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Faculty of Medicine, Dentistry and Health Sciences

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Simulating an adaptive trial

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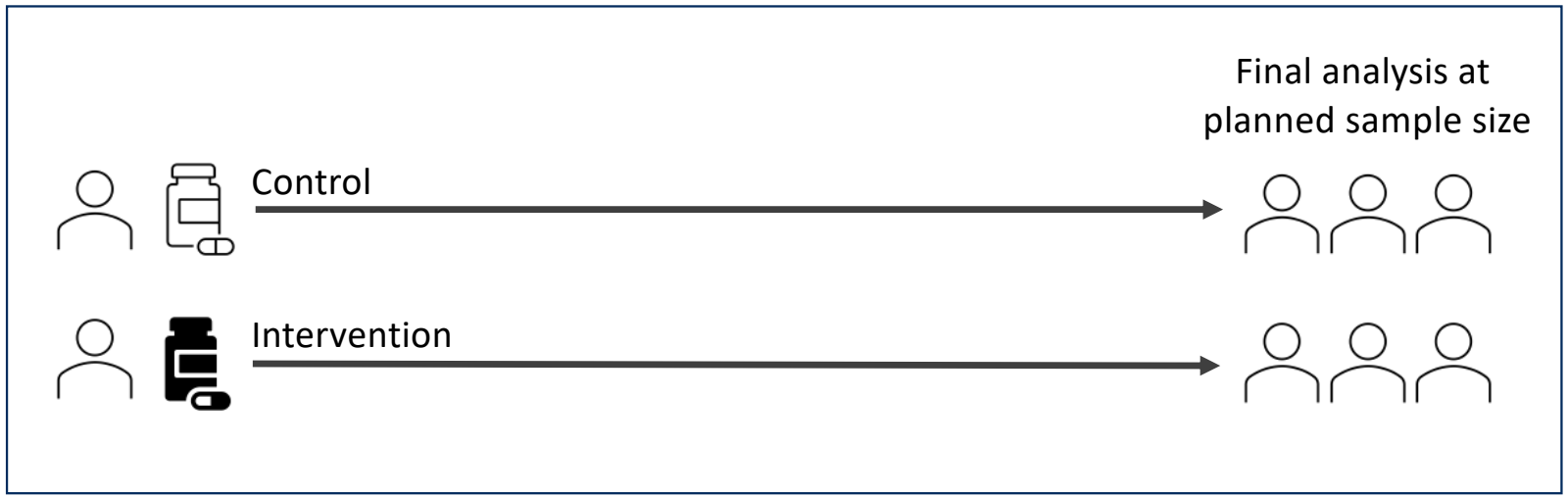
What you will learn about today

- Adaptive trial
- Operating characteristics
- Statistical simulation
- Simulating a fixed trial
- Elements of adaptive trial simulation
- Benefits of simulation

Aim is general understanding!

Uncertainties not resolved until final analysis

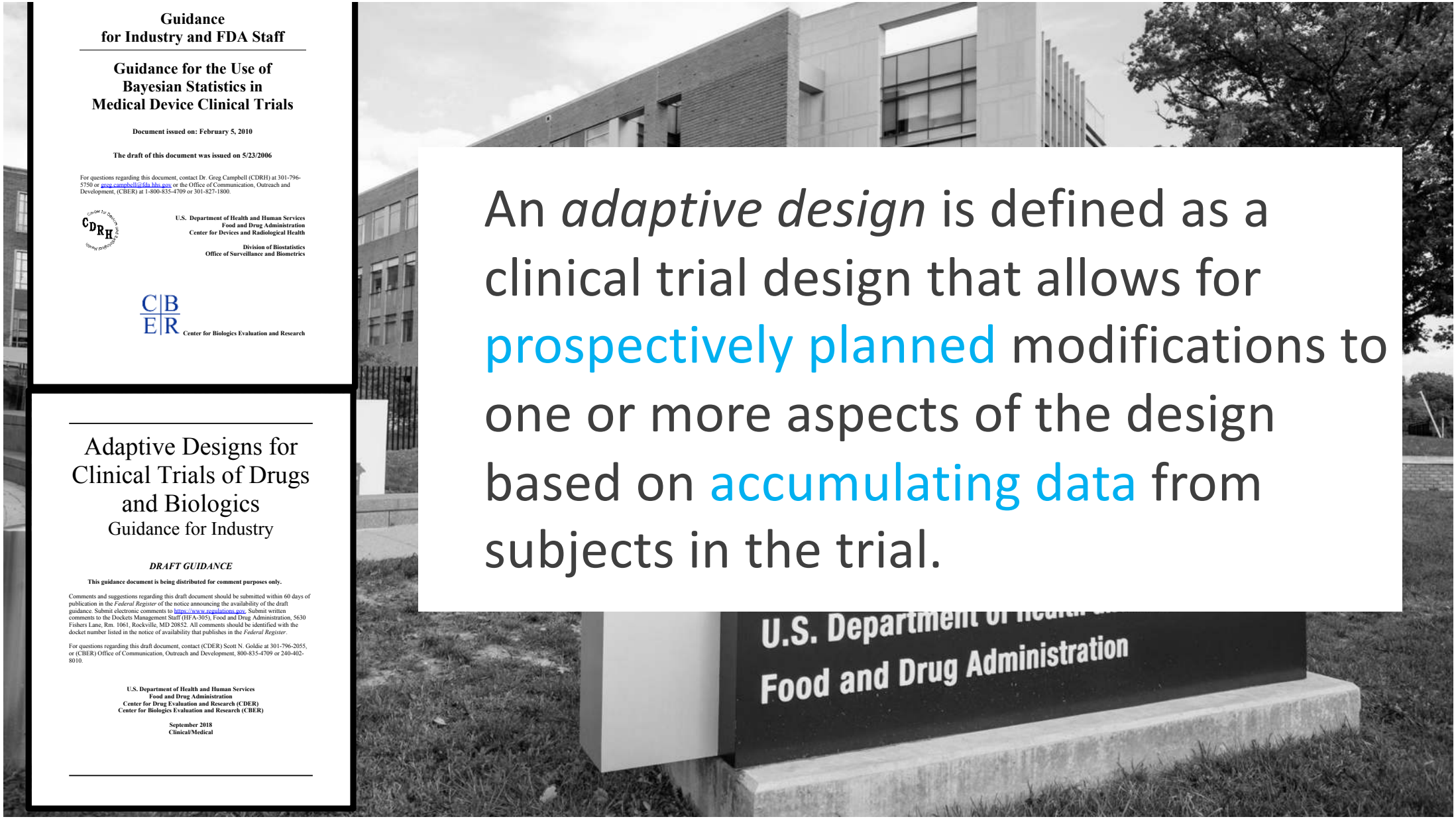


Reducing initial uncertainty can lead to more efficient trials

A priori uncertainty in trial design

- Interventions to include
- Dosage, duration, timing
- Population of interest
- Recruitment rates
- Effect sizes
- Samples needed for high power (true positives) and low type I error (false positives)

