Adaptive designs - an overview and some examples

Thomas Jaki Philip Pallmann
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- phase II: $>$80%
- phase III & submission: $\sim$50%

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Phase II (2011–2012)

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Likely causes for failure:

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- taking forward futile treatments

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- studying the wrong patient population

Likely causes for failure:

- taking forward futile treatments
- studying the wrong patient population
- poor precision (optimal dose, maximum tolerated dose, safety)

Can we do better?

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Can we do better?

- avoid going straight into large and expensive phase III

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- avoid going straight into large and expensive phase III
- take more care during phases I and II

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Can we do better?

- avoid going straight into large and expensive phase III
- take more care during phases I and II
- consider adaptive and Bayesian designs

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2. Adaptive Designs

Idea

Modify an ongoing trial

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by design or ad hoc

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Modify an ongoing trial

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based on reviewing accrued data at interim

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based on reviewing accrued data at interim

to enhance flexibility

without undermining the study's integrity and validity.

(Chow et al. 2005)

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Pros and cons

+ highly flexible
+ very efficient
+ reflects medical practice
+ shorter trial and/or more accurate estimates
+ ethical

– highly flexible
– inefficient
– time-consuming to design
– simple estimates may be biased
– interim analyses may require unblinding

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Fixed sample design

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Fixed sample design

- **total** sample size known in advance

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Fixed sample design

- **total** sample size known in advance
- no adjustment possible

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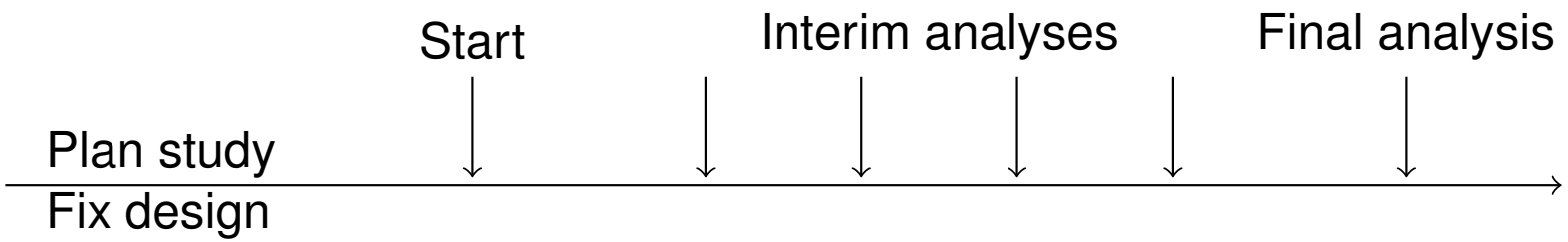
(Group-)sequential design



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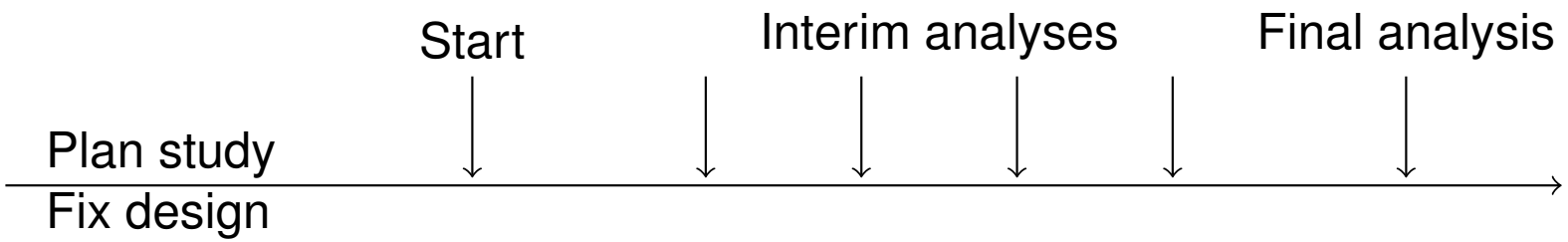

At each interim:

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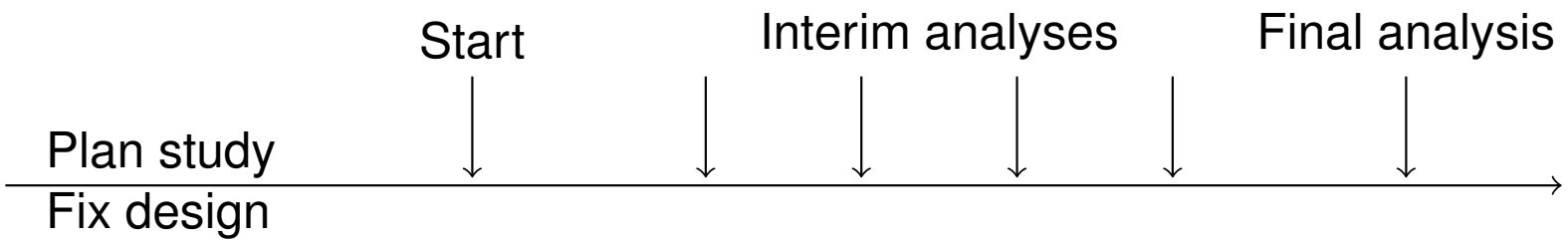

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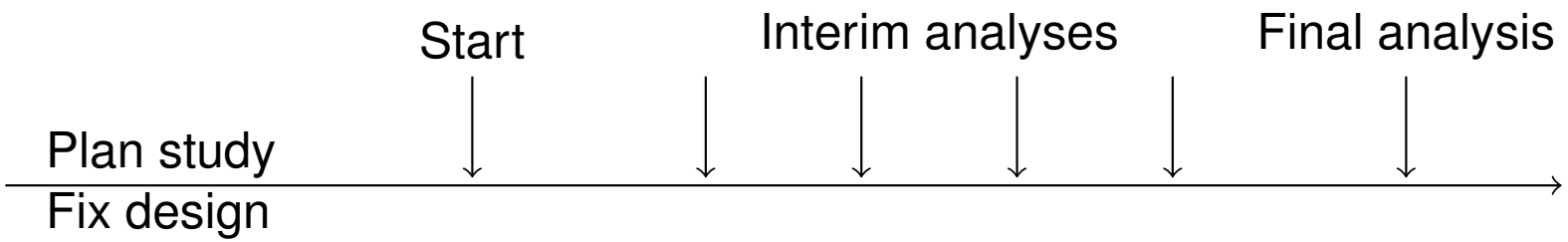

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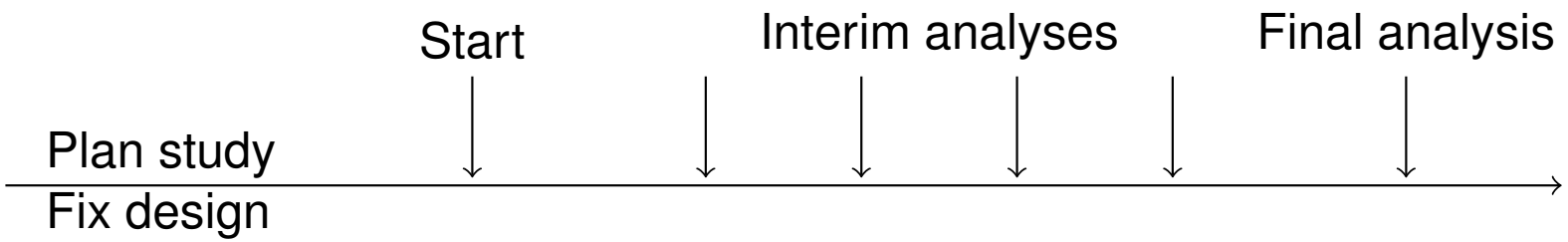

