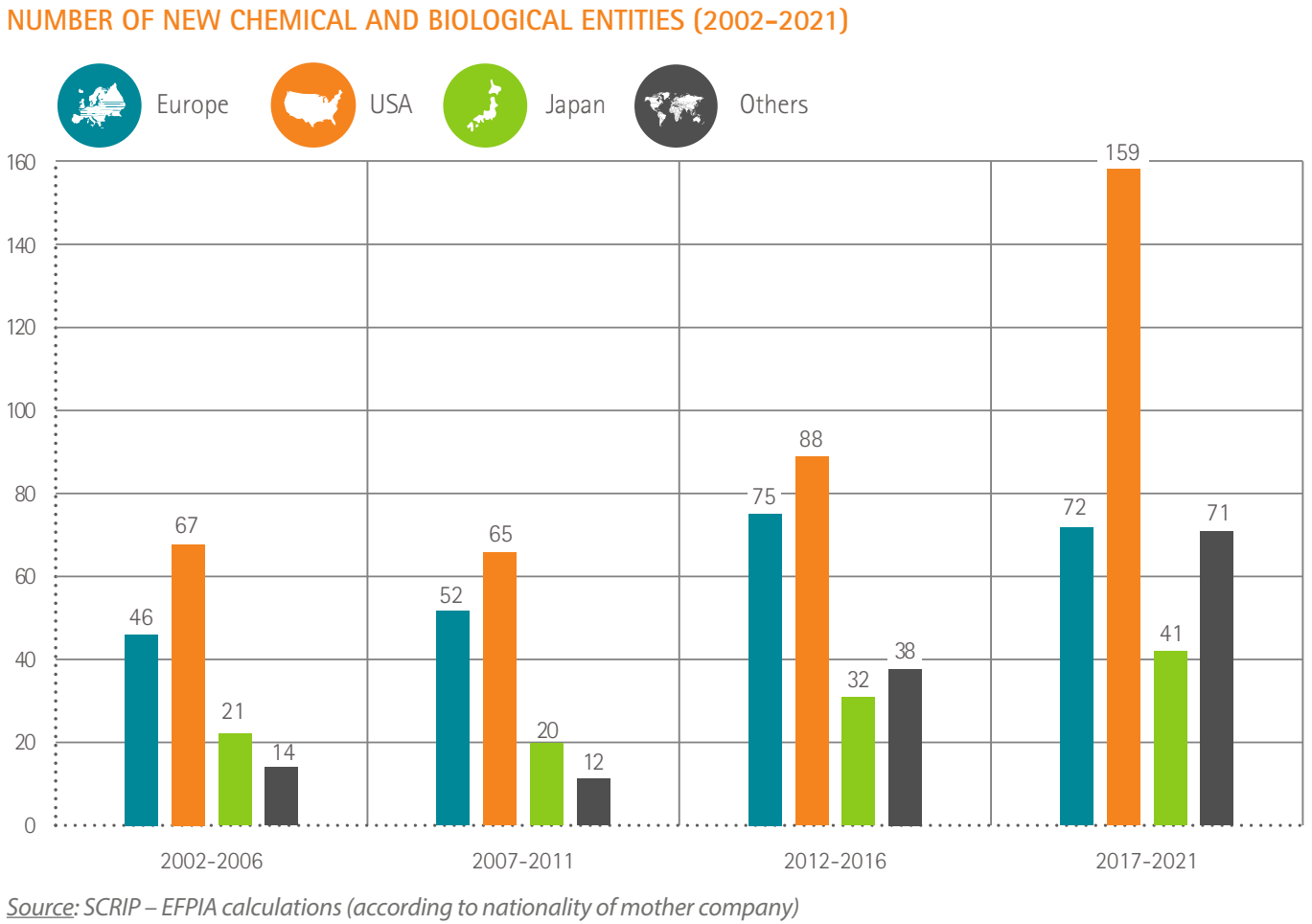
A dose of reality

Ben Goldacre, Guardian[1]:

- **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

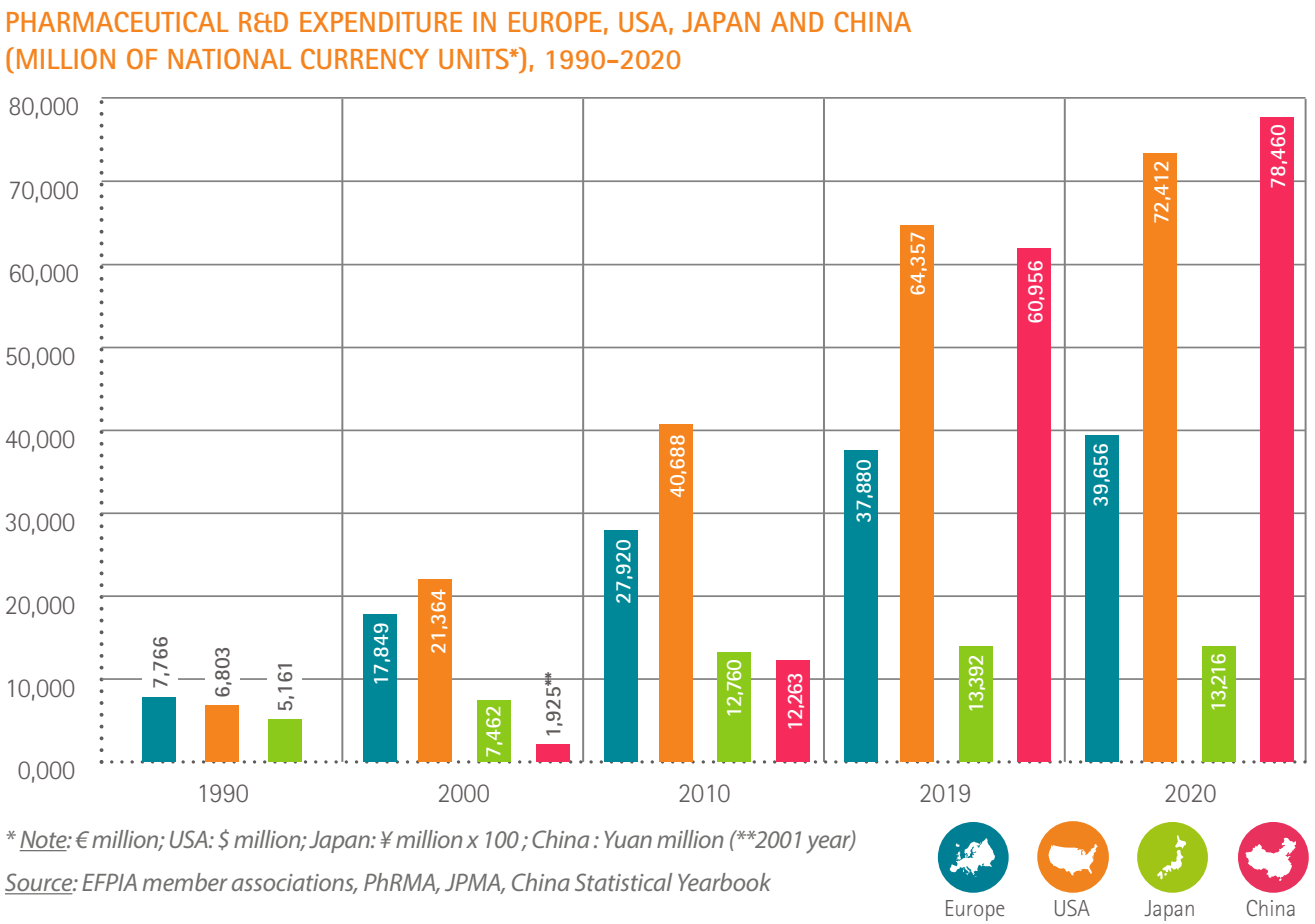
[1] `https://www.theguardian.com/business/2008/sep/01/pharmaceuticals.drugs`