Null hypothesis	**True**	**False**
Rejected	Type I error (False positive)	Correct (True positive) (a.k.a *power*)
Not rejected	Correct (True negative)	Type II error (False negative)


Guidance
for Industry and FDA Staff
Guidance for the Use of
Bayesian Statistics in
Medical Device Clinical Trials
Document issued on: February 5, 2010
The draft of this document was issued on 5/23/2006
For questions regarding this document, contact Dr. Greg Campbell (CDRH) at 301-796-5750 or greg.campbell@fda.hhs.gov or the Office of Communication, Outreach and Development, (CBER) at 1-800-835-4709 or 301-827-1800.
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Division of Biostatistics
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C|B
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Center for Biologics Evaluation and Research
Adaptive Designs for
Clinical Trials of Drugs
and Biologics
Guidance for Industry
DRAFT GUIDANCE
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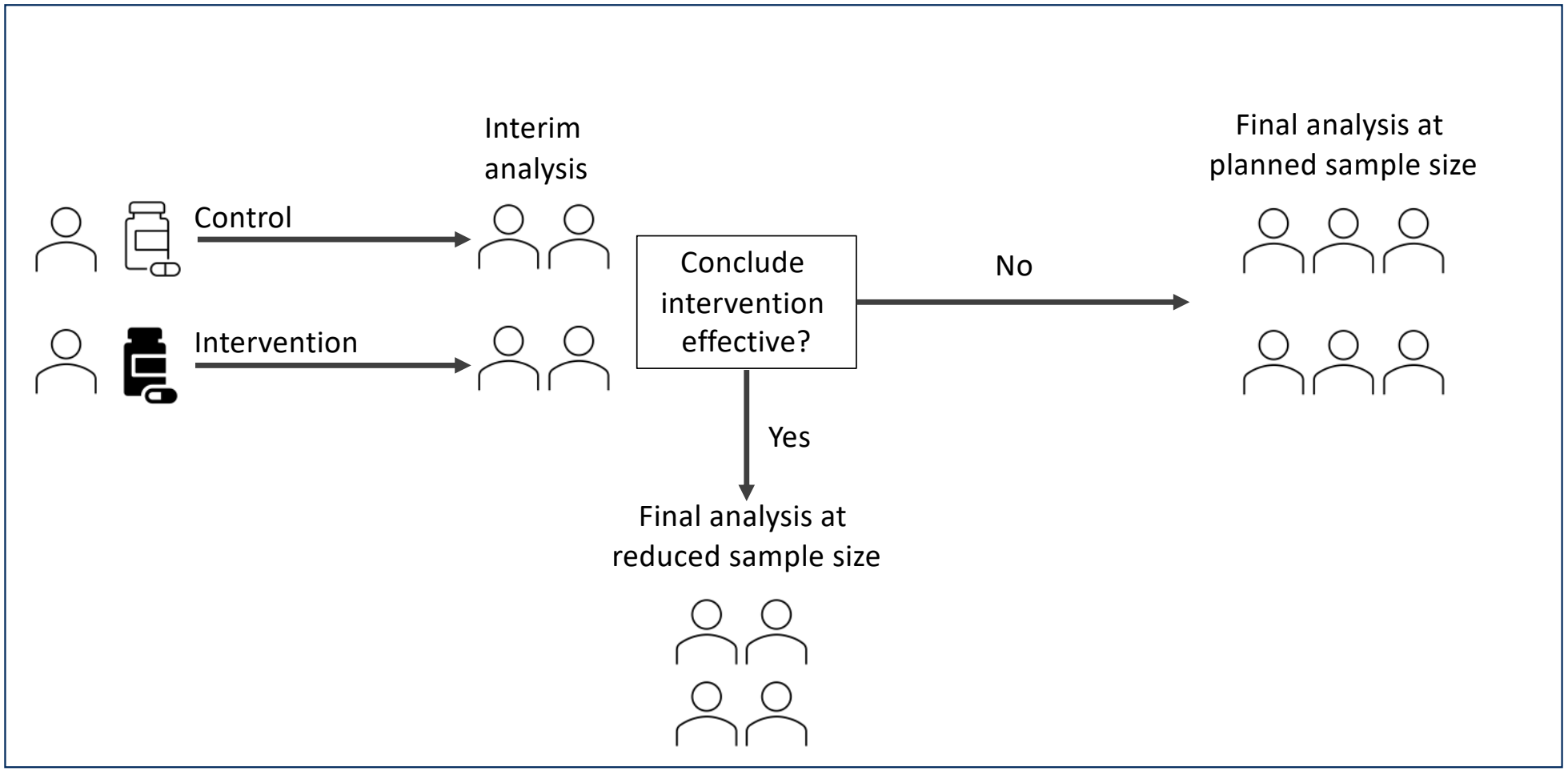
For questions regarding this draft document, contact (CDER) Scott N. Goldie at 301-796-2055, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
September 2018
Clinical/Medical
An adaptive design is defined as a clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial.
U.S. Department of
Food and Drug Administration

Basic idea (a.k.a group sequential)



Why use an adaptive design

- Fewer patients randomised to inferior treatment
  - Less harm
- Learn quickly about treatment efficacy
  - More population treated optimally
  - Useful in pandemics
- Better use of scarce resources
  - Quicker, smaller trials
  - More resources for other trials