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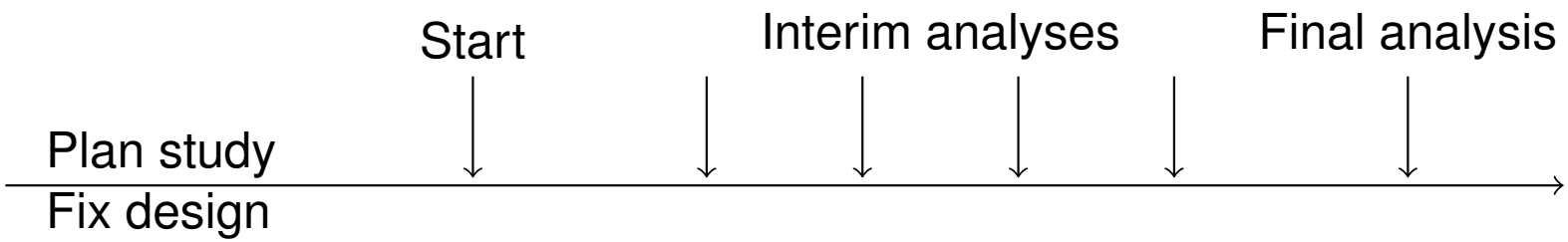

At each interim:

- decide whether or not to stop

- larger **maximum** sample size
- lower **expected** sample size

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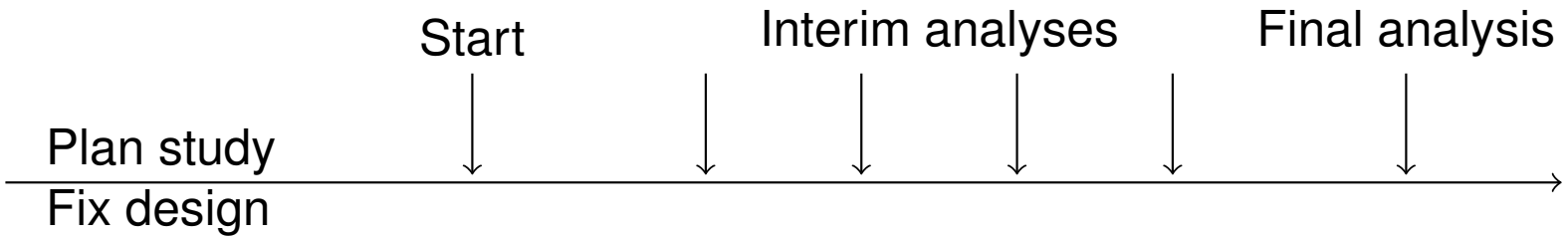
Adaptive design



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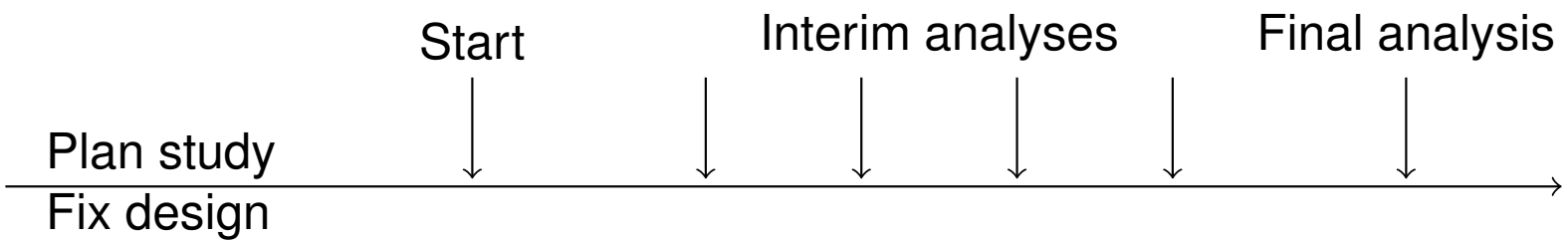

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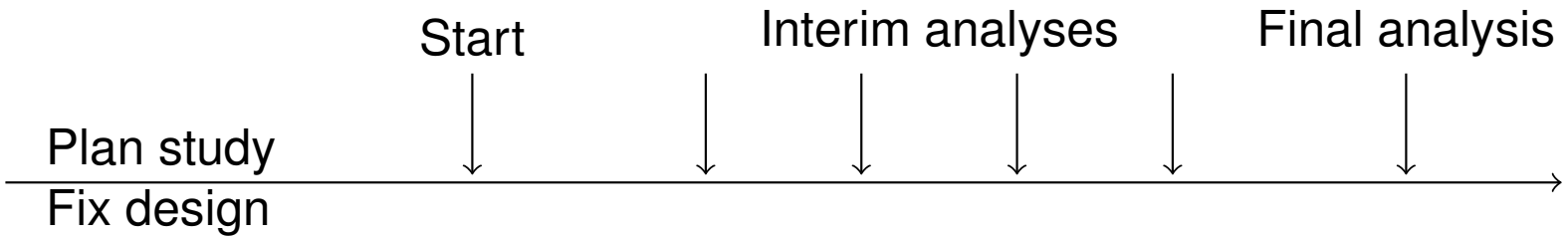

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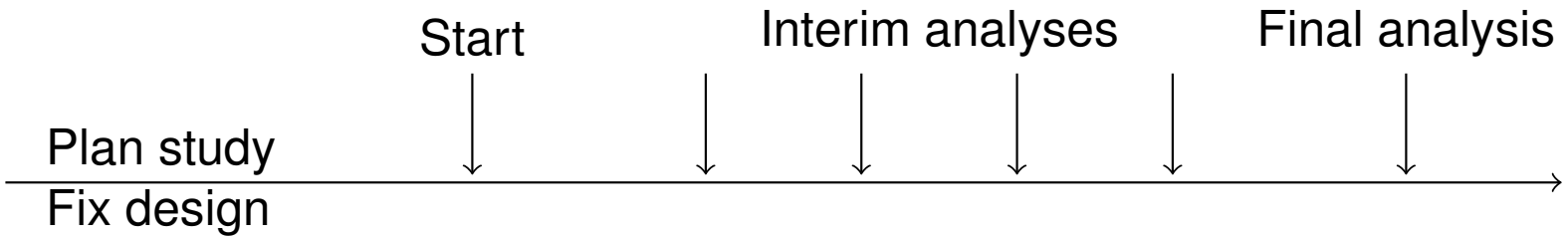

At each interim:

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- and many other options . . .

