Cytel
Shaping the Future of Drug Development

Introduction to Population Enrichment Trial Designs

Thomas Burnett

Mathematics & Statistics | Lancaster University

Medical and Pharmaceutical Statistics Research Unit

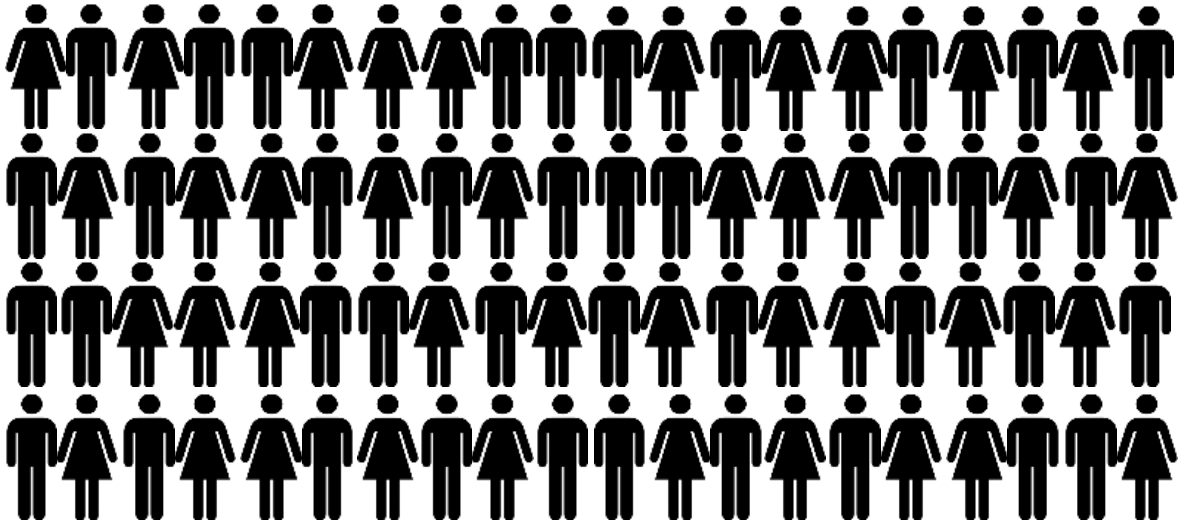
Contents

- Introduction to Population Enrichment
- Hypothesis Testing
- Decision Making
- Example: TAPPAS
- EAST