Limitations of adaptive designs

- Long-term primary outcomes
- Missing important secondary information
- Operational complexity
- Additional cost/resources
- Methodological challenges
- Communication

Wason et al, BMC Medicine, 2019 17:152

Understanding trial designs

- Trials understood by operating characteristics
  - Power
  - Type I error
  - Sample size
- Equations exist for simple group sequential designs
- Many adaptive trials are much more complex
- No equations exist for complex adaptive trials
- Understanding complex adaptive trials requires stochastic simulation

Different kinds of simulation

Interactive simulation

Deterministic simulation

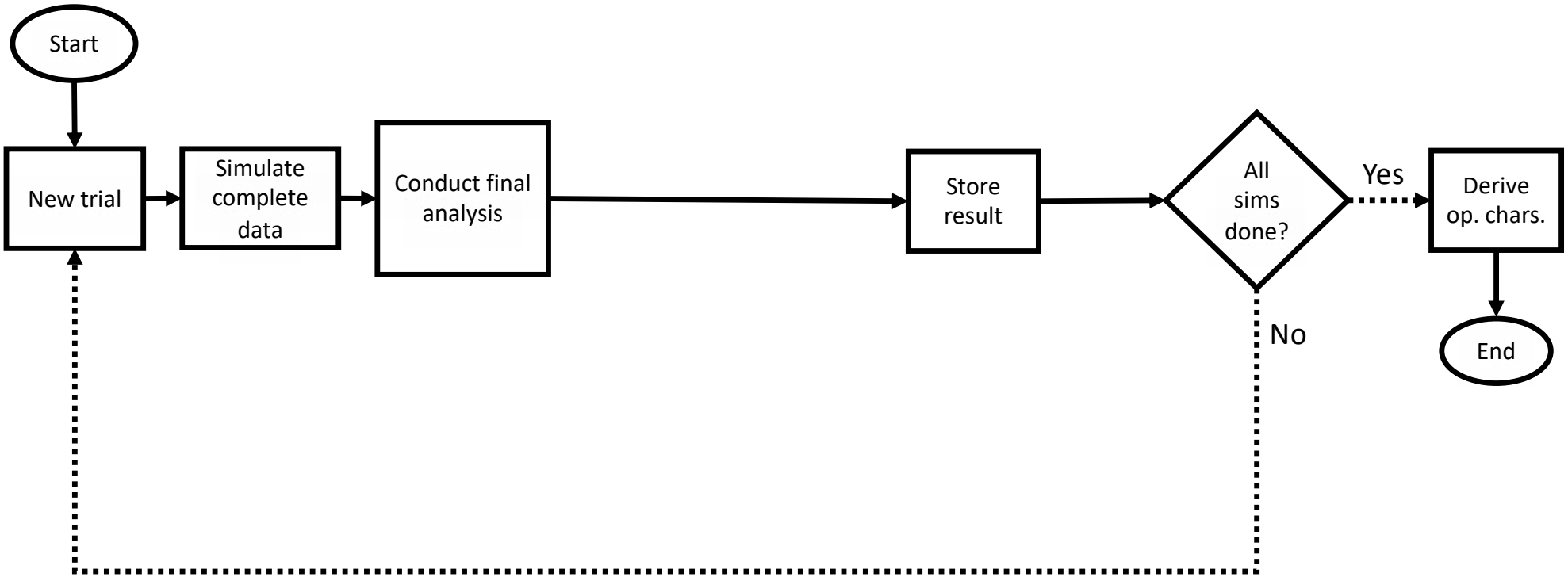
- Often 'prediction'-oriented
- What if?

Stochastic simulation

Stochastic simulation

- Many small artificial experiments to understand underlying process
- Useful to design and evaluate new statistical methods, particularly where mathematics is intractable
- Sampling data repeatedly, applying method, checking aggregate results
- Running artificial trial (with randomness), performing analysis, checking how many times the trial succeeded.

Basic simulation workflow



This workflow is specific to a single scenario!

Control

Patient no.	*1st simulation*
1	0

Intervention

Patient no.	*1st simulation*
1	0

Control

Patient no.	*1st simulation*
1	0
2	0

Intervention

Patient no.	*1st simulation*
1	0
2	0

Control

Patient no.	*1st simulation*
1	0
2	0
3	1
…	…

Intervention

Patient no.	*1st simulation*
1	0
2	0
3	0
…	…

Control

Patient no.	*1st simulation*
1	0
2	0
3	1
…	…
$N/2$	0

Intervention

Patient no.	*1st simulation*
1	0
2	0
3	0
…	…
$N/2$	1

Control

Patient no.	*1st simulation*
1	0
2	0
3	1
…	…
$N/2$	0

Intervention

Patient no.	*1st simulation*
1	0
2	0
3	0
…	…
$N/2$	1

Control

Patient no.	1^{st} *simulation*	2^{nd} *simulation*
1	0	0
2	0	0
3	1	0
…	…	…
$N/2$	0	0

Intervention

Patient no.	1^{st} *simulation*	2^{nd} *simulation*
1	0	0
2	0	1
3	0	1
…	…	…
$N/2$	1	0

Control

Patient no.	1^{st} *simulation*	2^{nd} *simulation*	3^{rd} *simulation*
1	0	0	0
2	0	0	1
3	1	0	0
…	…	…	…
$N/2$	0	0	1

Intervention

Patient no.	1^{st} *simulation*	2^{nd} *simulation*	3^{rd} *simulation*
1	0	0	0
2	0	1	0
3	0	1	0
…	…	…	…
$N/2$	1	0	0

Control

Patient no.	1^{st} *simulation*	2^{nd} *simulation*	3^{rd} *simulation*	…
1	0	0	0	…
2	0	0	1	…
3	1	0	0	…
…	…	…	…	…
$N/2$	0	0	1	…

Intervention

Patient no.	1^{st} *simulation*	2^{nd} *simulation*	3^{rd} *simulation*	…
1	0	0	0	…
2	0	1	0	…
3	0	1	0	…
…	…	…	…	…
$N/2$	1	0	0	…