New molecular entities



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

Cost of R&D in Pharmaceutical industry



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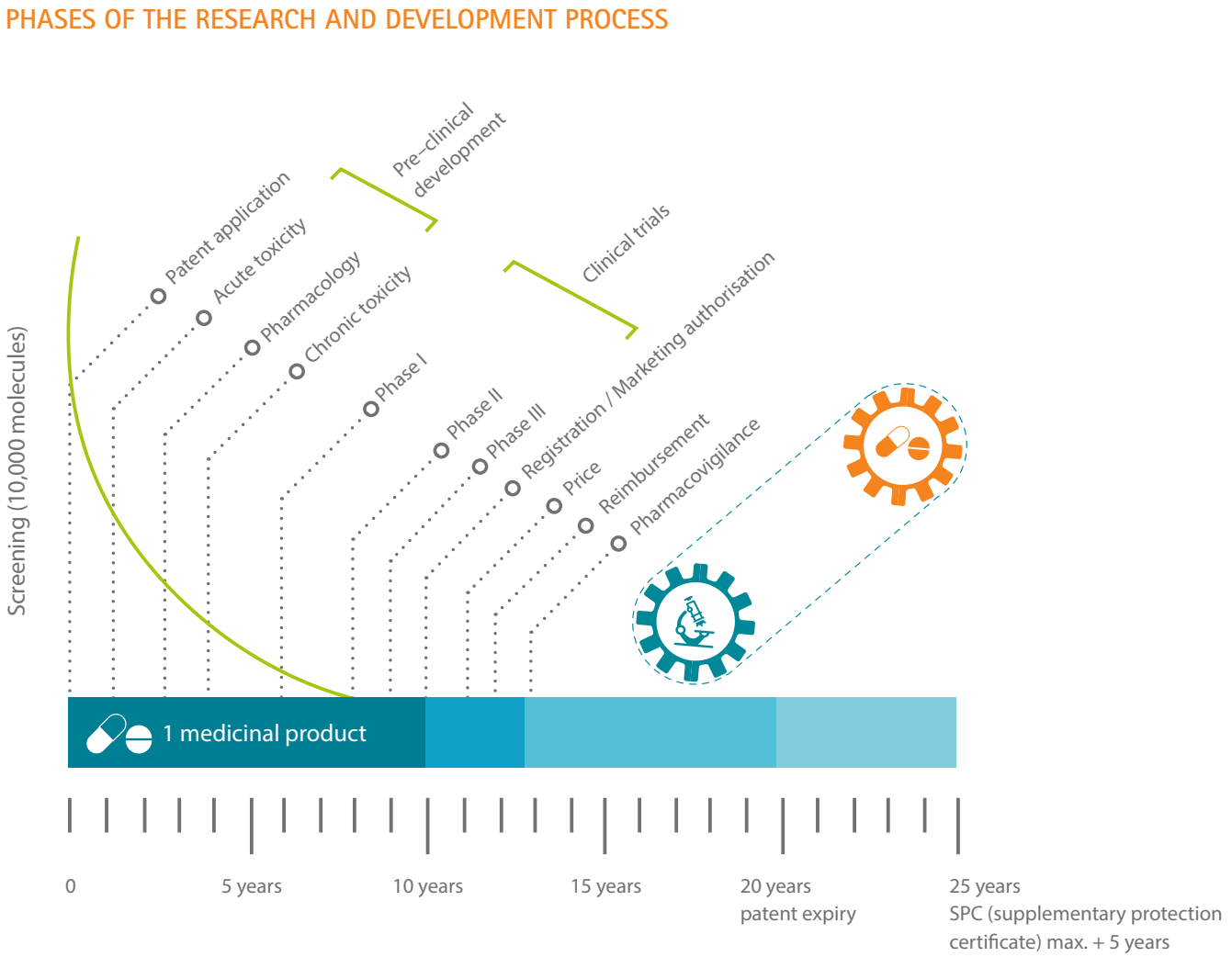
The development process



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

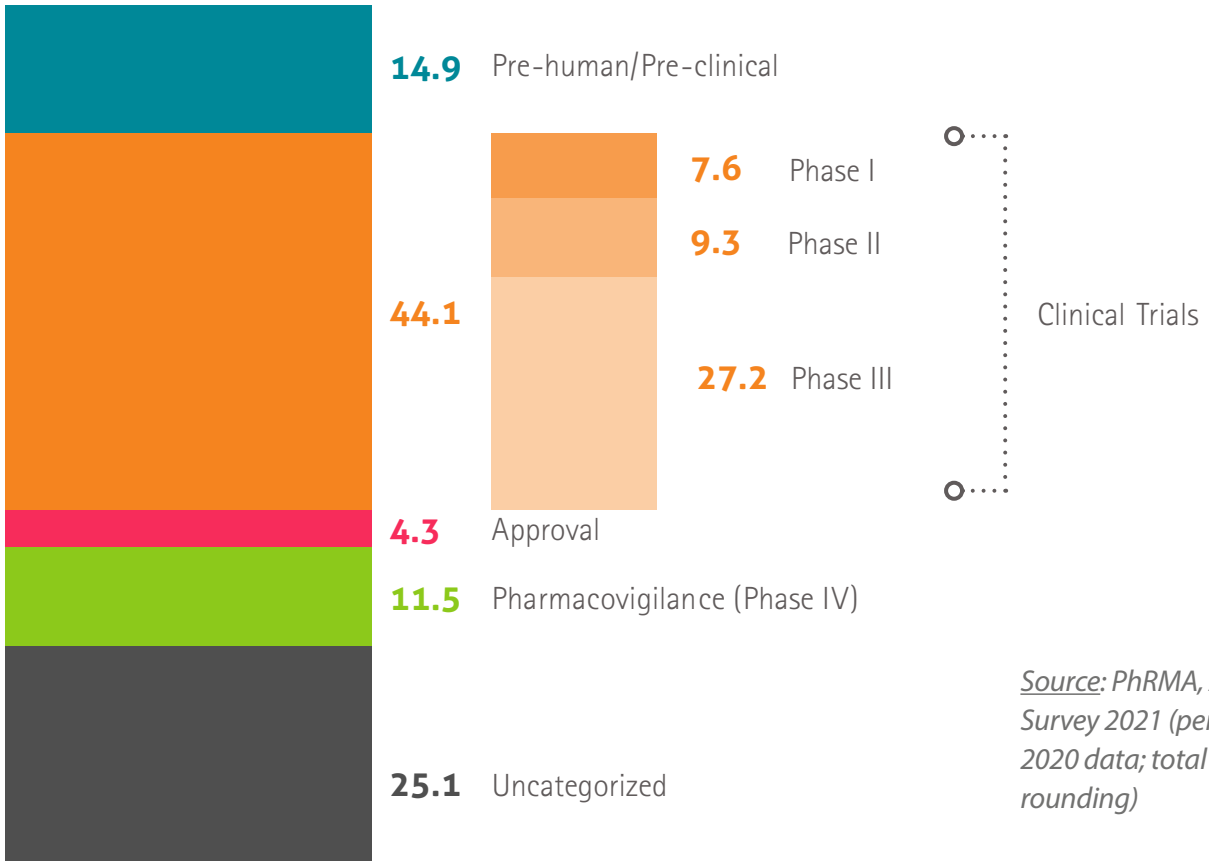
Drug development

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 with thousands of patients and follow-up period lasting years