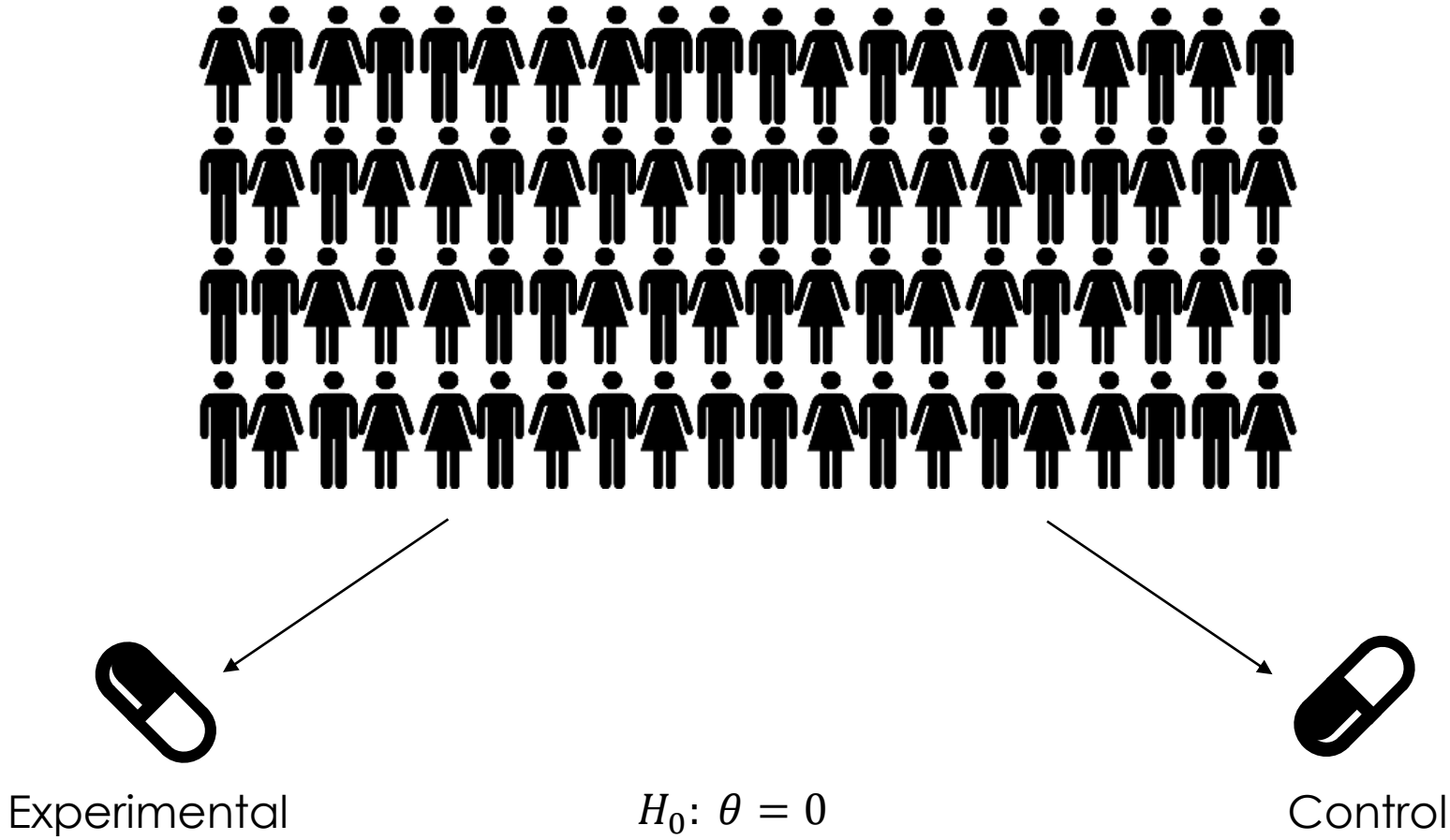
Cytel

Introduction to Population Enrichment

Target Population



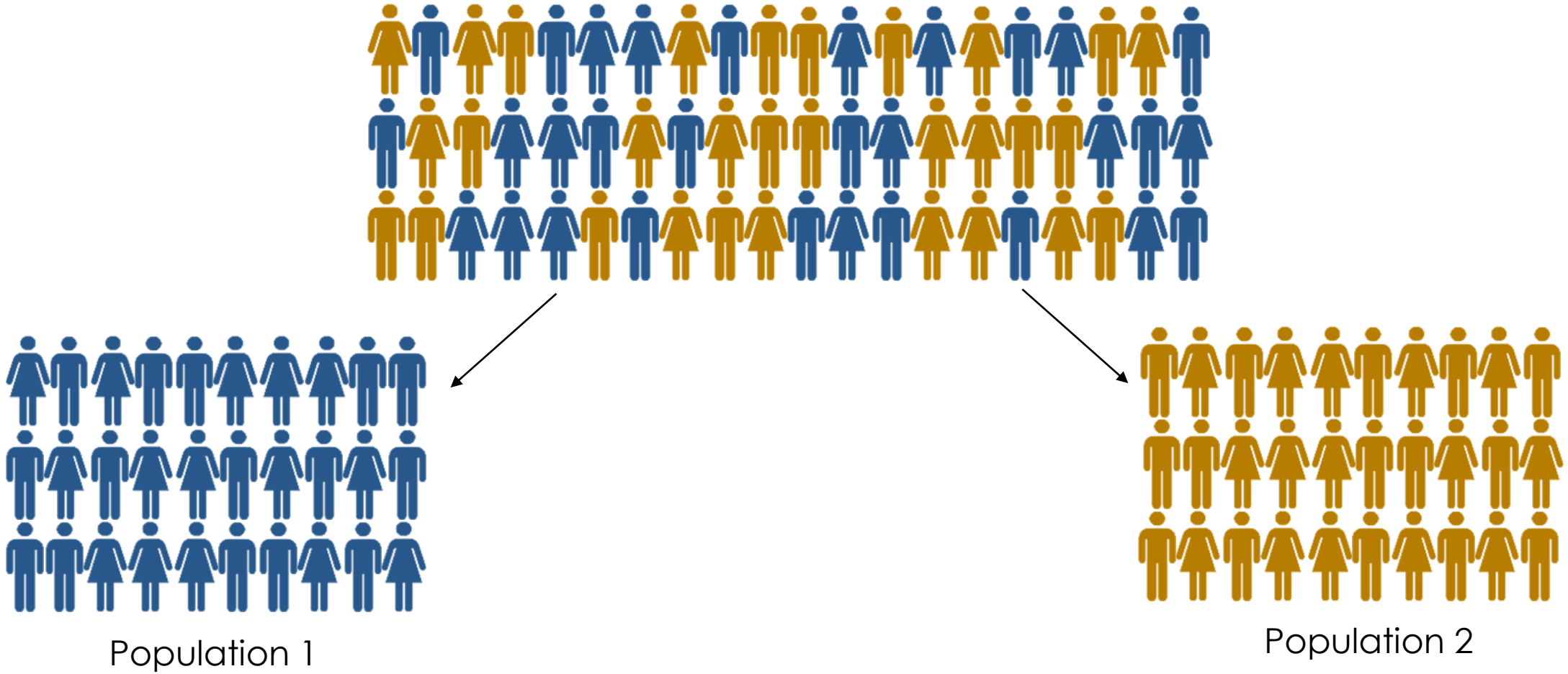
Randomised Controlled Trial



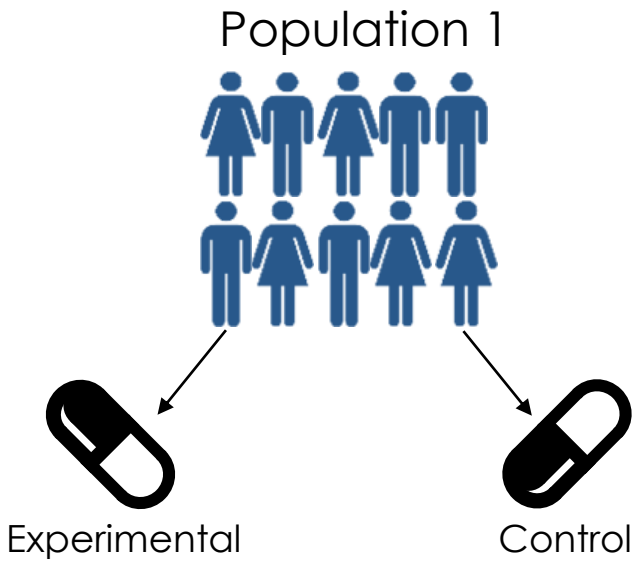
Null hypothesis not difference between treatment and control