Control

Patient no.	1^{st} *simulation*	2^{nd} *simulation*	3^{rd} *simulation*	…	K^{th} *simulation*
1	0	0	0	…	0
2	0	0	1	…	0
3	1	0	0	…	0
…	…	…	…	…	…
$N/2$	0	0	1	…	0

Intervention

Patient no.	1^{st} *simulation*	2^{nd} *simulation*	3^{rd} *simulation*	…	K^{th} *simulation*
1	0	0	0	…	1
2	0	1	0	…	0
3	0	1	0	…	0
…	…	…	…	…	…
$N/2$	1	0	0	…	0

Control

Patient no.	1^{st} *simulation*	2^{nd} *simulation*	3^{rd} *simulation*	…	K^{th} *simulation*
1	0	0	0	…	0
2	0	0	1	…	0
3	1	0	0	…	0
…	…	…	…	…	…
$N/2$	0	0	1	…	0

Statistical test

Intervention

Patient no.	1^{st} *simulation*	2^{nd} *simulation*	3^{rd} *simulation*	…	K^{th} *simulation*
1	0	0	0	…	1
2	0	1	0	…	0
3	0	1	0	…	0
…	…	…	…	…	…
$N/2$	1	0	0	…	0

Control

Patient no.	1^{st} *simulation*	2^{nd} *simulation*	3^{rd} *simulation*	…	K^{th} *simulation*
1	0	0	0	…	0
2	0	0	1	…	0
3	1	0	0	…	0
…	…	…	…	…	…
$N/2$	0	0	1	…	0

Intervention

Patient no.	1^{st} *simulation*	2^{nd} *simulation*	3^{rd} *simulation*	…	K^{th} *simulation*
1	0	0	0	…	1
2	0	1	0	…	0
3	0	1	0	…	0
…	…	…	…	…	…
$N/2$	1	0	0	…	0

Statistical test

Sim. No.	Reject H_0?
1	
2	
3	
…	
K	

Control

Patient no.	1^{st} *simulation*	2^{nd} *simulation*	3^{rd} *simulation*	...	K^{th} *simulation*
1	0	0	0	...	0
2	0	0	1	...	0
3	1	0	0	...	0
...	...	...	...	...	...
$N/2$	0	0	1	...	0