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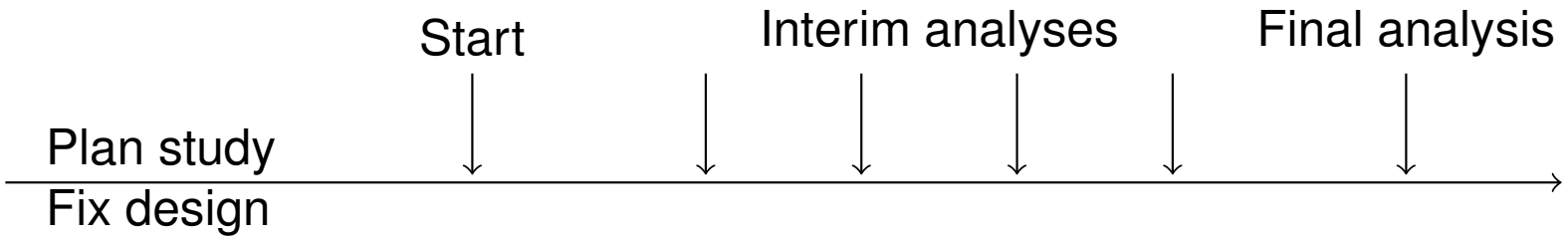

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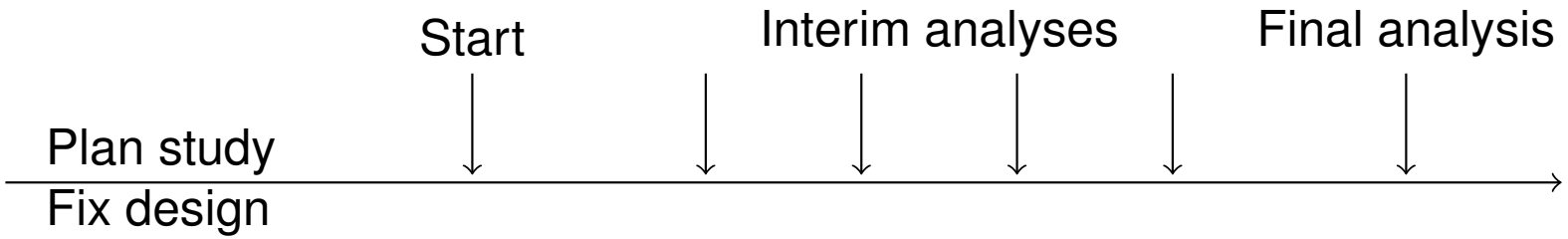

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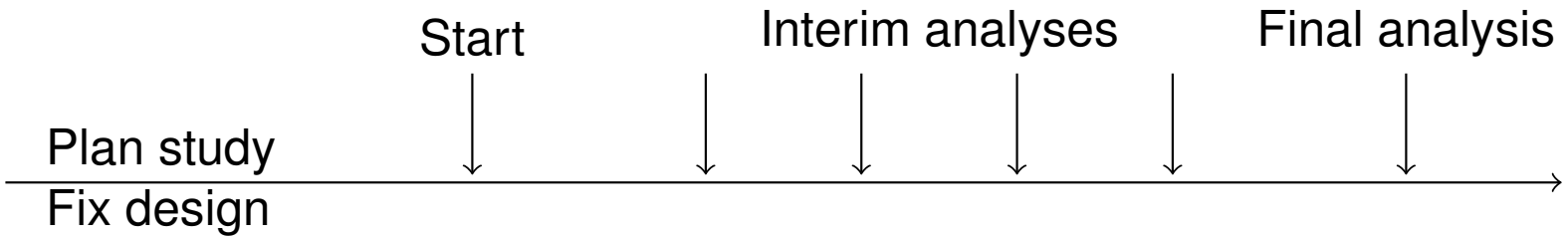

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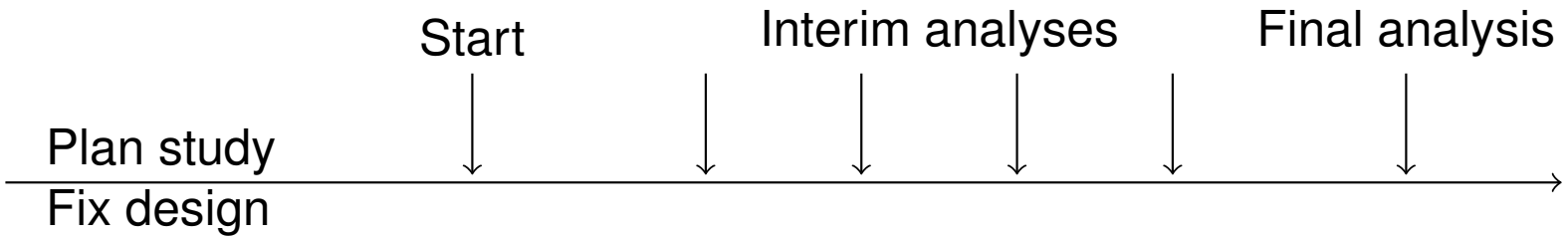

At each interim:

- decide whether or not to stop
- and many other options . . .

- larger **maximum** sample size
- lower **expected** sample size
- possibly more relevant answer

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How and what can we adapt?

Prospectively (“by design")

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- change primary endpoint
- modify doses
- extend treatment duration

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- adaptive randomization
- early stopping (safety, futility, efficacy)
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- sample size re-estimation (to achieve desired power)

Concurrently (“ad hoc")

- modify inclusion/exclusion criteria
- change primary endpoint
- modify doses
- extend treatment duration
- change trial objective (e.g., non-inferiority $\rightarrow$ superiority)

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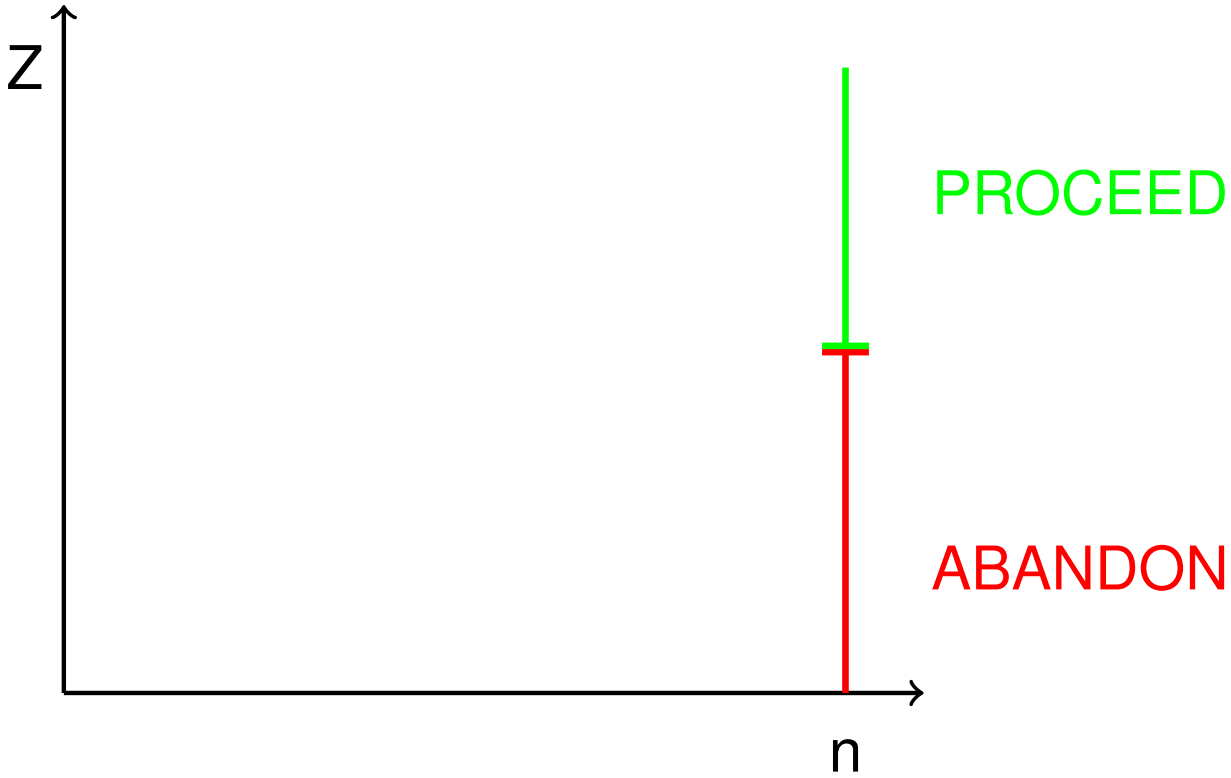
A single-stage design