Cost of R&D in Pharmaceutical industry

ALLOCATION OF R&D INVESTMENTS BY FUNCTION (%)



Source: PhRMA, Annual Membership Survey 2021 (percentages calculated from 2020 data; total values may be affected by rounding)

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

Success rates

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

- **59%** of confirmatory clinical trials overall and
- **36%** of confirmatory clinical trials in oncology

were successful.

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were successful.

- **14%** of treatments entering Phase I received approval
- In oncology only **3%** of treatments entering Phase I received 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:
  - Adaptive designs
  - Bayesian methods

Adaptive designs

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

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.

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- **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

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?

Single-arm binary outcome trials

We test $H_0 : p \leq p_0$ against $H_1 : p \geq p_1$. In general:

Single-arm binary outcome trials

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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 α when $p = p_0$ and power our trial to a level $1 - \beta$ under $p = p_1$, where:

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.

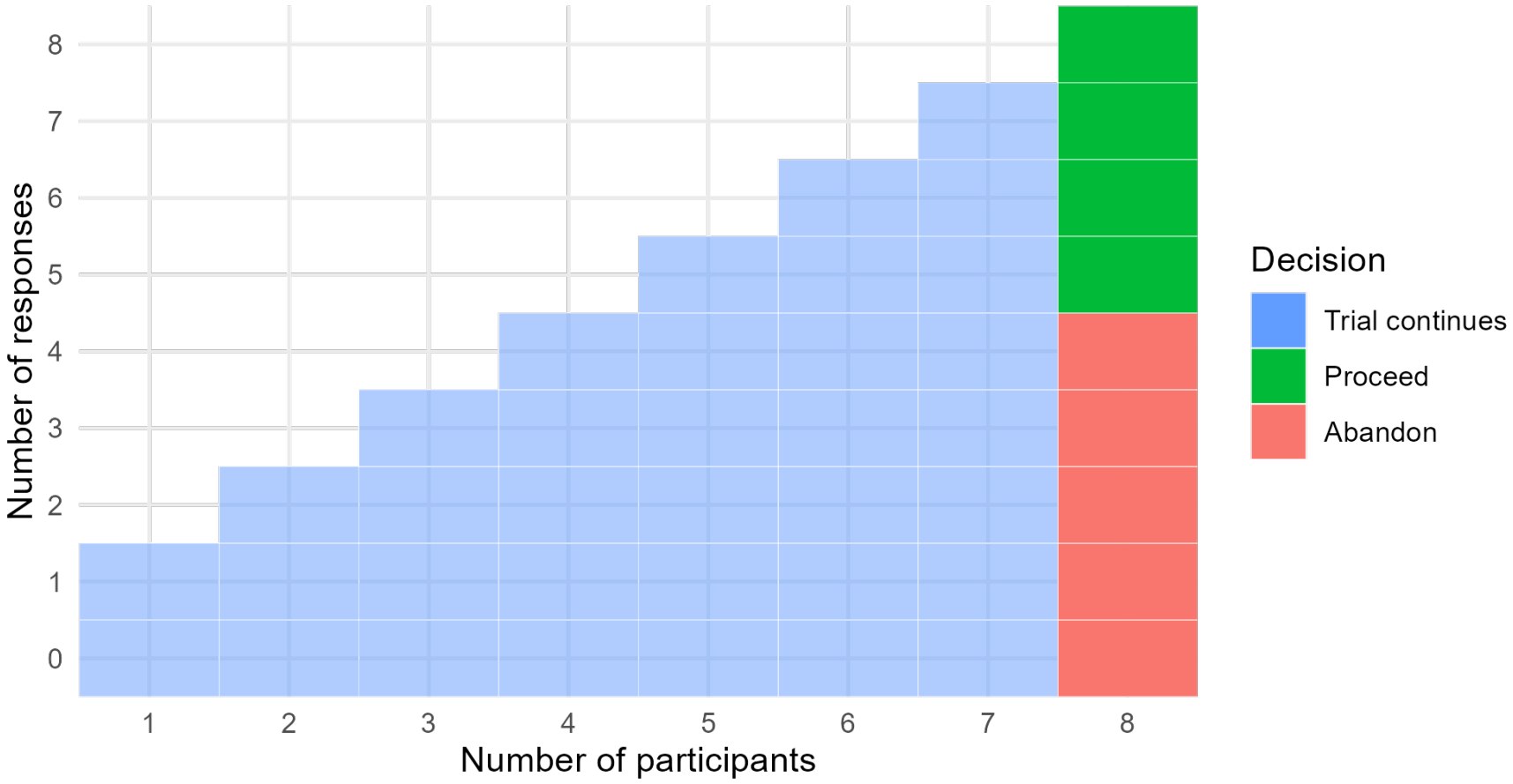
Single-stage design (A'Hern 2001)

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.

Single-stage design (A'Hern 2001)



Simon design (Simon 1989)