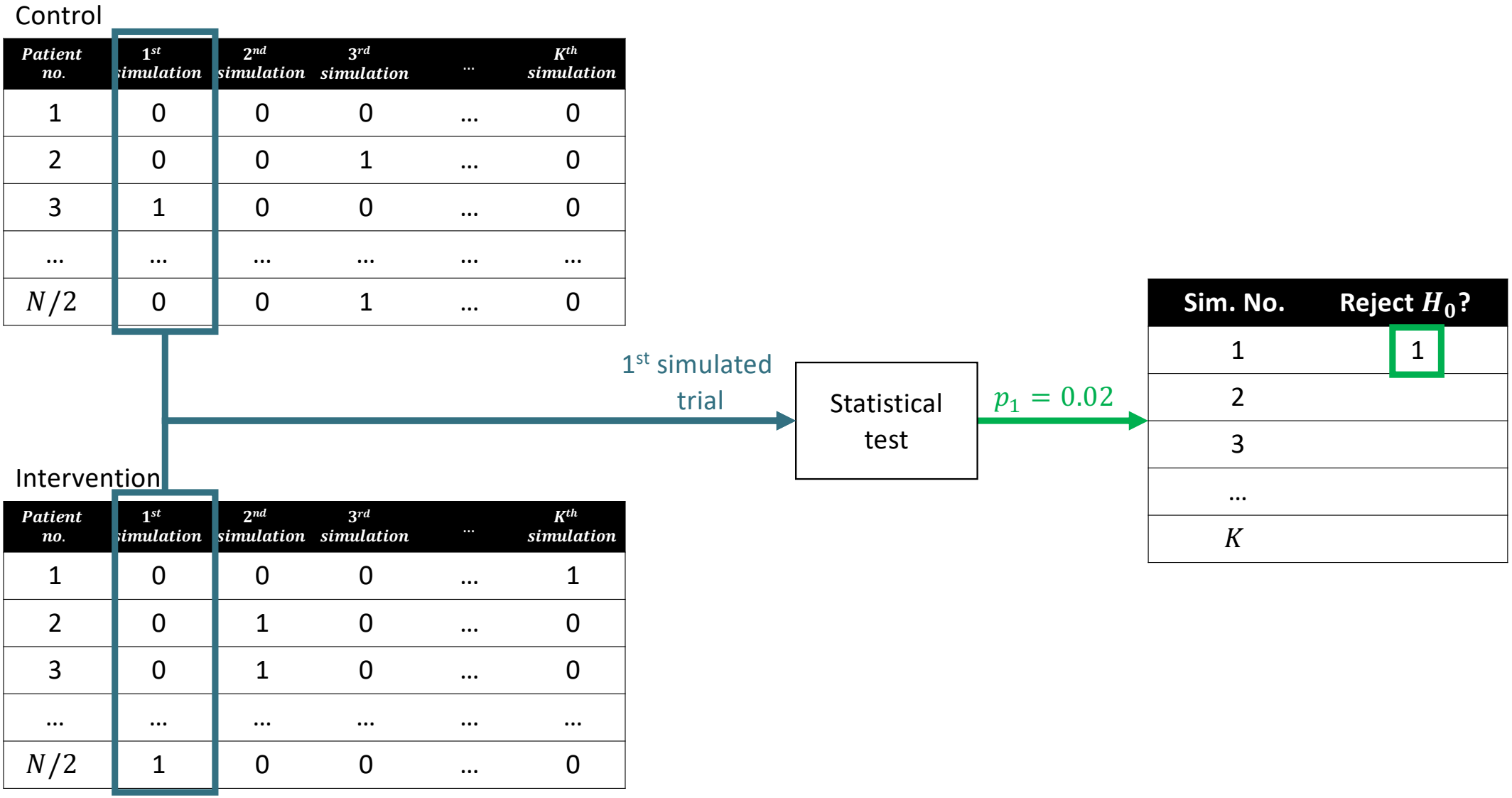
1^{st} simulated trial

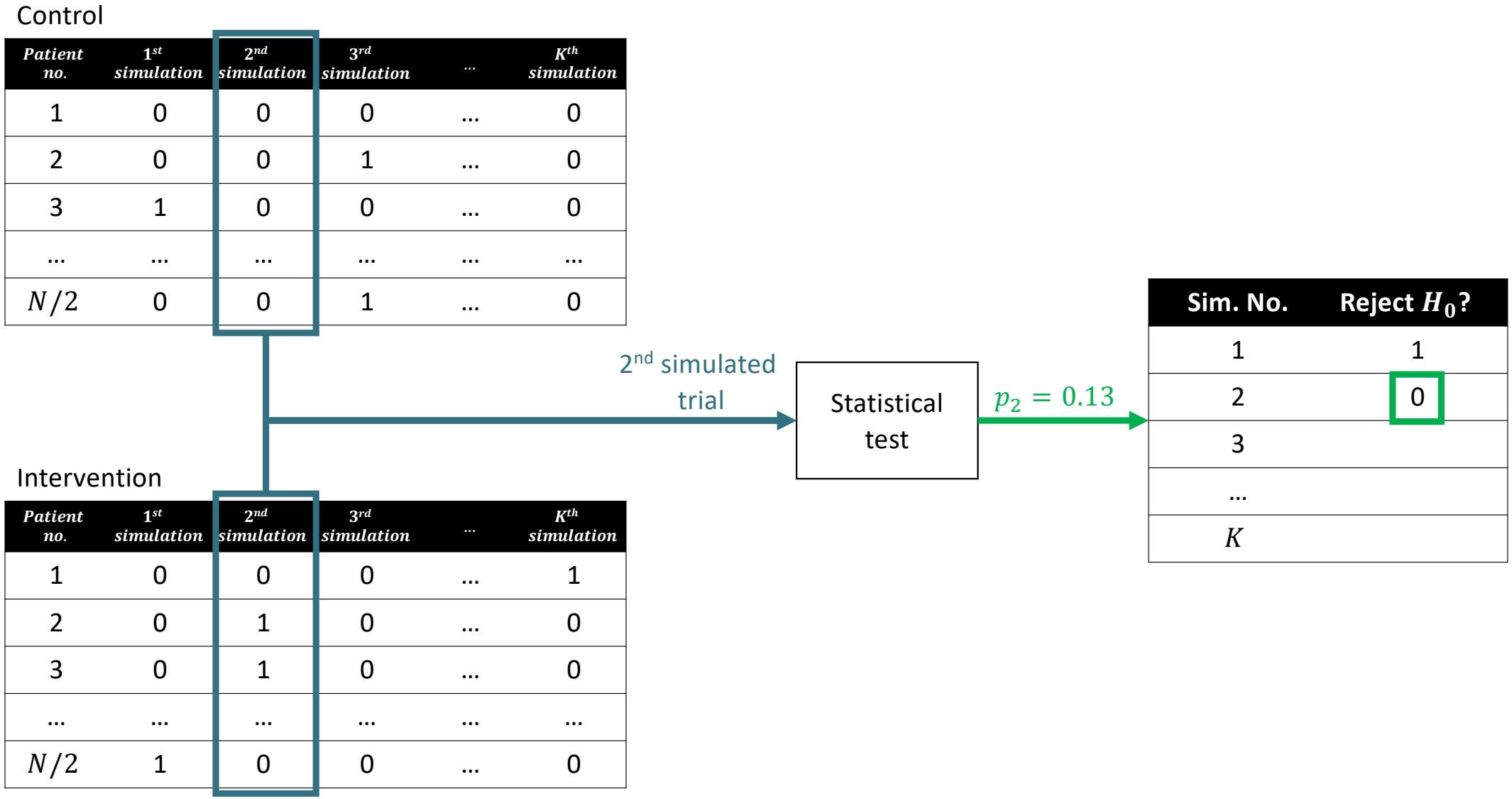
Statistical test

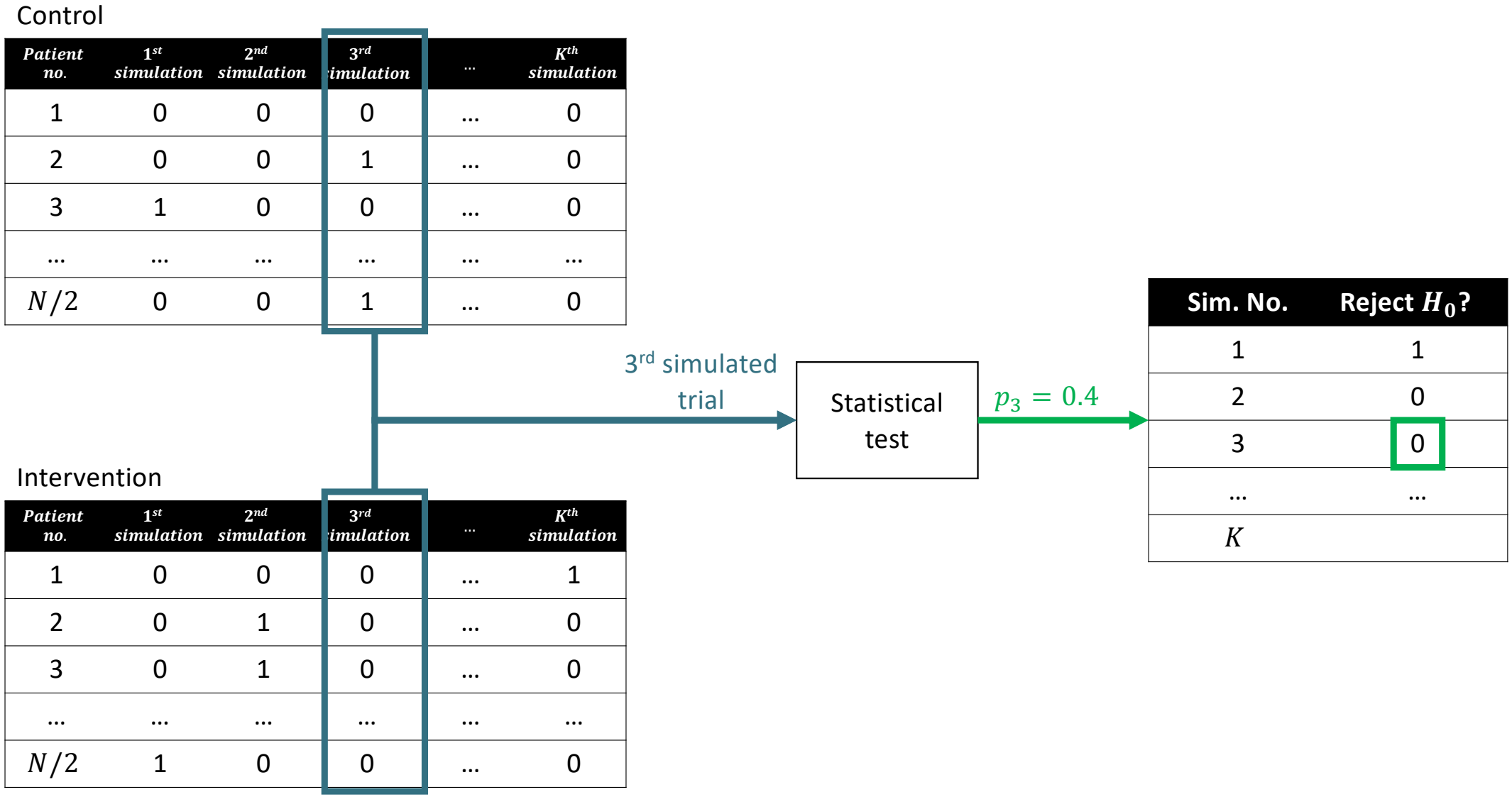
Intervention

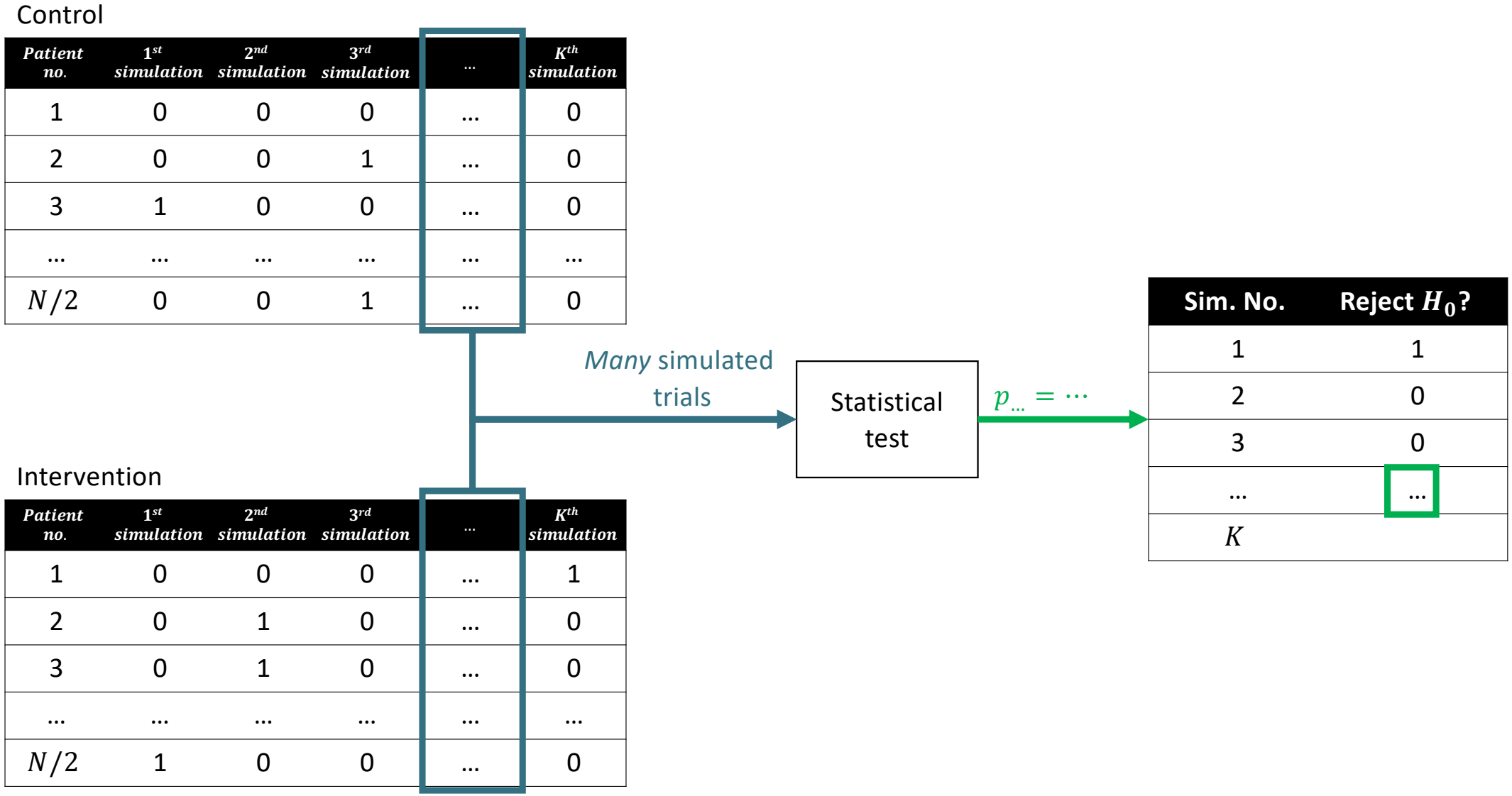
Patient no.	1^{st} *simulation*	2^{nd} *simulation*	3^{rd} *simulation*	...	K^{th} *simulation*
1	0	0	0	...	1
2	0	1	0	...	0
3	0	1	0	...	0
...	...	...	...	...	...
$N/2$	1	0	0	...	0