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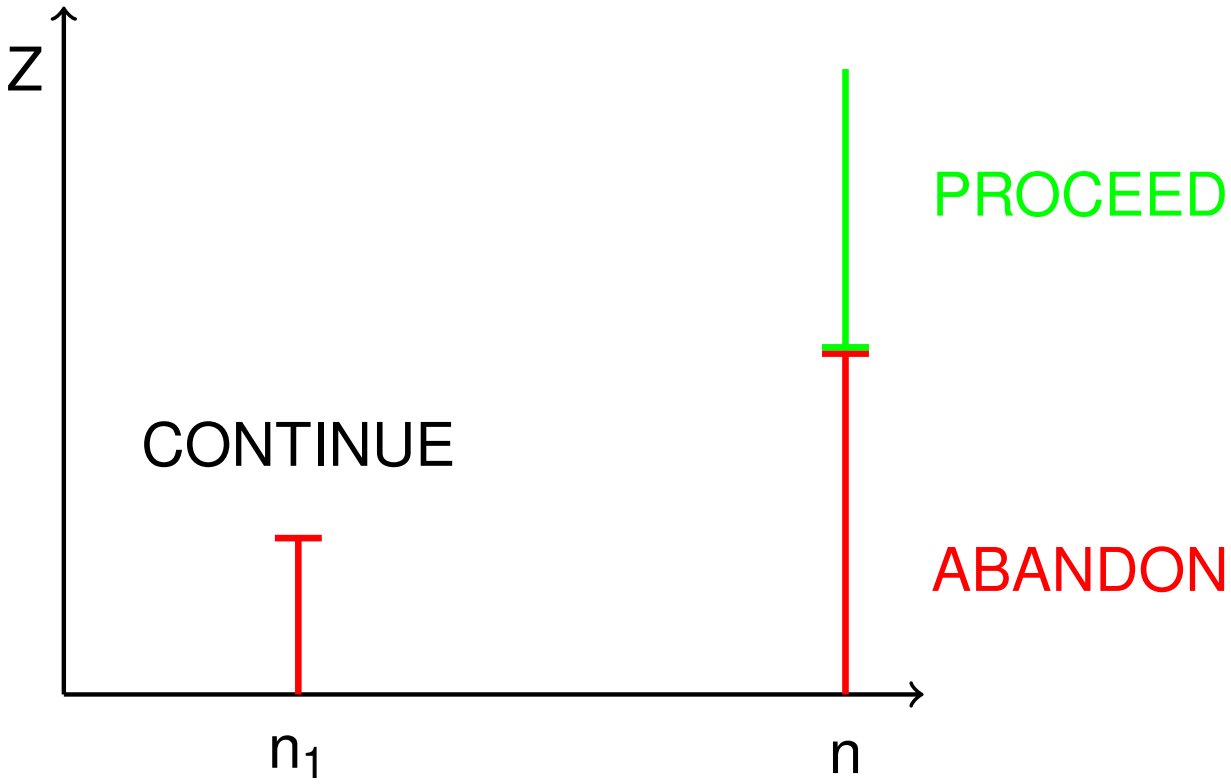
Simon's two-stage design



(Simon 1989)

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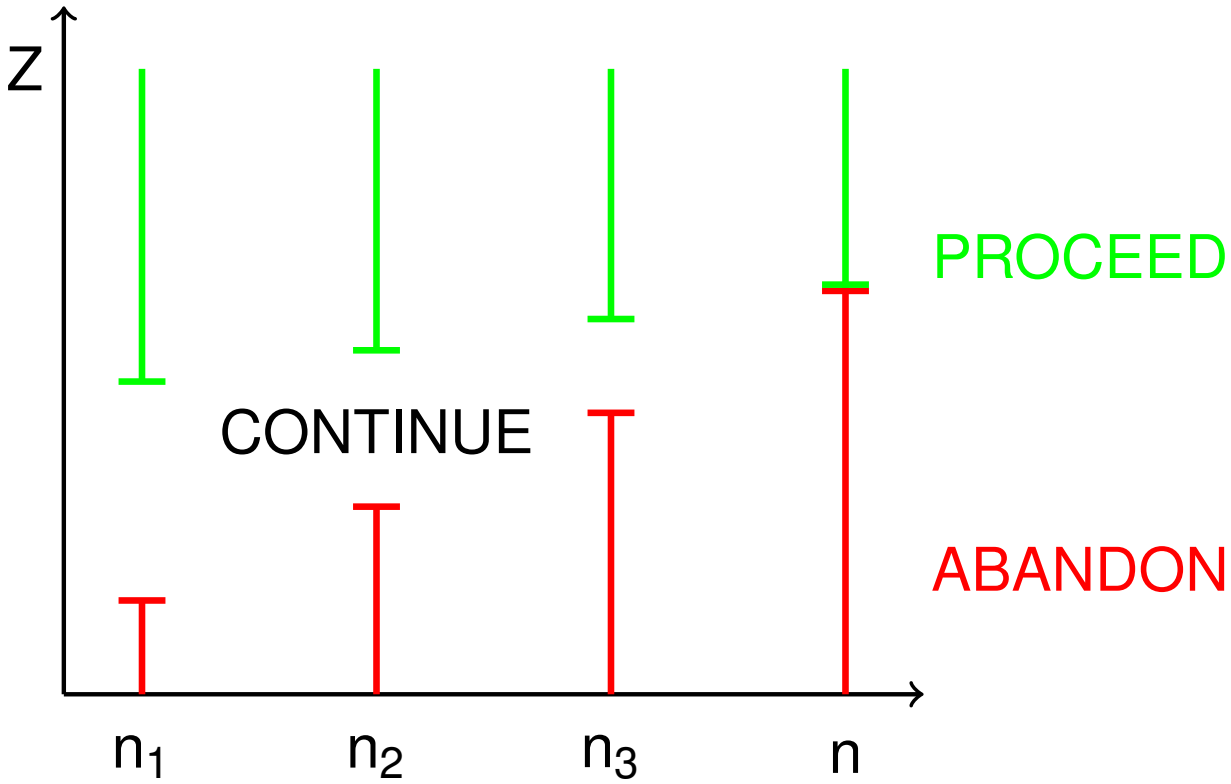
A multi-stage design