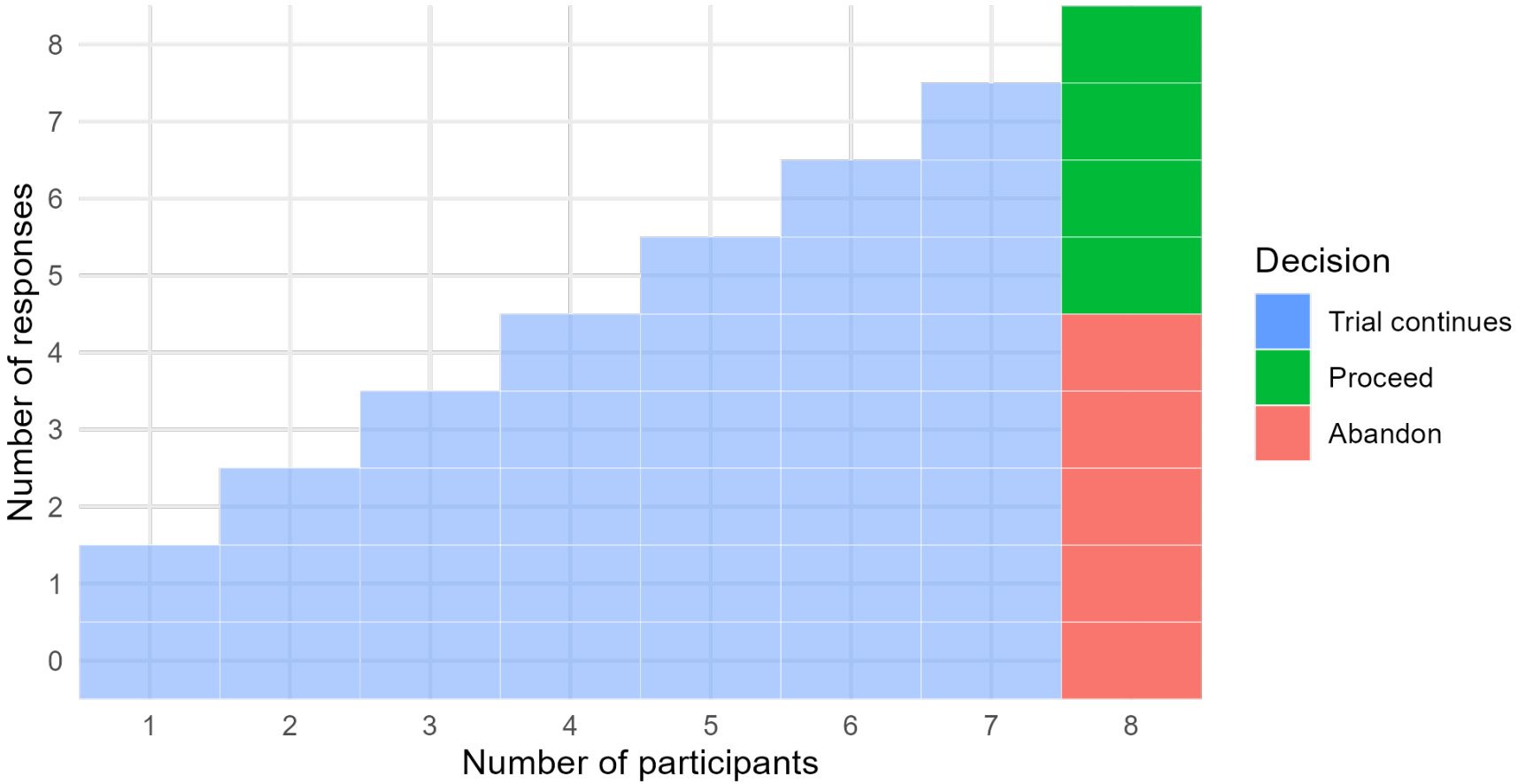
Simon design is a simple adaptation to the single-stage design:

Include single interim analysis after n_1 participants.

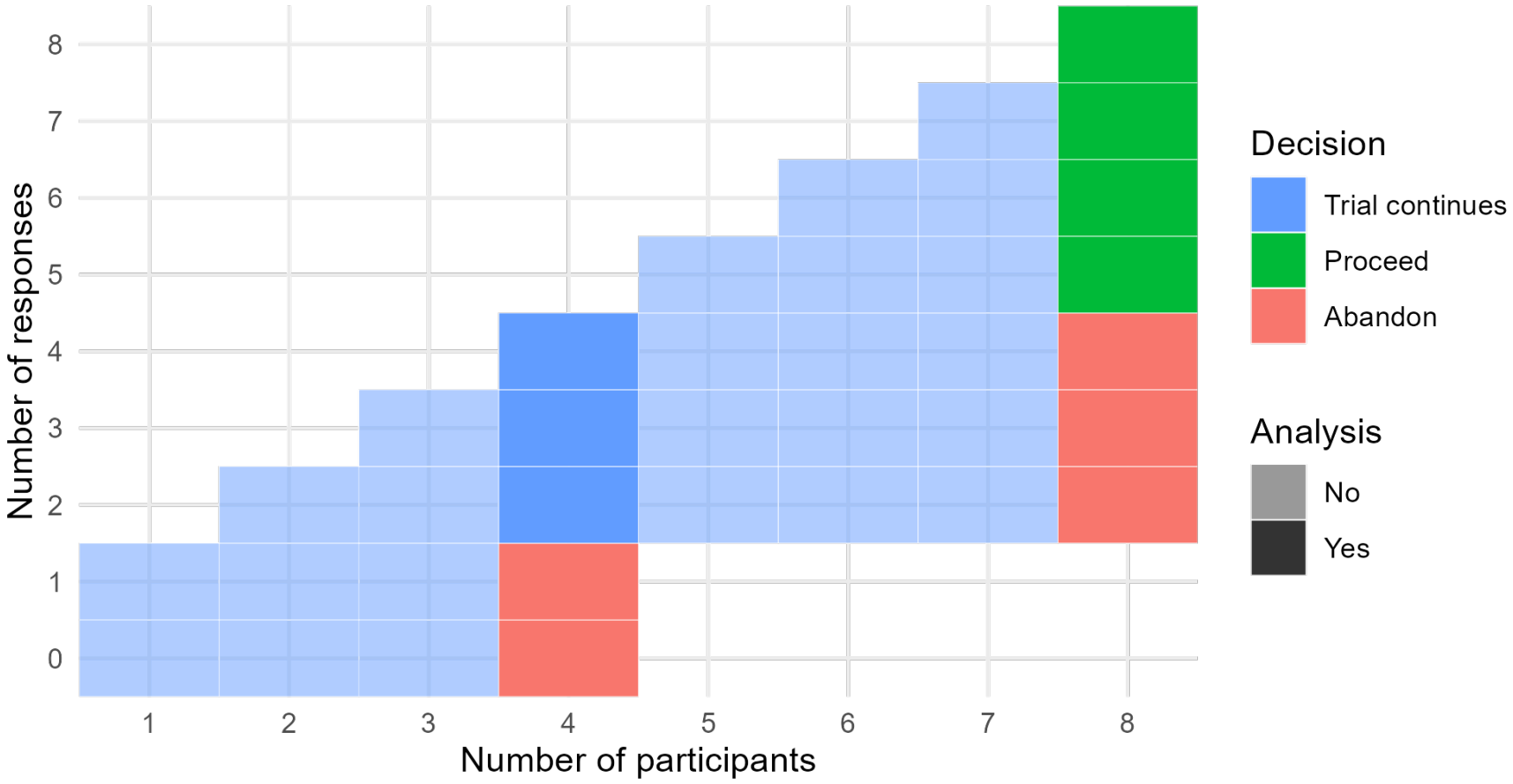
If $S_{n_1} \leq r_1$, stop for lack of benefit.