Sim. No.	Reject H_0?
1	1
2	
3	
...	
K	


Control
Patient no.
1st simulation
2nd simulation
3rd simulation
...
Kth simulation
1 0 0 0 ... 0
2 0 0 1 ... 0
3 1 0 0 ... 0
... ...
N/2 0 0 1 ... 0
1st simulated trial
Statistical test
$p_1 = 0.02$
Sim. No.
Reject H_0?
1 1
2
3
...
K
Intervention
Patient no.
1st simulation
2nd simulation
3rd simulation
...
Kth simulation
1 0 0 0 ... 1
2 0 1 0 ... 0
3 0 1 0 ... 0
... ...
N/2 1 0 0 ... 0


Control
Patient no.
1st simulation
2nd simulation
3rd simulation
...
Kth simulation
1 0 0 0 ... 0
2 0 0 1 ... 0
3 1 0 0 ... 0
... ...
N/2 0 0 1 ... 0
2nd simulated trial
Statistical test
p2 = 0.13
Sim. No.
Reject H0?
1 1
2 0
3
...
K
Intervention
Patient no.
1st simulation
2nd simulation
3rd simulation
...
Kth simulation
1 0 0 0 ... 1
2 0 1 0 ... 0
3 0 1 0 ... 0
... ...
N/2 1 0 0 ... 0


Control
Patient no.
1st simulation
2nd simulation
3rd simulation
...
Kth simulation
1 0 0 0 ... 0
2 0 0 1 ... 0
3 1 0 0 ... 0
... ...
N/2 0 0 1 ... 0
3rd simulated trial
Statistical test
p3 = 0.4
Sim. No.
Reject H0?
1 1
2 0
3 0
... ...
K
Intervention
Patient no.
1st simulation
2nd simulation
3rd simulation
...
Kth simulation
1 0 0 0 ... 1
2 0 1 0 ... 0
3 0 1 0 ... 0
... ...
N/2 1 0 0 ... 0


Control
Patient no.
1st simulation
2nd simulation
3rd simulation
...
Kth simulation
1 0 0 0 ... 0
2 0 0 1 ... 0
3 1 0 0 ... 0
... ...
N/2 0 0 1 ... 0
Many simulated trials
Statistical test
p... = ⋯
Sim. No.
Reject H0?
1 1
2 0
3 0
... ...
K
Intervention
Patient no.
1st simulation
2nd simulation
3rd simulation
...
Kth simulation
1 0 0 0 ... 1
2 0 1 0 ... 0
3 0 1 0 ... 0
... ...
N/2 1 0 0 ... 0


Control
Patient no.
1st simulation
2nd simulation
3rd simulation
...
Kth simulation
1 0 0 0 ... 0
2 0 0 1 ... 0
3 1 0 0 ... 0
... ...
N/2 0 0 1 ... 0
Kth simulated trial
Statistical test
p_K = 0.31
Sim. No.
Reject H_0?
1 1
2 0
3 0
... ...
K 0
Intervention
Patient no.
1st simulation
2nd simulation
3rd simulation
...
Kth simulation
1 0 0 0 ... 1
2 0 1 0 ... 0
3 0 1 0 ... 0
... ...
N/2 1 0 0 ... 0

Control

Patient no.	*1st simulation*	*2nd simulation*	*3rd simulation*	...	*Kth simulation*
1	0	0	0	...	0
2	0	0	1	...	0
3	1	0	0	...	0
...	...	...	...	...	...
$N/2$	0	0	1	...	0

Intervention

Patient no.	*1st simulation*	*2nd simulation*	*3rd simulation*	...	*Kth simulation*
1	0	0	0	...	1
2	0	1	0	...	0
3	0	1	0	...	0
...	...	...	...	...	...
$N/2$	1	0	0	...	0

K^{th} simulated trial

Statistical test

$p_K = 0.4$

Sim. No.	Reject H_0?
1	1
2	0
3	0
...	...
K	0

Power = Proportion of K trials that reject H_0

Control

Patient no.	1^{st} *simulation*	2^{nd} *simulation*	3^{rd} *simulation*	…	K^{th} *simulation*
1	0	0	0	…	0
2	0	0	1	…	0
3	1	0	0	…	0
…	…	…	…	…	…
$N/2$	0	0	1	…	0

Intervention

Patient no.	1^{st} *simulation*	2^{nd} *simulation*	3^{rd} *simulation*	…	K^{th} *simulation*
1	0	0	0	…	1
2	0	1	0	…	0
3	0	1	0	…	0
…	…	…	…	…	…
$N/2$	1	0	0	…	0

K^{th} simulated trial

Statistical test

$p_K = 0.31$

Sim. No.	Reject H_0?
1	1
2	0
3	0
…	…
K	0

Power = Proportion of K trials that reject H_0

- For a given sample size N:
  - **IF H_0** is simulation 'truth' **THEN power ~ Type I error**
- Simulated power is *estimated*, better accuracy with larger K

Elements of *any* trial simulation

- **Clinical endpoint**
  - Binary, continuous, time-to-event, etc.
  - Estimand
  - Effect sizes
  - Number of effect size scenarios
    - Null, alternative, variations
- **Treatment randomisation**
  - Number of treatments
  - Randomisation ratios
  - Planned sample size (or required power)
- **Statistical methods**
  - Different methods for different designs
  - Threshold for making a conclusion
- **Simulation methods**
  - Number of simulations to be confident
    - Monte Carlo (simulation) error
  - Availability of computational resources
    - Personal computers
    - High-performance clusters

Elements of *adaptive* design simulations

- **Timing**
  - Recruitment rate (expected rate, ramp-ups)
  - Time to the clinical endpoint
- **Interim analyses**
  - Number
  - Timing (calendar time, recruitment targets, or observed endpoints; equally spaced?)
- **Threshold for statistical tests at each interim**
  - Fixed, ramp-up, ramp-down
- **Type of adaptations**
  - Early stopping
  - Response adaptive randomisation
  - Enrichment