(Whitehead 1997)

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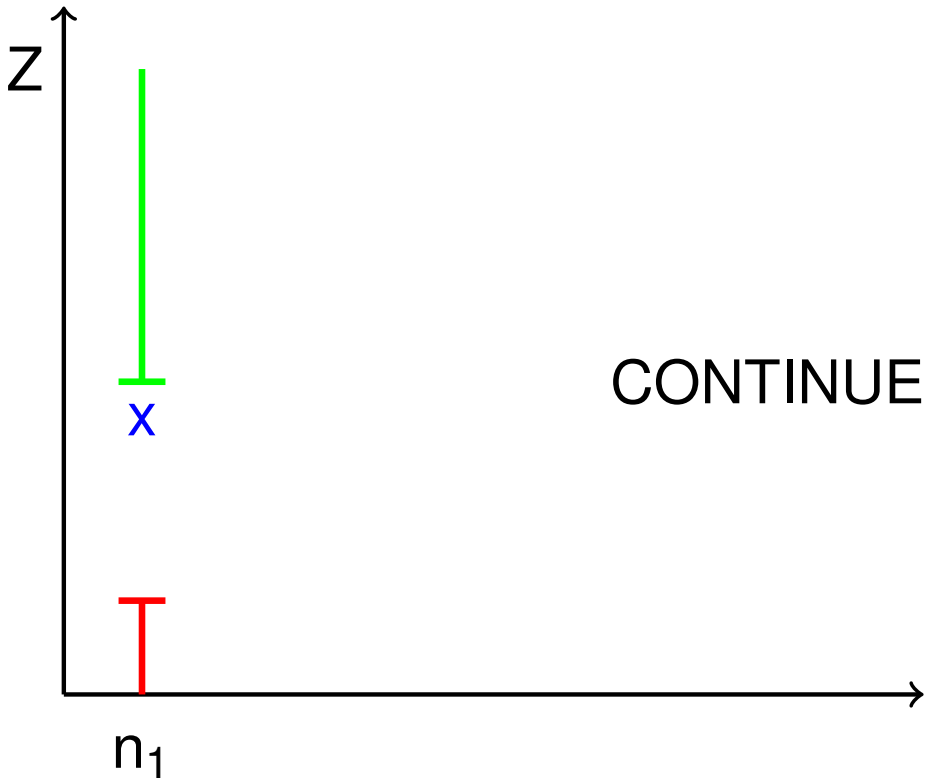
A multi-stage design



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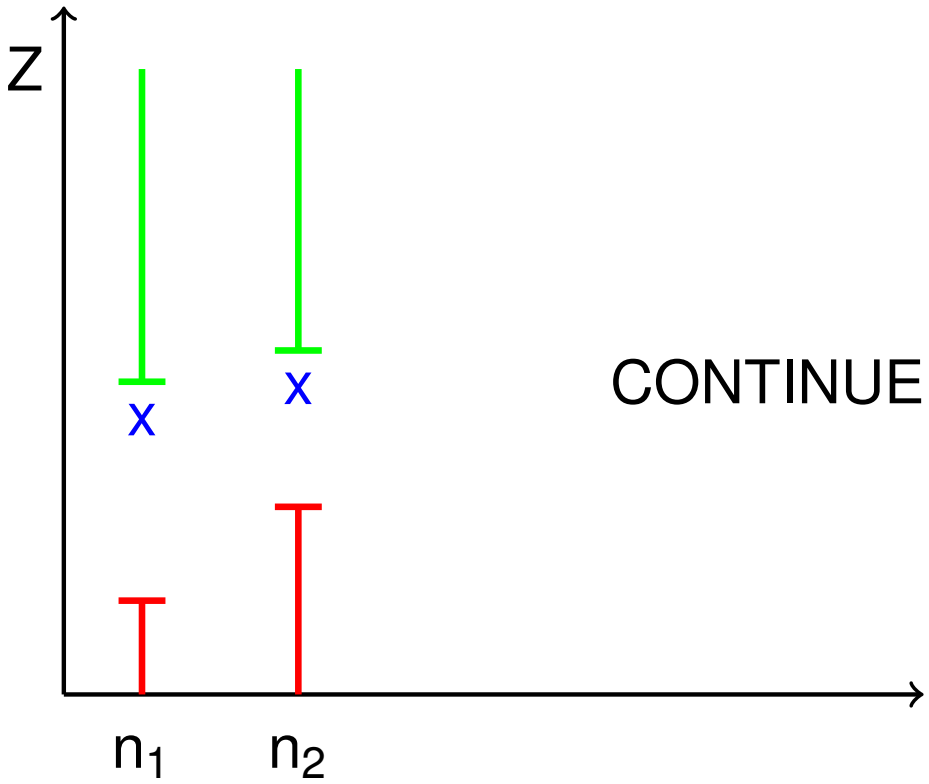

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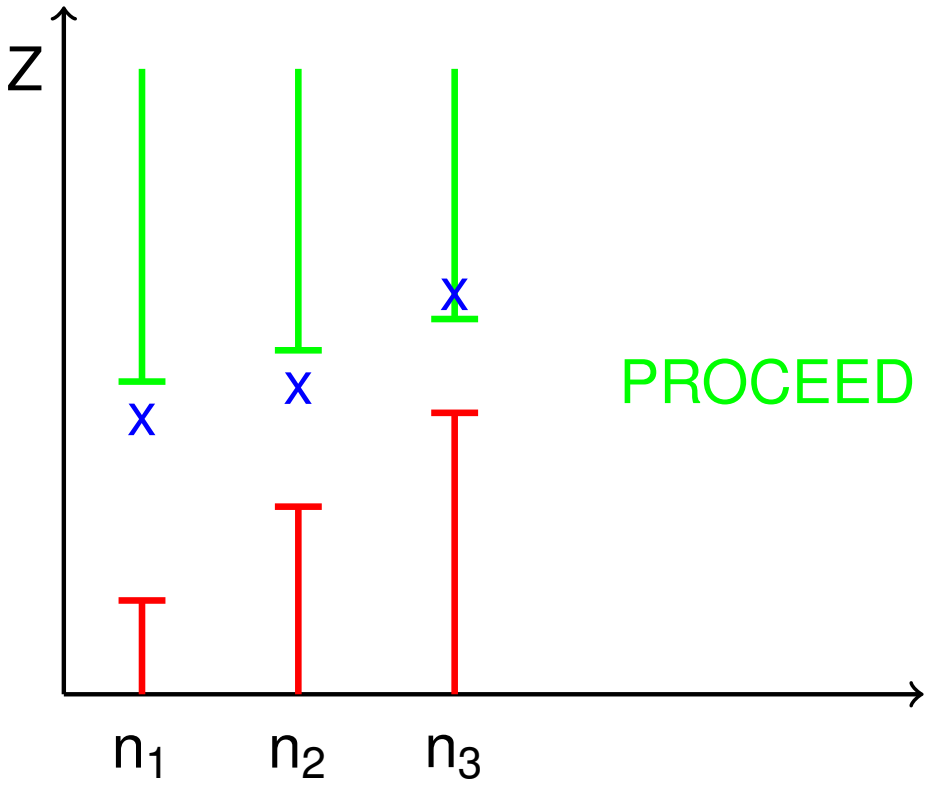