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

Single-stage design



Simon design



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 design

```
##
##  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

Simon design: qLo, qHi?

Instead of minimising n_{max} *or* minimising $ESS(H_0)$, consider minimising the following weighted sum:

$$\omega n_{max} + (1 - \omega) ESS(H_0).$$

Each returned design minimises this sum for $\omega \in$ [qLo, qHi].

In other words, `qLo` and `qHi` denote the interval of weights for maximum sample size for which each design is best.

Mander and Thompson design (2010)

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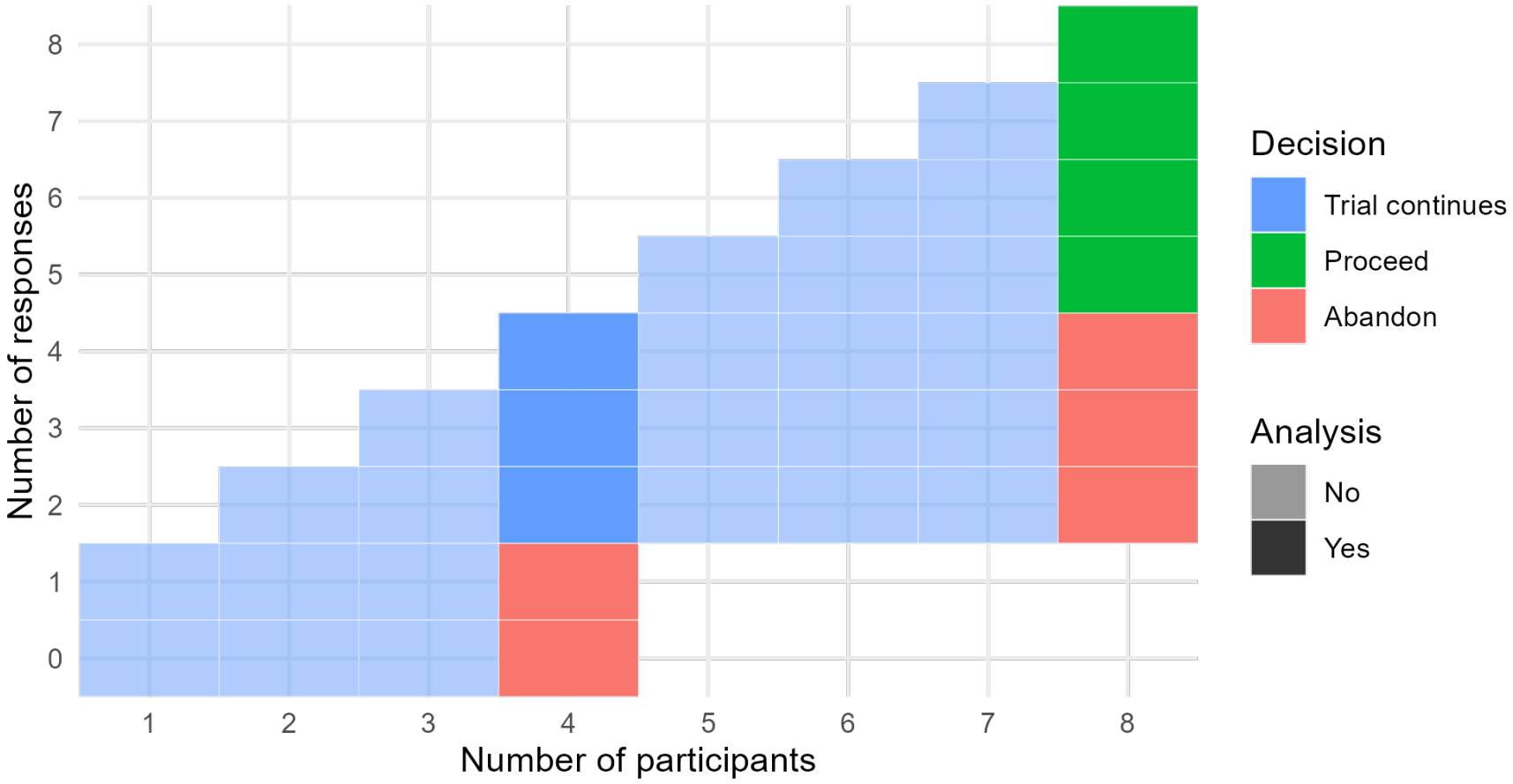
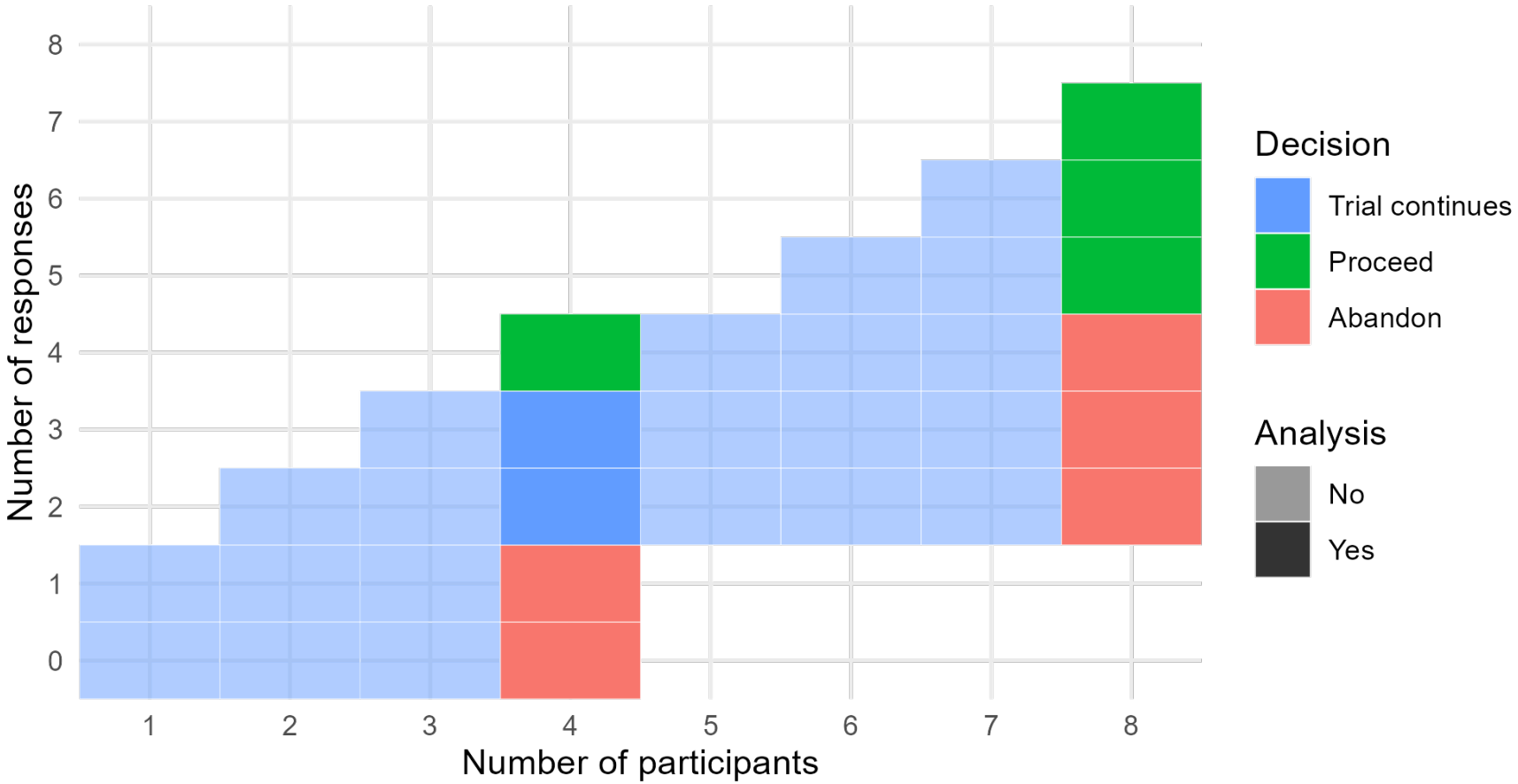
An extension to the Simon design, where the trial may additionally end early for a go decision after n_1 participants if $S_{n_1} > e_1$.

Simon design