Cytel

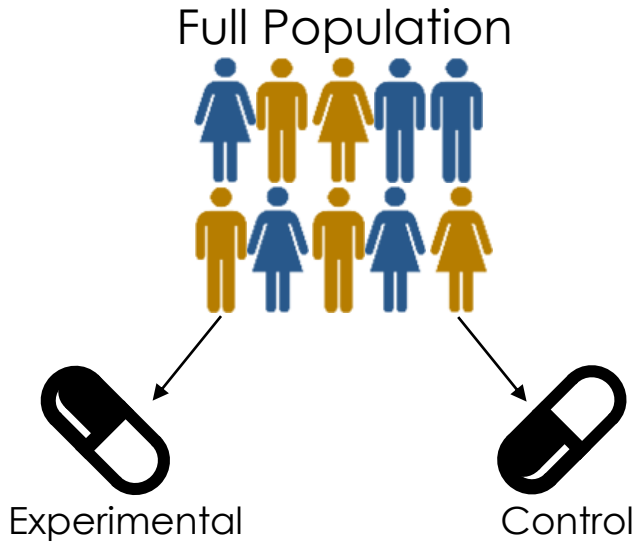
Pre-defined sub-populations



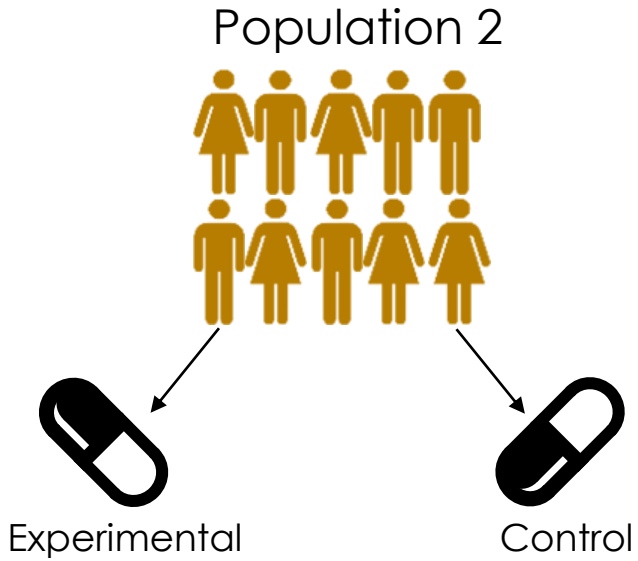
Defining study hypotheses



$H_{01}: \theta_1 = 0$



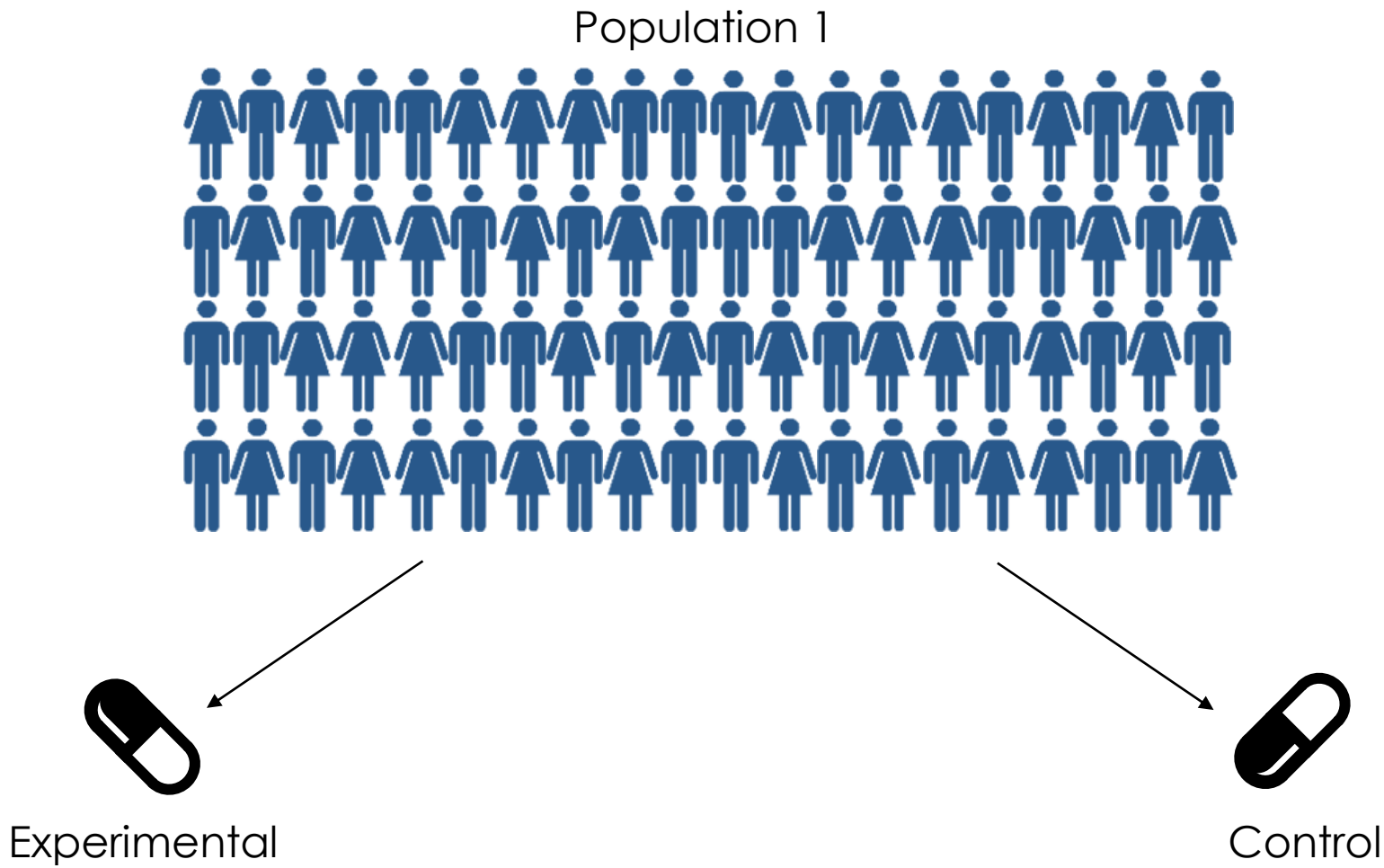
$H_{03}: \theta_3 = 0$



$H_{02}: \theta_2 = 0$

Cytel

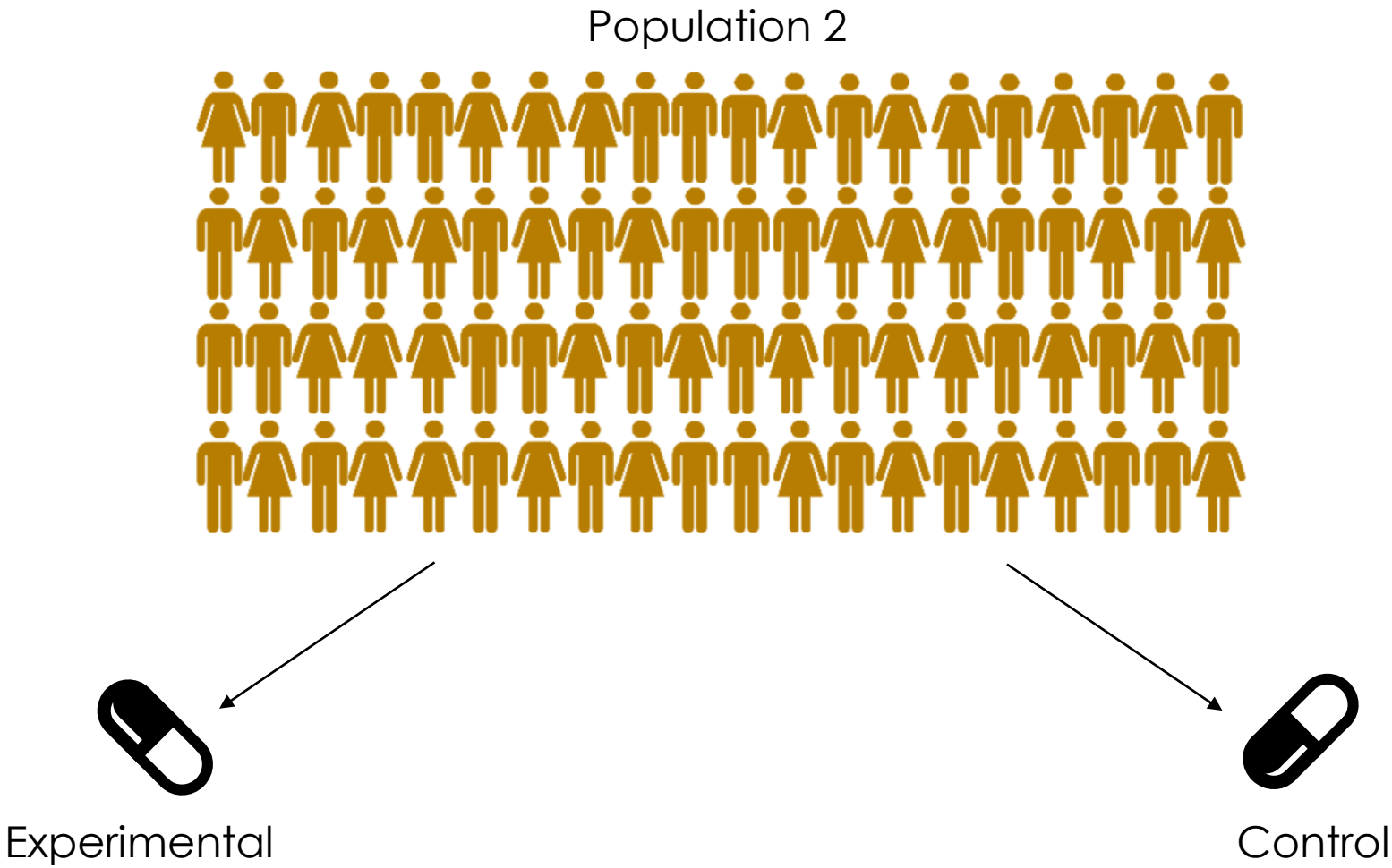