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Example 1: Sample size re-estimation

Problem:

sample size formulae depend on nuisance parameters e.g., σ^2

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- exact (with unblinding) or approximate (without unblinding) (Gould 1995)

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Example 1: Sample size re-estimation

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Idea:

estimate the nuisance parameter(s) at interim and recalculate sample size

Methods:

- for binary, Gaussian or survival outcomes
- exact (with unblinding) or approximate (without unblinding) (Gould 1995)
- negligible effect on type I error

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Sample size re-estimation

Example: DEVELOP-UK trial

- transplantation of reconditioned vs. standard donor lungs
- ex vivo lung perfusion (EVLP)
- phase III, multi-centre, unblinded, non-randomised, non-inferiority observational study
- primary endpoint: 12 months survival
- uncertainty in design parameters (only 50 transplants worldwide)

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Example 1: Sample size re-estimation
DEVELOP-UK trial

- 408 patients randomised to EVLP and standard
- 3:1 in favour of standard to ensure all available lungs are used
- interim analyses after 1/3 and 2/3 of total sample size
  - first: early stopping
  - second: early stopping, sample size re-assessment
- significance levels: 0.005 (first), 0.014 (second), 0.045 (final)

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Example 2: Phase I cancer trials

Dilemma:

low doses inefficient $\longleftrightarrow$ high doses toxic

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low doses inefficient $\longleftrightarrow$ high doses toxic

Goal:

find a **maximum tolerated dose** (MTD)

where a prespecified proportion p_0 of patients

experience **dose-limiting toxicities** (DLTs)

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Example 2: Phase I cancer trials

Designs:

Example 2: Phase I cancer trials

Designs:

- 3 + 3 design (Carter 1973)
- . . . and variations (A + B, rolling 6, . . .)
- other 1- or 2-stage up-and-down designs
- accelerated titration design (Simon et al. 1999)
- continual reassessment method (O'Quigley et al. 1990)

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Example 2: Phase I cancer trials

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} rule-based

- continual reassessment method (O'Quigley et al. 1990) — model-based

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Dose-finding / Phase I

Do NOT use rule based designs

Example 2: Phase I cancer trials

Continual reassessment method (CRM):

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- Bayesian adaptive design

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Example 2: Phase I cancer trials

Continual reassessment method (CRM):

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- model-based
- synthesizes prior belief about MTD and accumulating data

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Example 2: Phase I cancer trials

Continual reassessment method (CRM):

- Bayesian adaptive design
- model-based
- synthesizes prior belief about MTD and accumulating data
- uses information from **all** previous patients (“memory")

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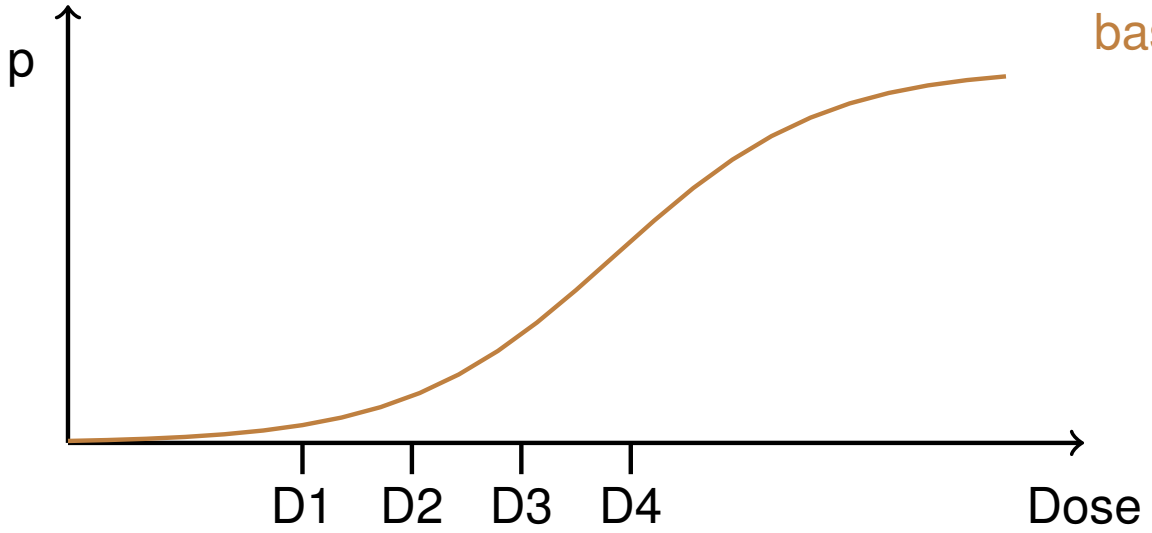
Example 2: Phase I cancer trials

A CRM design:



based on prior belief

p: proportion of DLTs

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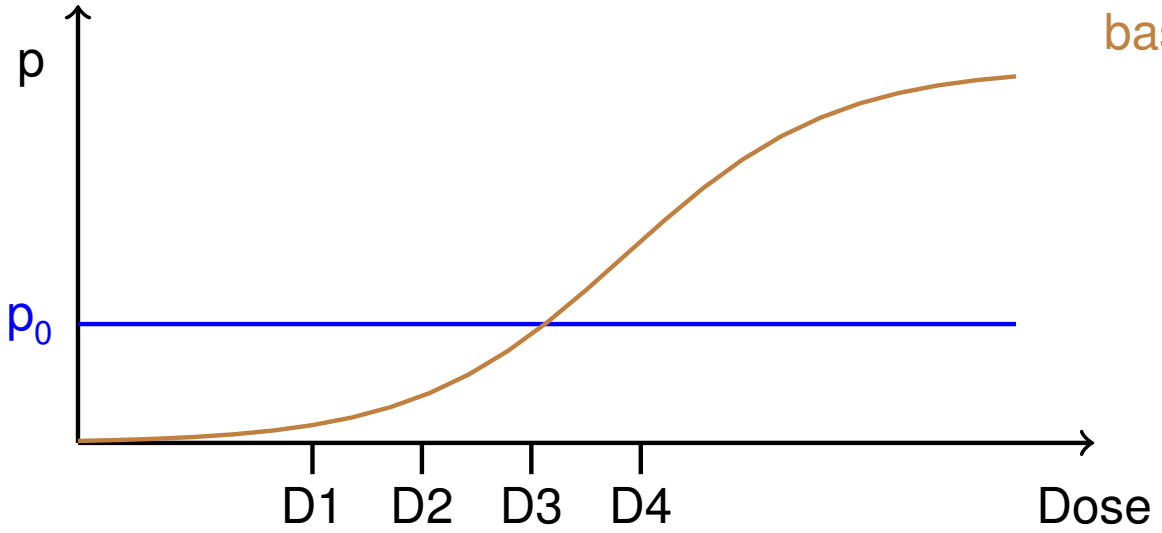