Mander and Thompson design



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 α 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, α and $1 - \beta$.

Curtailment in trial design

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Non-stochastic curtailment

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Non-stochastic curtailment

Stop when either success or failure is *certain*.

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Stochastic curtailment

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:

Conditional power (CP)

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Conditional power is the current probability of trial success, conditional on some response rate p. This can be interpreted in different ways:

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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 very likely: $CP > \theta_E$ (SC)

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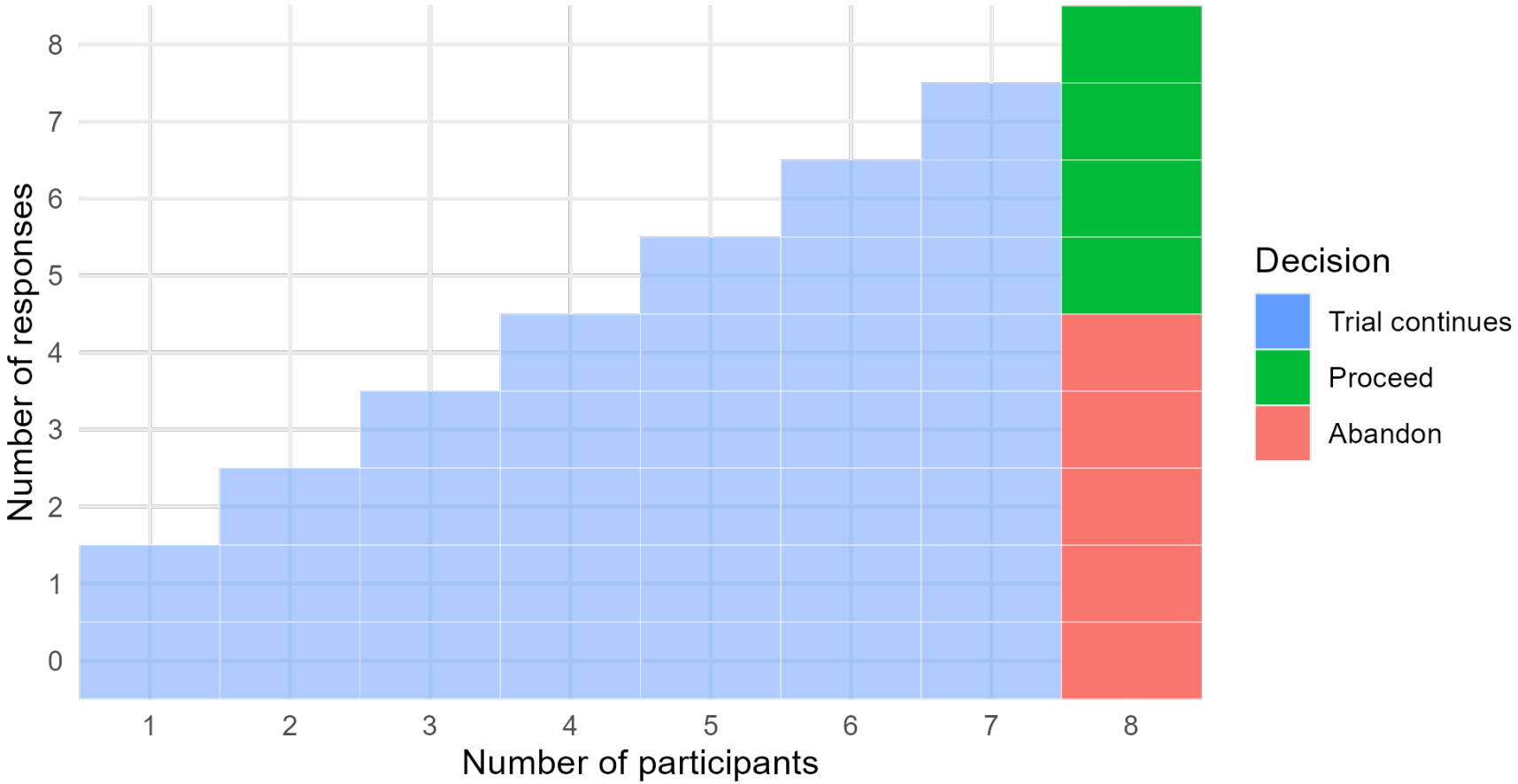
R package for Mander and Thompson design, non-stochastic curtailment and stochastic curtailment designs: `curtailment`. Latest version on github (older version on CRAN), link in References.

Add NSC to single-stage design



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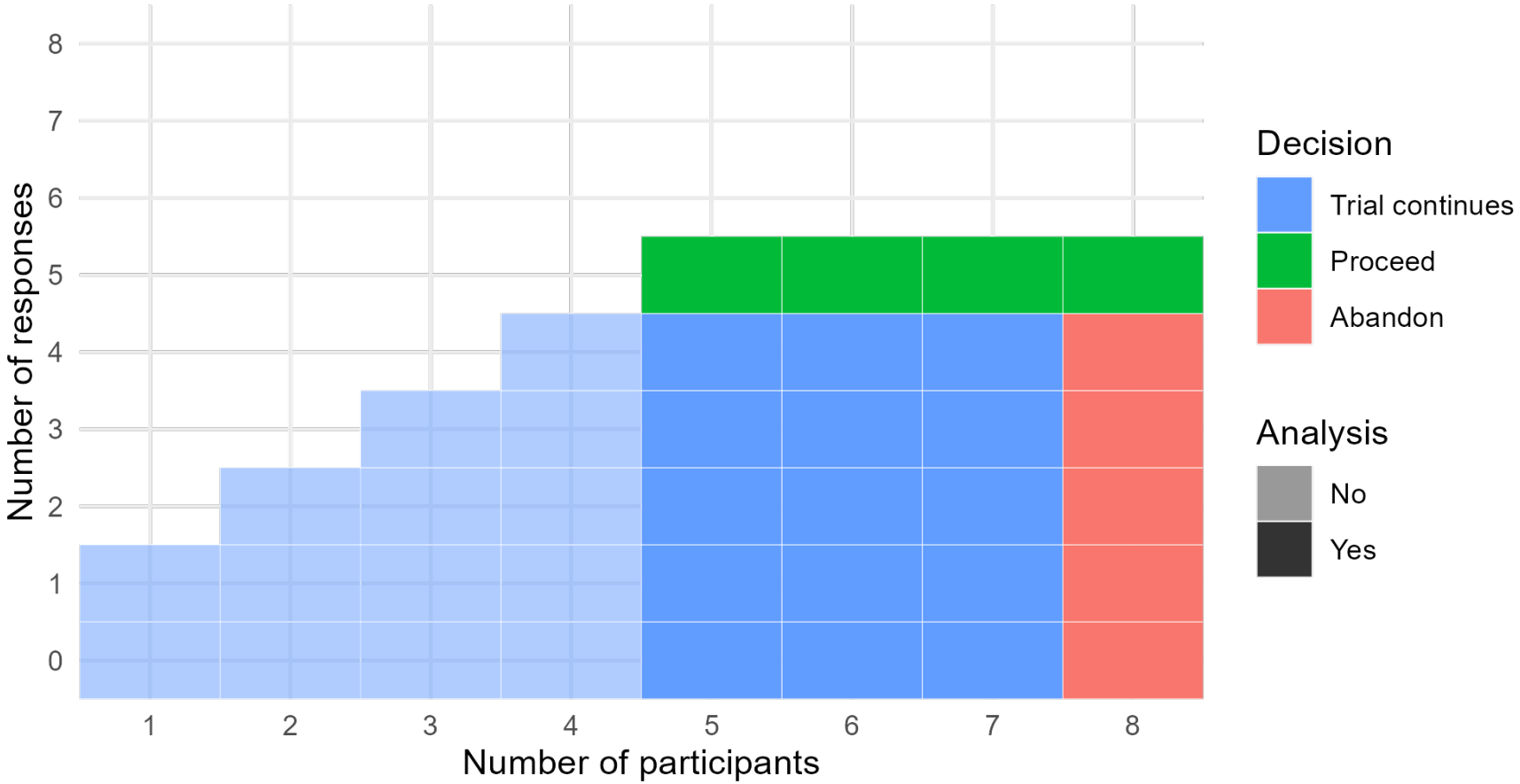

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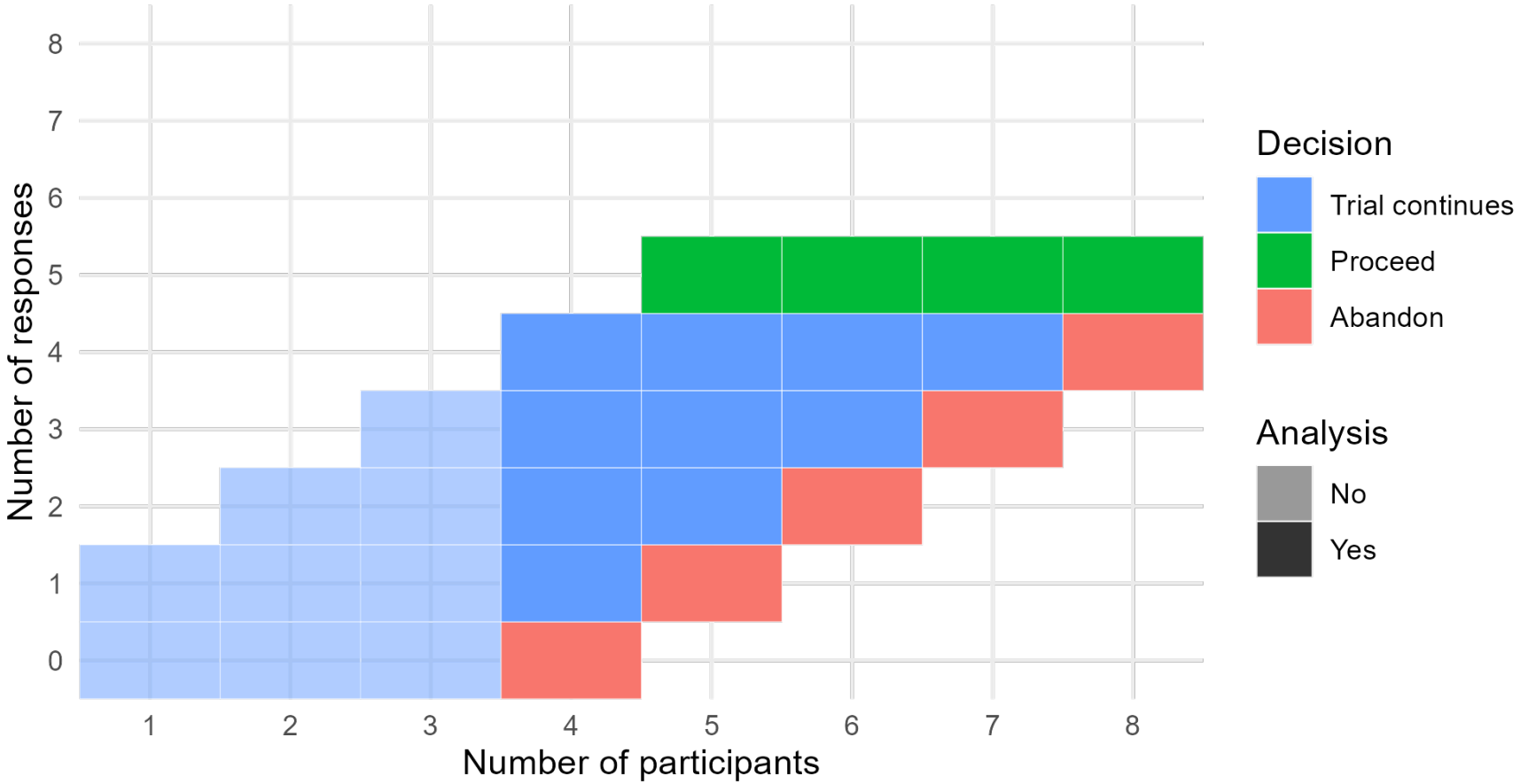

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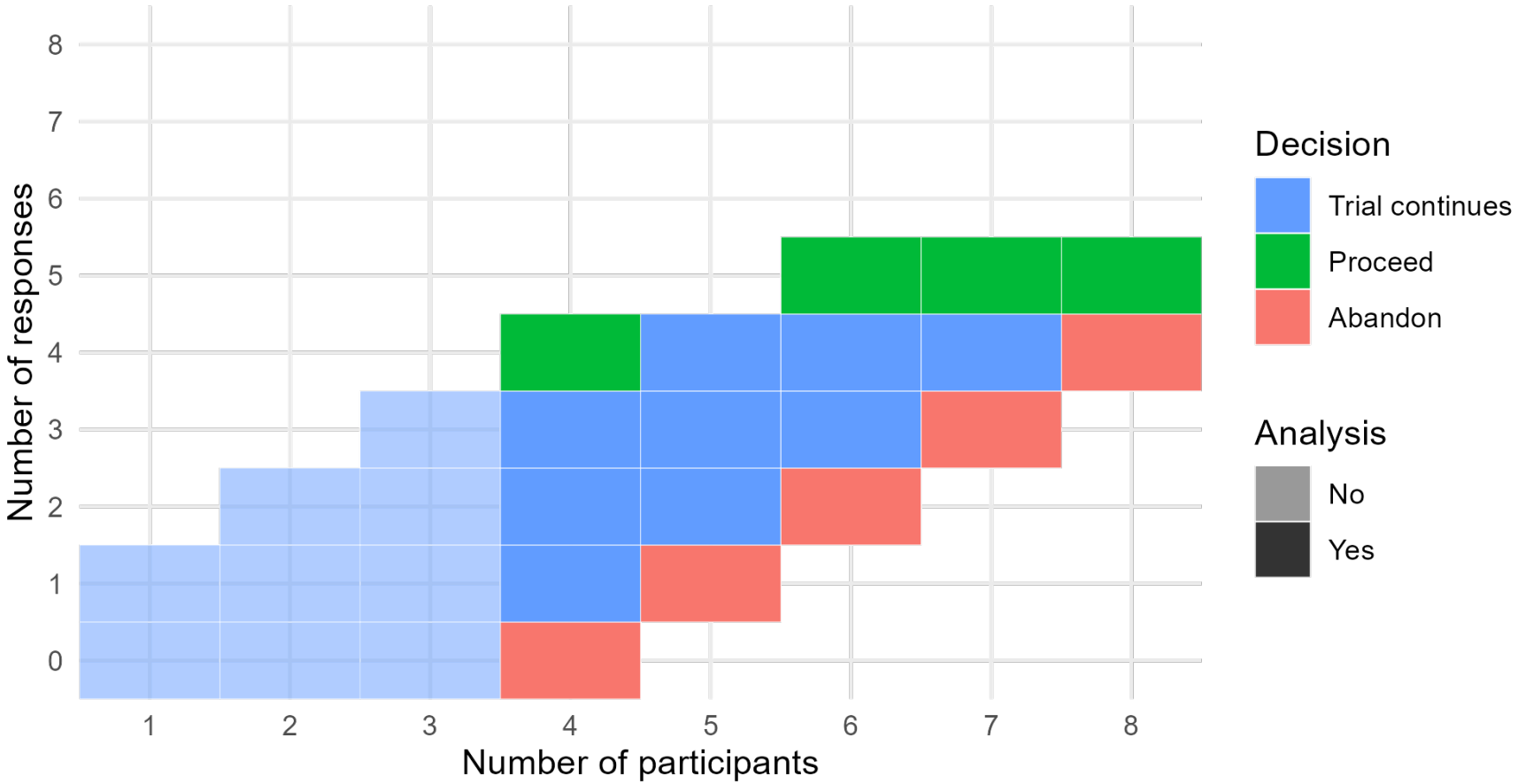

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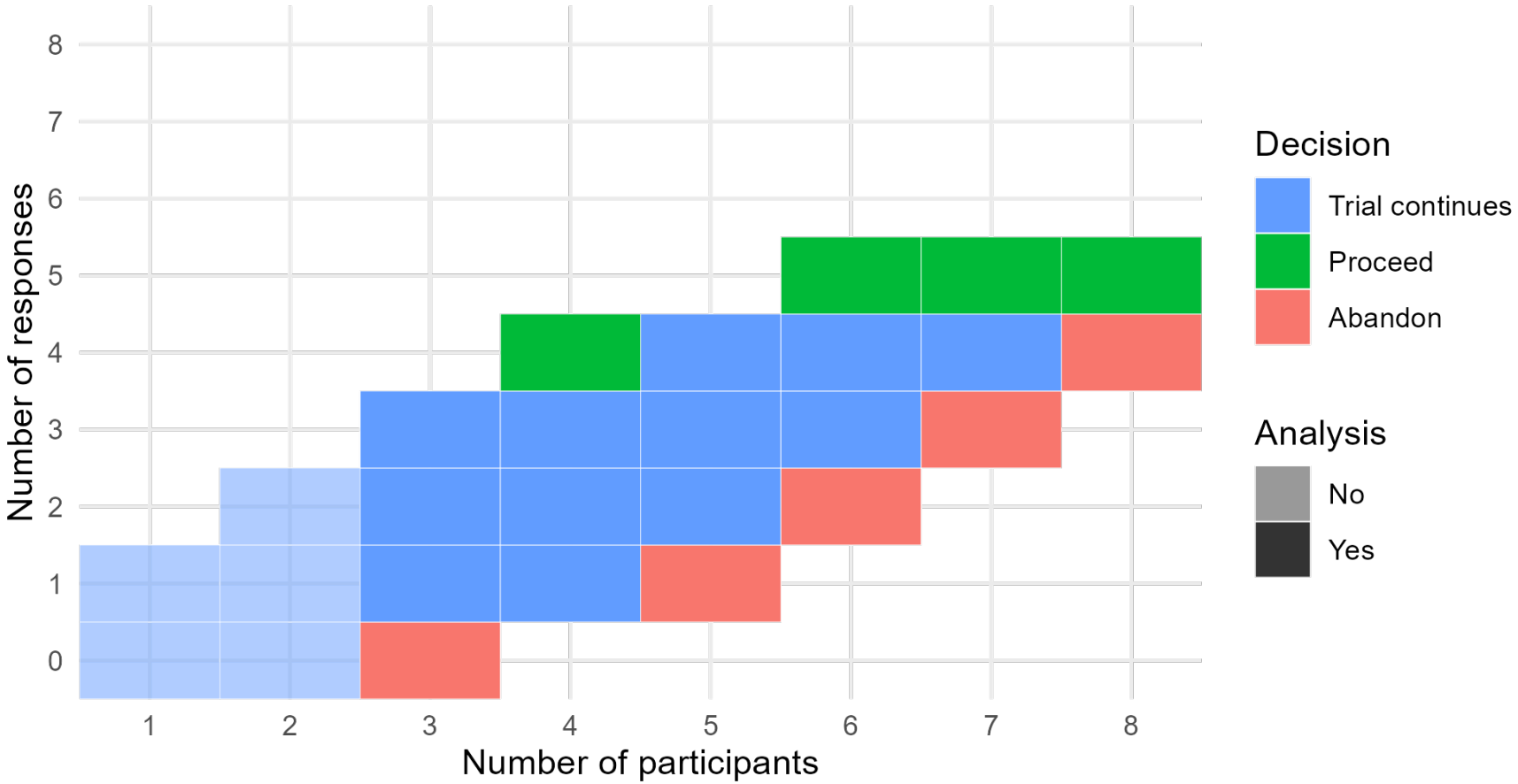

Advantages, disadvantages: Simon design

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 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
- Less information (as smaller ESS)

Beyond single-arm single-stage designs

- Curtailment can also be used in the two-arm setting

Beyond single-arm single-stage designs

- Curtailment can also be used in the two-arm setting
- Next: Practical session using some of these designs
- Next lecture: Group sequential designs

References

- R.P. A'Hern. Sample size tables for exact single-stage phase II designs. Statistics in Medicine, 20(6):859–866, 2001
- R. Simon. Optimal two-stage designs for phase II clinical trials. Controlled Clinical Trials, 10:1–10, 1989.
- A.P. Mander and S.G. Thompson. Two-stage designs optimal under the alternative hypothesis for phase II cancer clinical trials. Contemporary Clinical Trials, 31(6):572-578, 2010.
- M. Law, M.J. Grayling, and A.P. Mander. A stochastically curtailed single-arm phase II trial design for binary outcomes" Journal of biopharmaceutical statistics 32.5: 671-691, 2022.
- M. Law. Github repository. `https://github.com/martinlaw/curtailment`, 2023