How to study the treatment: Option 1



$$H_{01}\colon \theta_1 = 0$$

Cytel

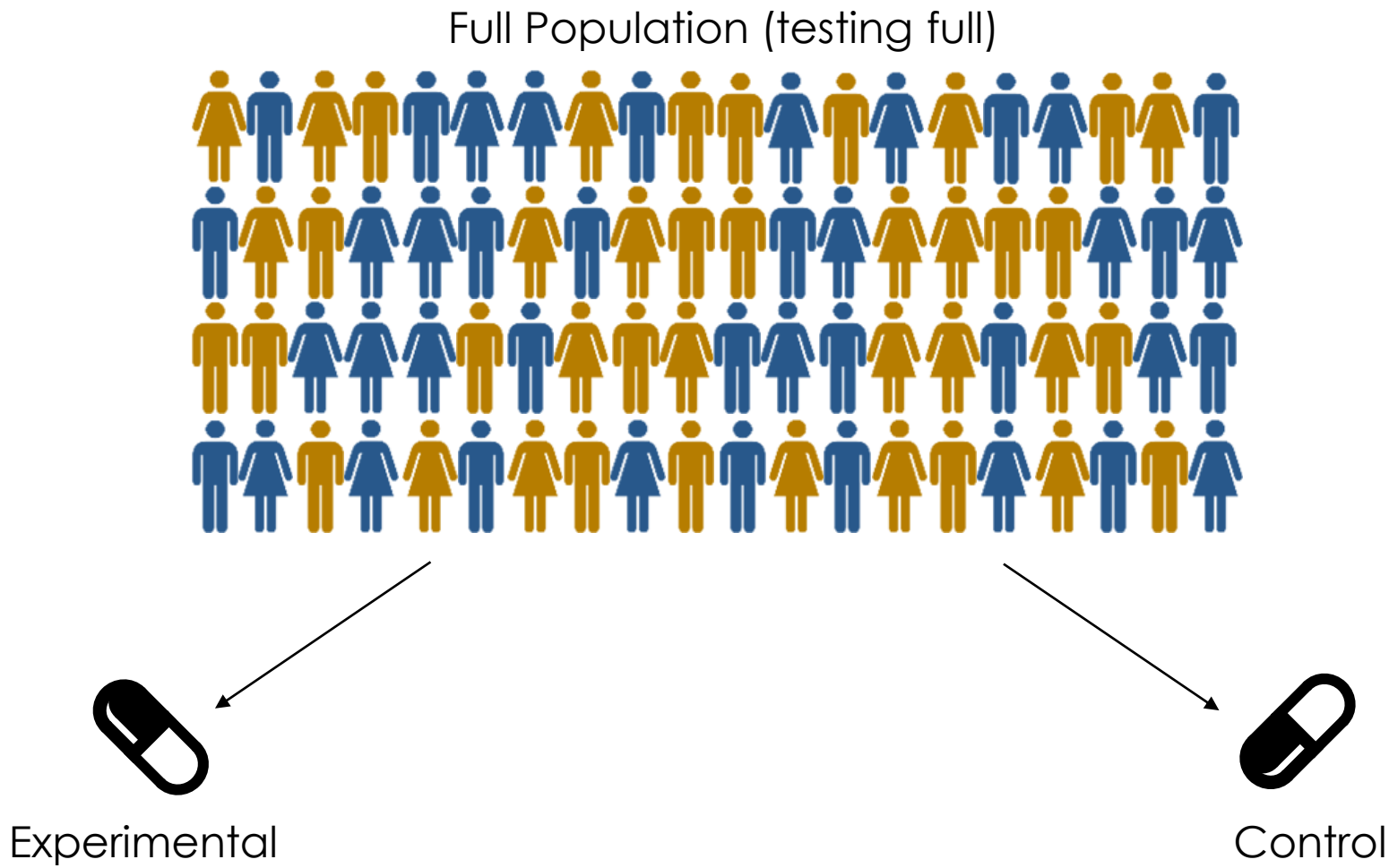
How to study the treatment: Option 2



$$H_{02}\colon \theta_2 = 0$$

Cytel

How to study the treatment: Option 3



$$H_{03}\colon \theta_3 = 0$$

How to study the treatment: Option 4

Full Population (testing sub-groups)