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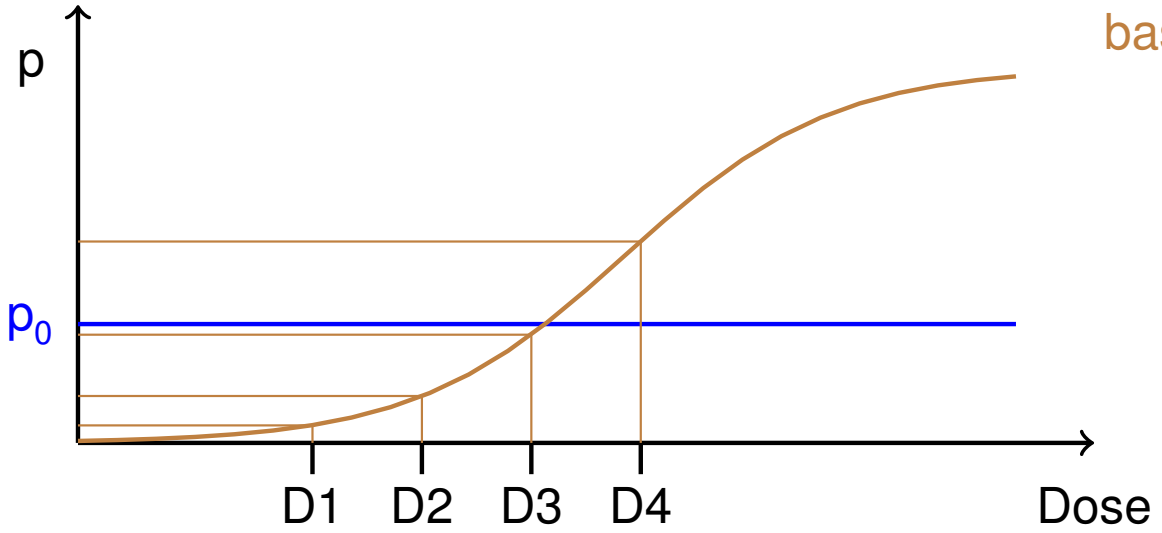

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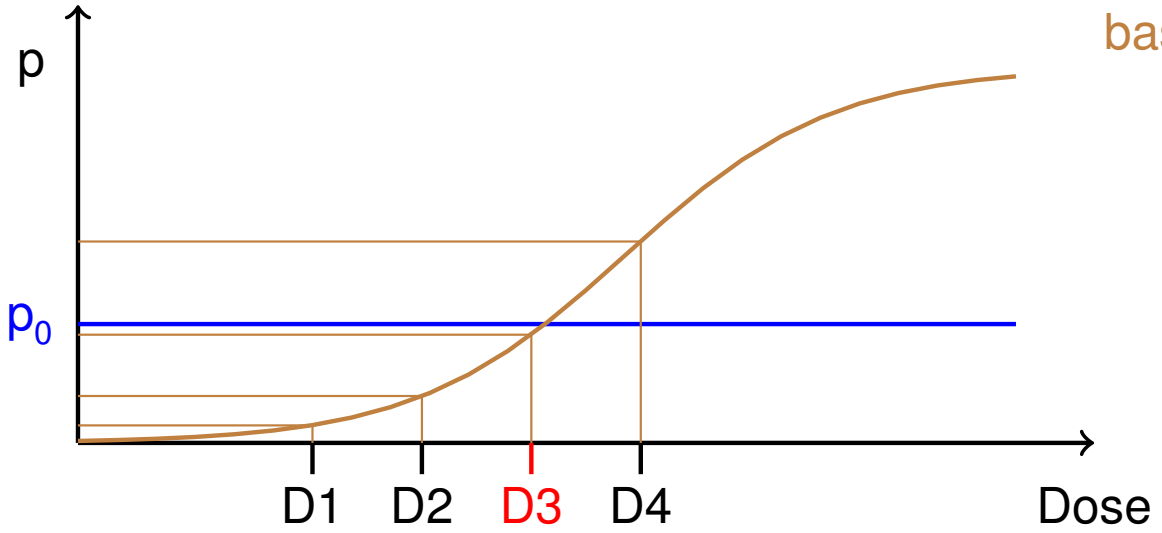

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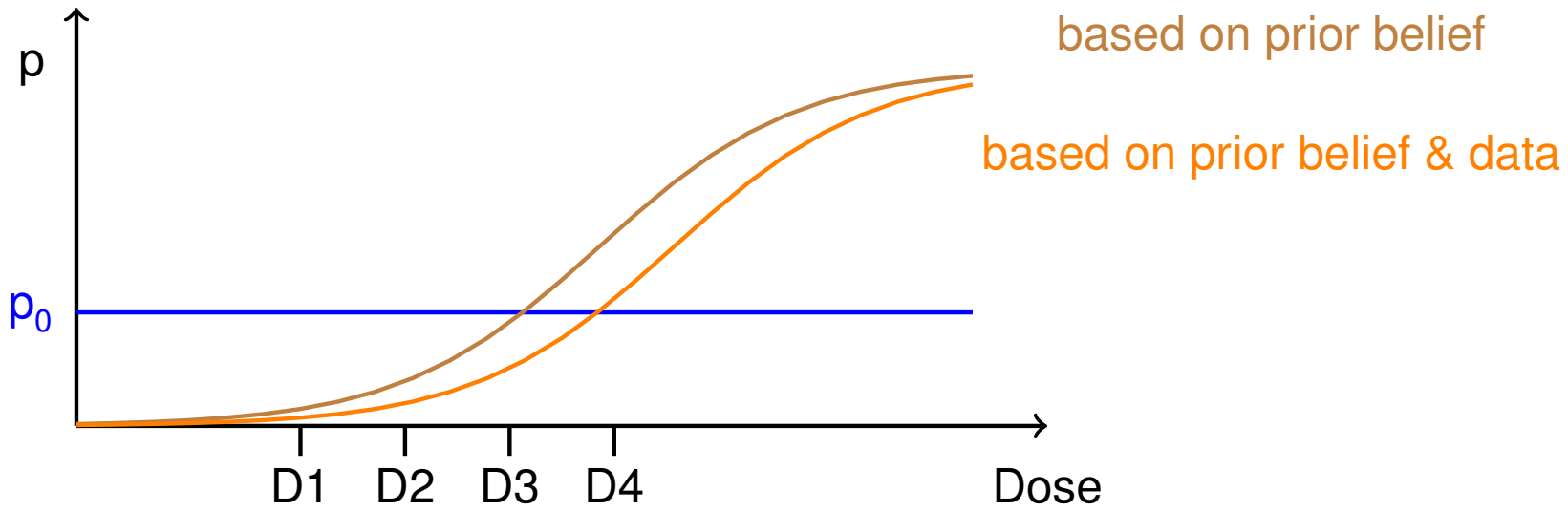