Timing

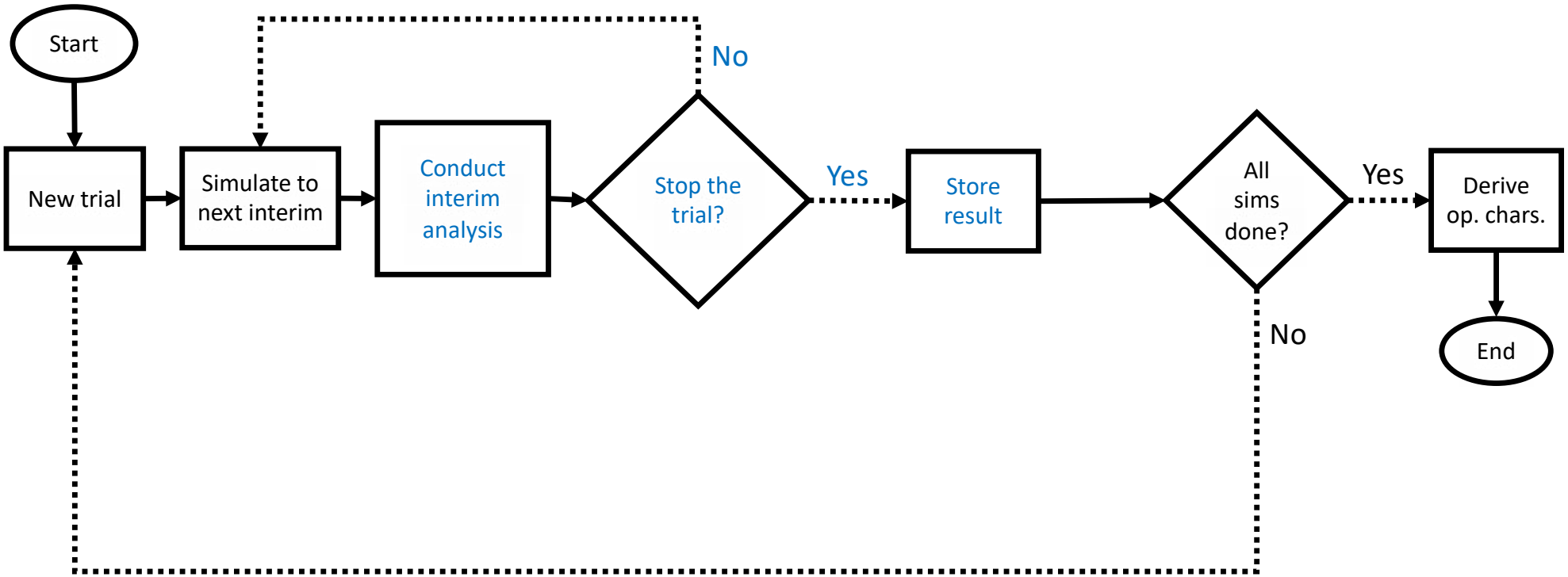
- **Simulate number of patients entering the trial**
  - Typically a Poisson distribution (e.g. expected rate per day)
  - Can often start with/get away with a fixed number
- **Simulate time to clinical endpoint**
  - Use appropriate distributions (e.g. hazards and hazard ratios)
  - Not needed for fixed time points, just add time to patient recruitment date
- **Rapid recruitment and time to endpoint**
  - Trial can recruit completely before first interim!

Interim analyses and thresholds

- **Multiple 'looks' at the data inflate type I error**
  - Common to both frequentist and Bayesian designs
  - More 'looks' → more power, more type I error
- **Decision making thresholds (e.g. *p*-values)**
  - Make thresholds more conservative at each interim (e.g. $p < 0.01$)

    → less power, less type I error
- **Often interim timing dictated by what is feasible**
  - Focus on tweaking decision making thresholds
  - First interim may need to be quite late to control type I error

Extending to a basic adaptive trial



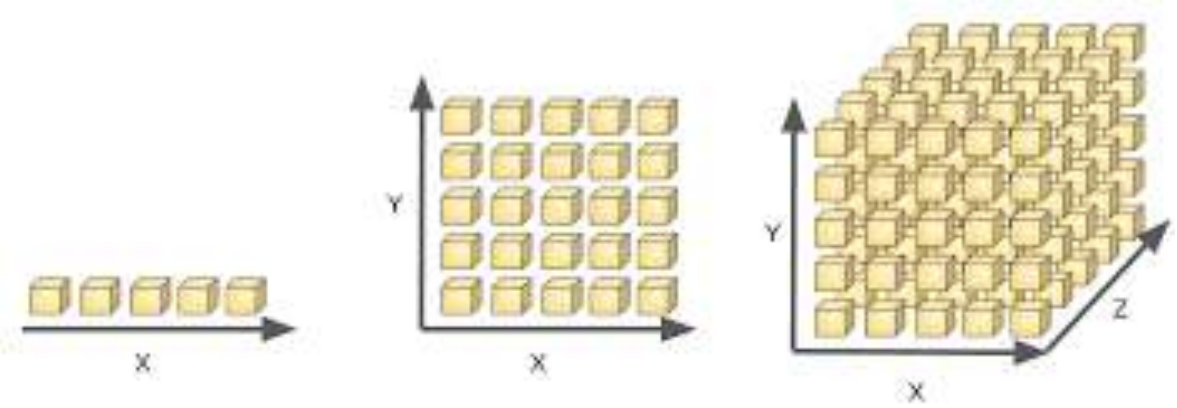
This workflow is specific to a single scenario!

Benefits of simulation

- Can easily incorporate other sources of uncertainty
  - Recruitment uncertainty, time to endpoint uncertainty
- A touchstone to gauge what is important to investigators
- Encourages dialogue
- A way for investigators ‘practice’ the trial
- Complex as computationally (and pragmatically) feasible

Computational considerations

- ‘Curse of dimensionality’
- Post-process where possible
  - Simulate a complete trial
  - Look at different interims
- Parallel processing (high performance computing)



Things to consider

- Start small, with single trials, scale up
- Simulation model will be simpler than real-world model
- Adopt software design best practices
  - Modularity
  - Don’t repeat yourself
  - Version control
- Maintain constant dialogue with investigator
- Grant writing
- Off-the-shelf options

What we learnt

- Adaptive trials: definitions, pros, cons
- Operating characteristics: power, type I error, sample size
- Statistical simulation: why its needed
- Simulating a fixed trial: workflow
- Elements of adaptive trial simulation: interim analyses, thresholds, workflow
- Benefits of simulation: dialogue, practice trials
- Computational issues: curse of dimensionality

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Thank you

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