Experimental

Control

H_{01}: $\theta_1 = 0$

H_{02}: $\theta_2 = 0$

Cytel

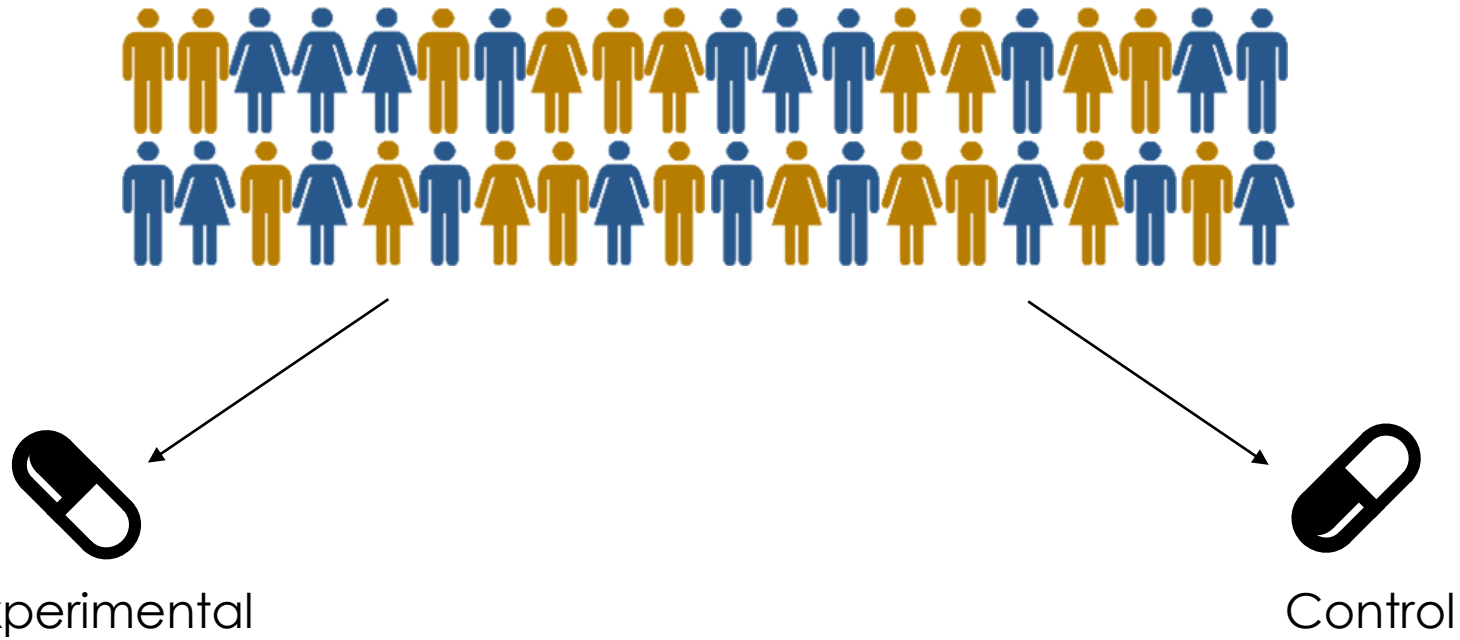
Choosing the trial design

?

Cytel

Population Enrichment: Stage 1

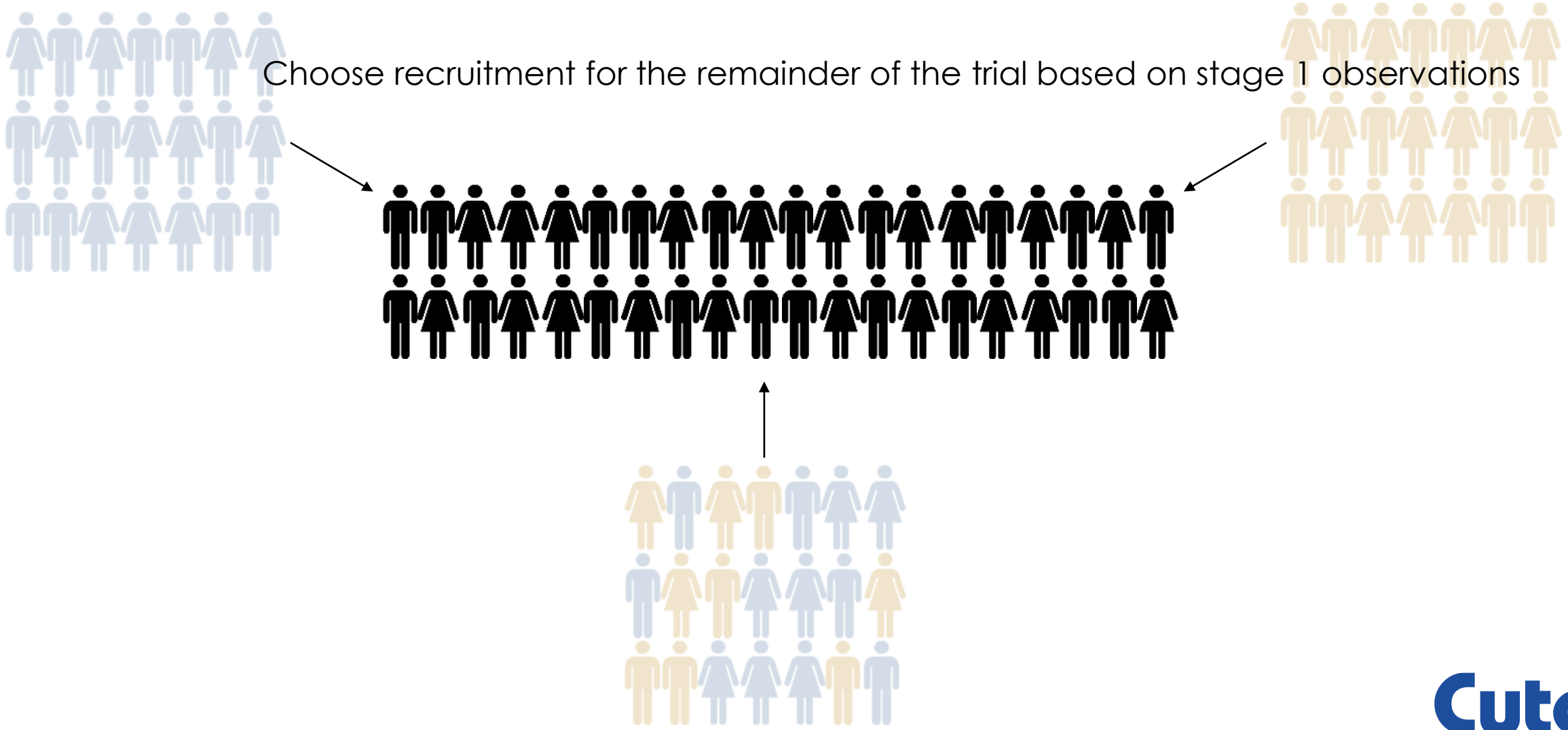
Recruit a portion of the total sample



Choose how to recruit the remainder of the trial

Cytel

Population Enrichment: Stage 2



Note: participants continue to be randomised in stage 2

Some considerations

Availability of data to make informed decision at the interim analysis

- Quickly available
- Delayed responses
- Survival data
- Repeated measures
- Progression free survival
- Surrogate endpoints

There is a trade off to achieve the flexibility

Cytel

Summary

- Pre-defined sub-groups
- Pre-planned adaptation options
- Offers a compromise between fixed sampling alternatives
- Making data driven decision at the interim analysis
- Can be applied to multiple data types and settings
- Desirable that data allow a well informed decision at the interim analysis

Cytel

Poll Question

Do you use Population Enrichment designs?