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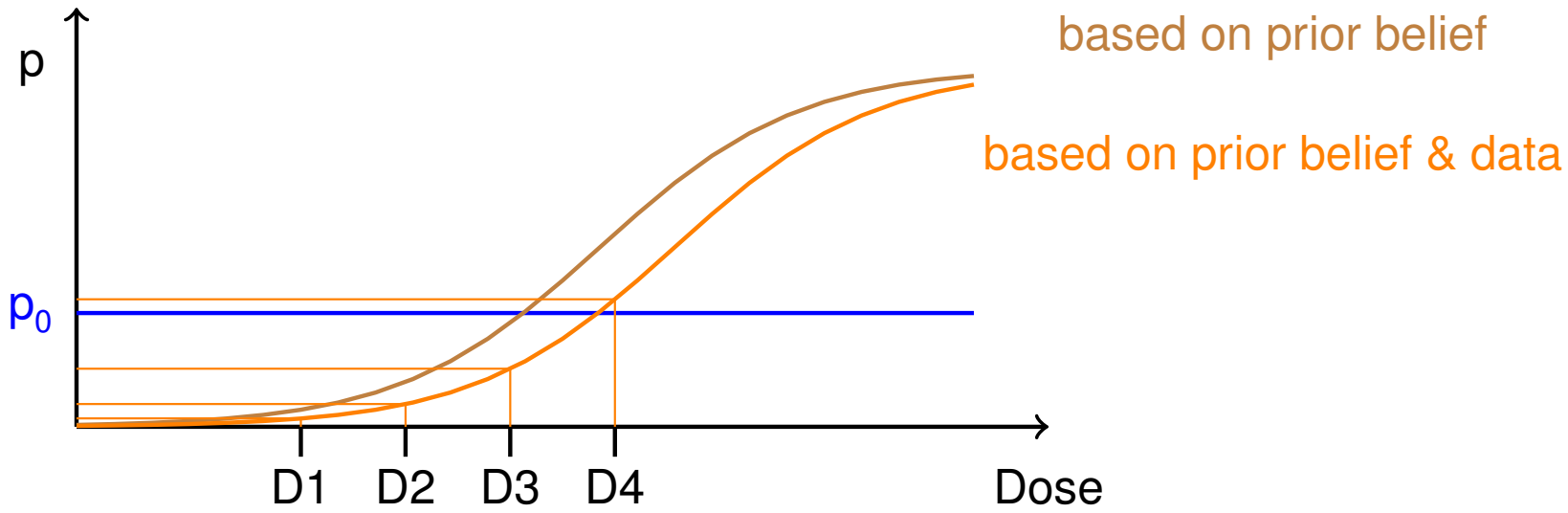

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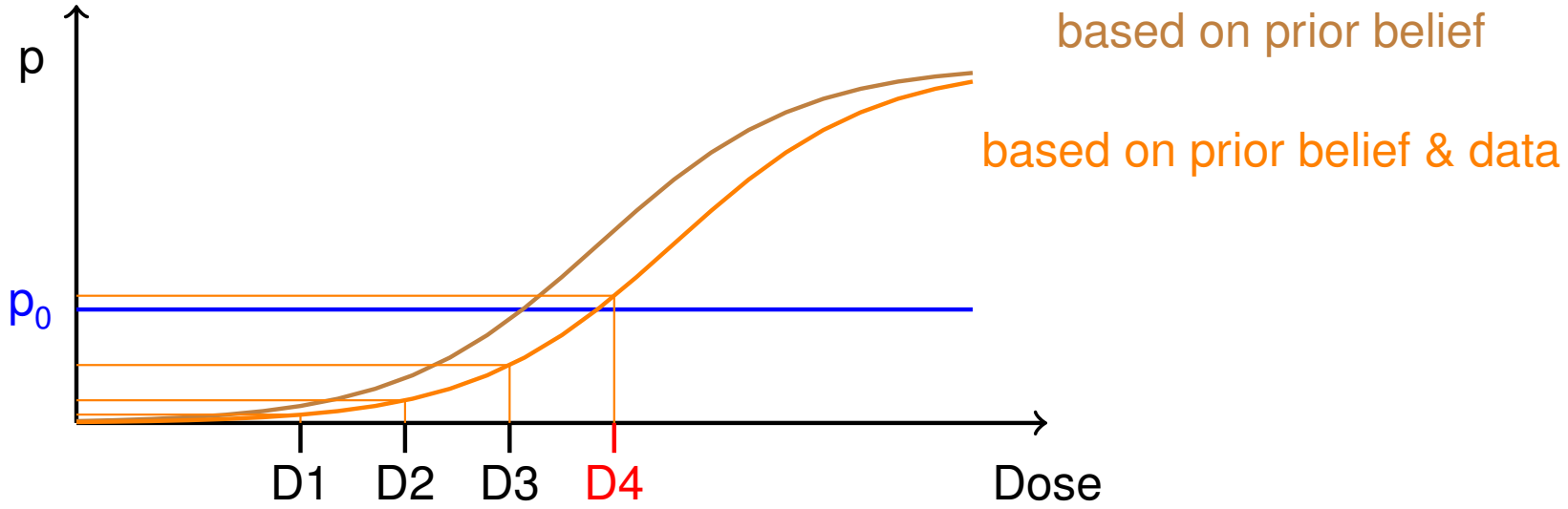

p: proportion of DLTs

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Example 2: Phase I cancer trials

CRM vs. 3 + 3:

- more likely to identify the correct dose
- more patients receive doses near MTD
- fewer overdoses
- clearly defined MTD
- MTD estimated with a measure of precision
- efficient use of all data
- flexible choice of toxicity levels
- easily extendable

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Example 2: Phase I cancer trials

Seamless phase I/II designs:

- phase I study “with a phase II flavour" (O’Quigley et al. 2001)

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- model toxicity and efficacy together
- identify the most successful dose (MSD) rather than MTD
- efficient (patient population of interest in phase I)
- various methods using different models and stopping rules:
  - efficacy-toxicity trade-off (Thall & Russell 1998, Thall & Cook 2004)

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- phase I study “with a phase II flavour" (O’Quigley et al. 2001)
- model toxicity and efficacy together
- identify the most successful dose (MSD) rather than MTD
- efficient (patient population of interest in phase I)
- various methods using different models and stopping rules:
  - efficacy-toxicity trade-off (Thall & Russell 1998, Thall & Cook 2004)
  - CRM-like (O’Quigley et al. 2001, Zohar & O’Quigley 2006)

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  - decision procedure for continuous response (Zhou et al. 2006)

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Example 3: Multi-arm multi-stage trials (MAMS)

TAILoR trial (Pushpakom et al. 2015)

- Phase II study to evaluate treatment for side effect of HIV tri-regimen treatment (TAILoR)
- Superiority trial
- Several possible doses
- Normal distributed endpoint

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Example 3: Multi-arm multi-stage trials (MAMS)

Design (Magirr et al, 2012)

- 3 active arms compared to control
- Equal randomization between actives and control
- one interim analysis
  - Stop for superiortiy
  - Stop if no active arm appears promising
  - Drop any active arms that are not sufficiently promising
- In the trial we underestimated drop-out and could adjust at interim

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General considerations

- New methods either get results faster or are more accurate
- Tend to take more time to develop upfront
  - How can this cost be covered?
- Are the ideas sensible to implement?
  - Is an interim analysis feasible?
  - Can Bayesian methods be updated online?