1 – Yes

2 – Yes, but rarely

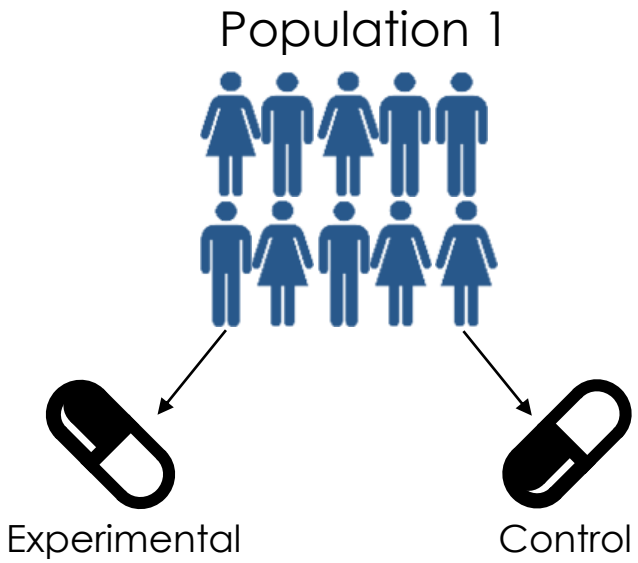
3 – No

Cytel

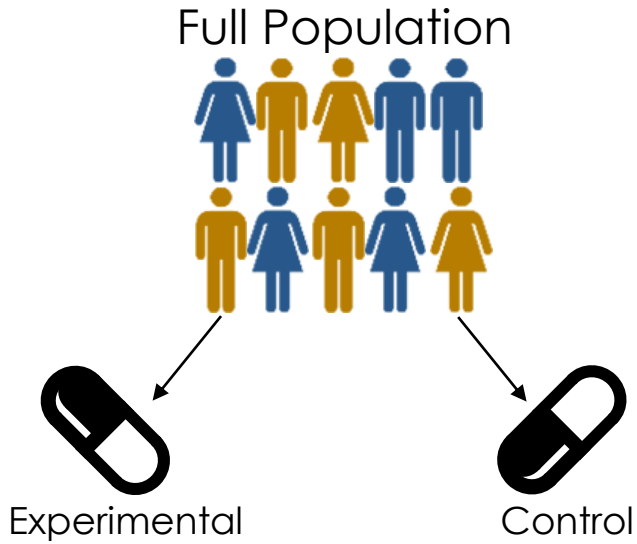
Questions?

Hypothesis Testing

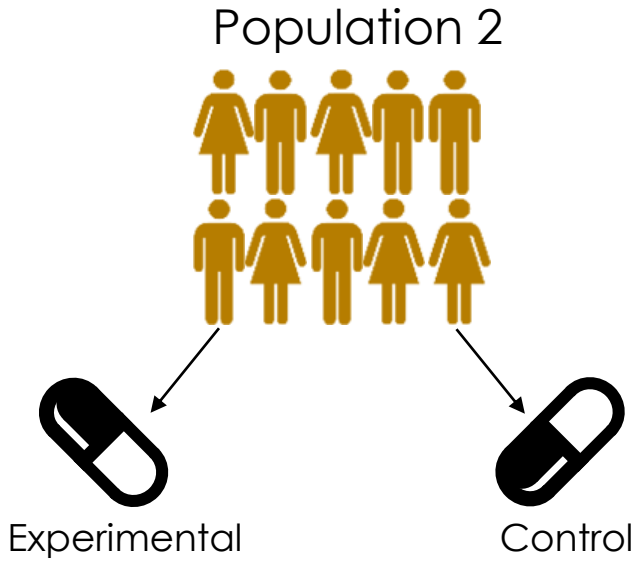
Recap of Study Hypotheses



H_{01}: $\theta_1 = 0$



H_{03}: $\theta_3 = 0$



H_{02}: $\theta_2 = 0$

Cytel

Error Control

Single hypothesis

Concerned with falsely declaring efficacy: Type I error

Reject H_0: $\theta = 0$ when H_0 is **TRUE**

Multiple hypothesis

Concerned with falsely declaring efficacy: FamilyWise Error

Reject one or more **TRUE** H_{0i}

Cytel

FamilyWise Error Rate

Strong control is often required:

$$P_{\boldsymbol{\theta}}(\text{Reject one or more } \textbf{TRUE } H_0) \leq \alpha$$

for all configurations of $\boldsymbol{\theta} = (\theta_1, \theta_2)$

Cytel

Pre-planned Trial Options

Possible interim decisions defined before the trial begins

Continue recruitment in population 1

(testing H_{01}: $\theta_1 = 0$)

Continue recruitment in population 2

(testing H_{02}: $\theta_2 = 0$)

Continue recruitment in both

(testing H_{01}: $\theta_1 = 0$ and H_{02}: $\theta_2 = 0$)

Cytel

Closed Testing Procedure

We require hypothesis tests of

$$H_{01}: \theta_1 = 0$$

$$H_{02}: \theta_2 = 0$$

$$H_{01} \cap H_{02}: \theta_1 = 0 \ \& \ \theta_2 = 0$$

Cytel

Global Rejection

Population 1

Reject H_{01} **GLOBALLY** at level α when:

Reject a test of H_{01}: $\theta_1 = 0$ at level α

AND

Reject a test of $H_{01} \cap H_{02}$: $\theta_1 = 0$ & $\theta_2 = 0$ at level α

Population 2

Reject H_{02} **GLOBALLY** at level α when:

Reject a test of H_{02}: $\theta_2 = 0$ at level α

AND

Reject a test of $H_{01} \cap H_{02}$: $\theta_1 = 0$ & $\theta_2 = 0$ at level α

Cytel

Testing $H_{01} \cap H_{02}$

For example test this by Simes' method.

Let p_1 and p_2 be p-values for the tests of $H_{01}: \theta_1 = 0$ and $H_{02}: \theta_2 = 0$

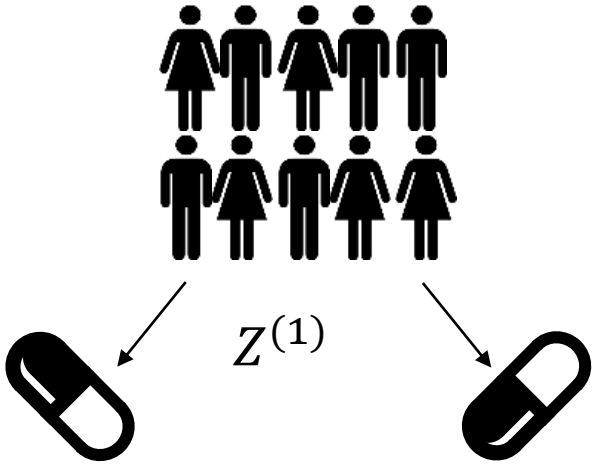
Then for $H_{01} \cap H_{02}$

$$p_{1,2} = \min\{2\min(p_1, p_2), \max(p_1, p_2)\}$$

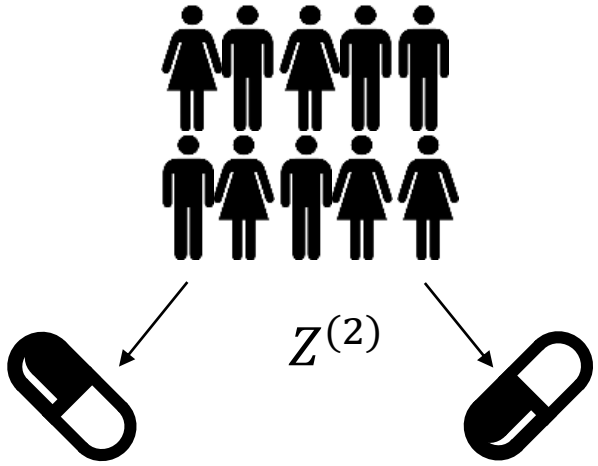
Cytel

Combining Stages

Stage 1



Stage 2



Combined statistic $$Z^{(c)} = w_1 \, Z^{(1)} + w_2 \, Z^{(2)}$$

(**Note:** weights pre-defined with $w_1^2 + w_2^2 = 1$)

Cytel

An Overall Testing Procedure

Stage 1

$p_1^{(1)}$ and $p_2^{(1)}$ from data, Simes' method gives $p_{1,2}^{(1)}$

Stage 2

$p_1^{(2)}$ and $p_2^{(2)}$ from data, Simes' method gives $p_{1,2}^{(2)}$

Combined

$p_i^{(c)}$ found using weighted inverse normal from $p_i^{(1)}$ and $p_i^{(2)}$

to test each H_{01}, H_{02} and $H_{01} \cap H_{02}$

Cytel

Key Point of Hypothesis Testing Structure

- Pre-defined paths through the trial
- A fixed list of possible hypotheses to test
- Test procedure controls the error rate for all possible decisions

This last point is crucial this grants complete freedom in how the interim decision is made as **THE ERROR RATE IS ALWAYS CONTROLLED**

Cytel

Decision Making

Available Information from Stage 1

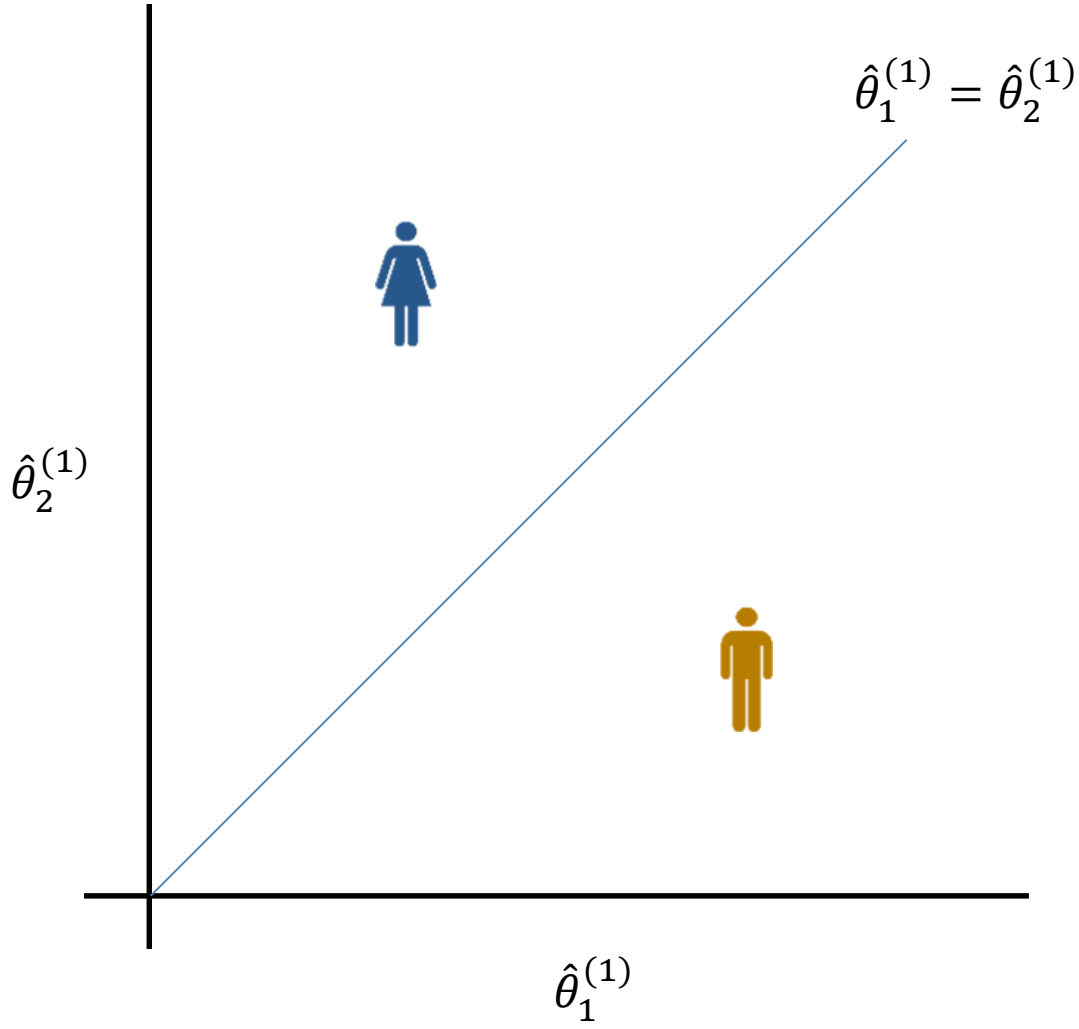
Estimates of the treatment effect:

In population 1 $\hat{\theta}_1^{(1)}$

In population 2 $\hat{\theta}_2^{(1)}$

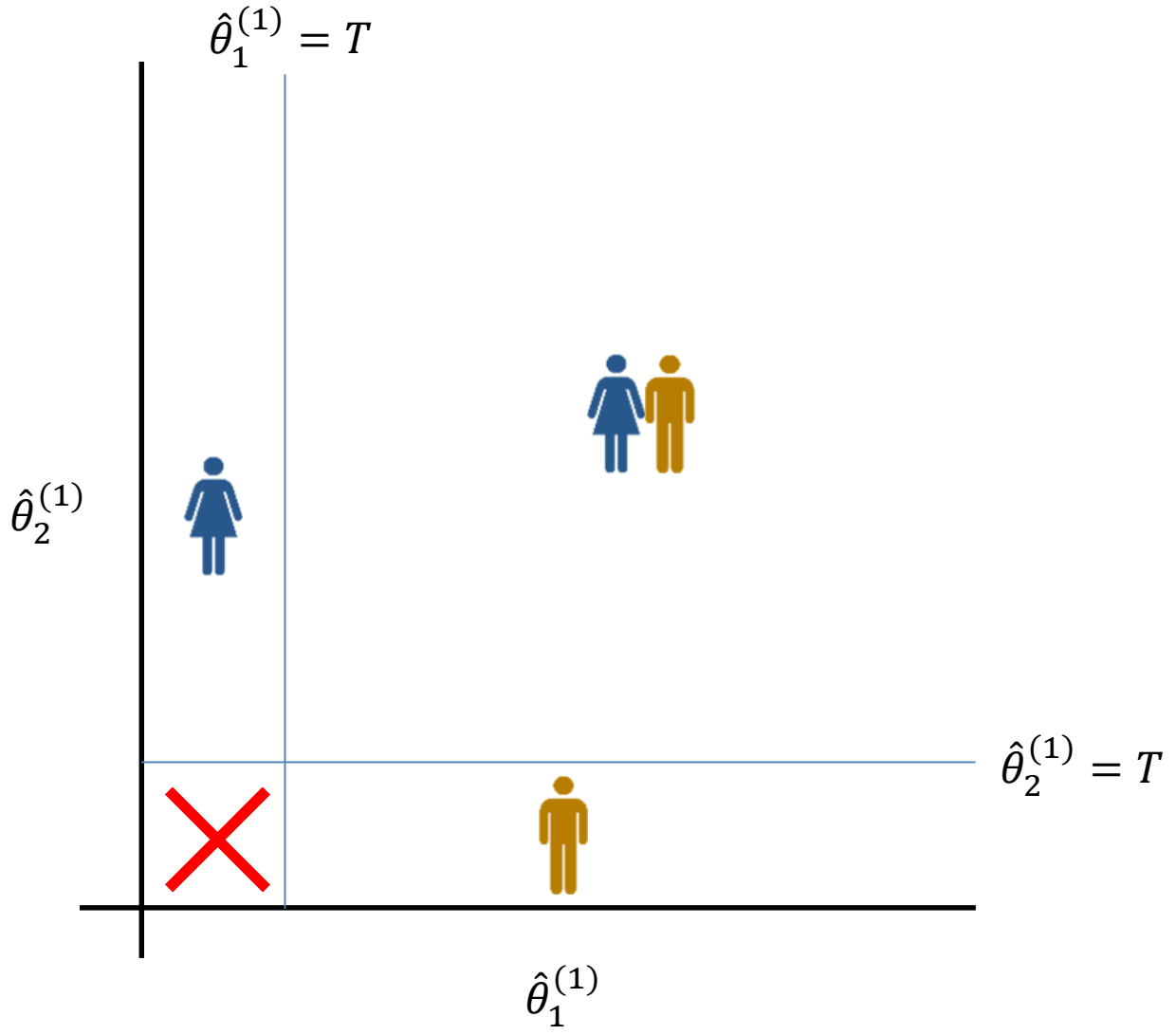
Cytel

Select the Best



Cytel

Threshold Selection



Cytel

Bayesian Decision Making

Capture prior uncertainty about treatment effect before the trial

$$\pi(\boldsymbol{\theta})$$

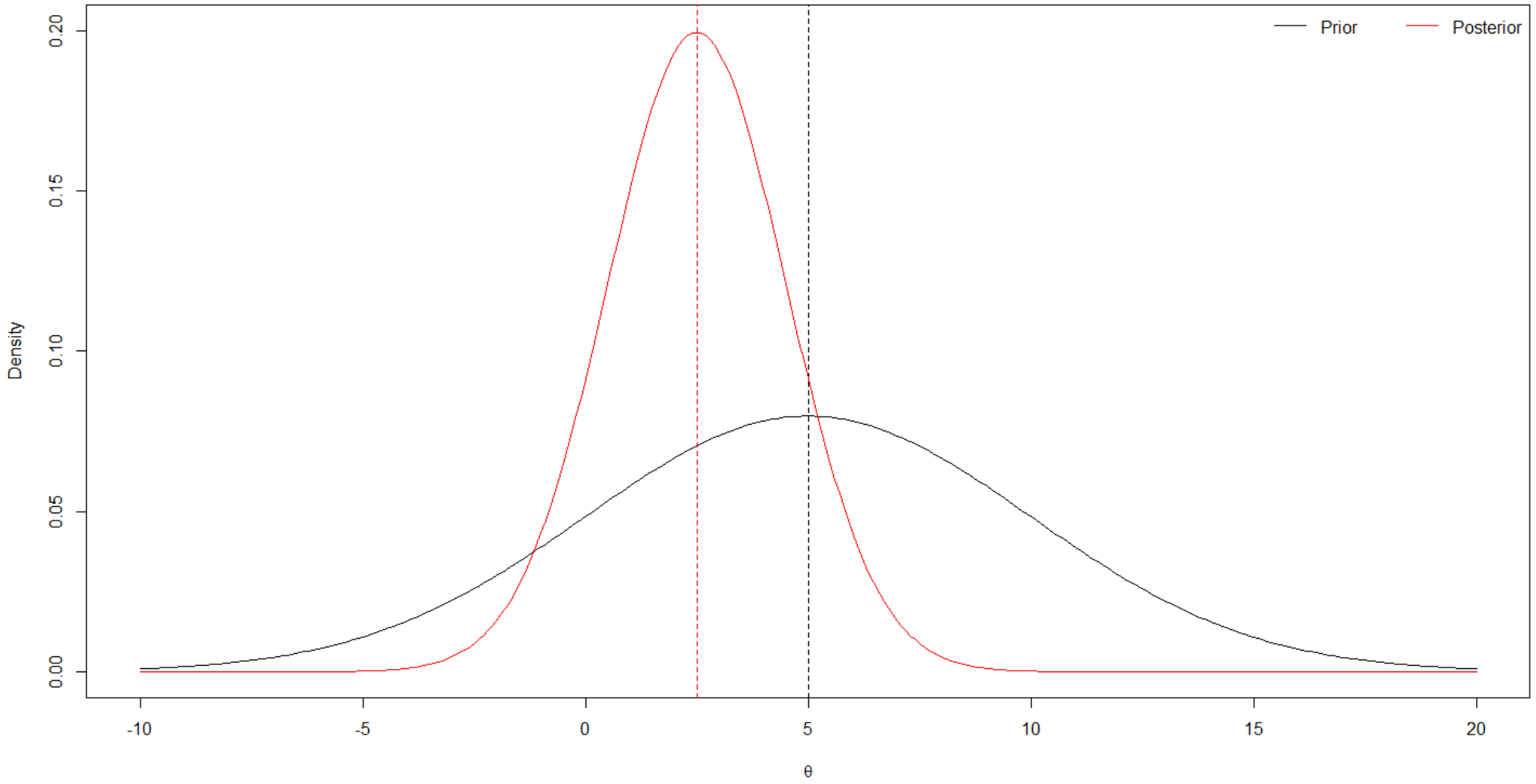
Update this opinion at the interim analysis

$$\pi\left(\boldsymbol{\theta}|\widehat{\boldsymbol{\theta}}^{(1)}\right)$$

Use this to inform the interim decision

Cytel

Prior/Posterior distributions



Utility Functions

A single measure of trial performance

Consider a simple gain function

$$G(\boldsymbol{\theta}, \boldsymbol{X}) = a(\theta_1)\mathbb{I}(RejectH_{01}) + b(\theta_2)\mathbb{I}(RejectH_{02})$$

Where $a(\theta_1)$ and $b(\theta_2)$ are chosen to reflect the benefit of being able to reject the corresponding hypothesis

Cytel

Bayesian Optimisation

Aim to maximise $\mathrm{E}\{G(\boldsymbol{\theta}, \boldsymbol{X})\}$ under present understanding of the treatment effect

After stage 1 choose

to maximise $E_{\pi(\boldsymbol{\theta}|\hat{\boldsymbol{\theta}}^{(1)})}\{G(\boldsymbol{\theta}, \boldsymbol{X})\}$

Cytel

Promising Zone Approach

3 options at the interim analysis (assuming 1 favourable population)

Choose based on conditional probability $P(Reject\ H_0|\widehat{\boldsymbol{\theta}}^{(1)})$

Favourable zone

Promising zone

Enrichment zone

Note: an unfavourable and futility zones may be defined

Cytel

Cytel
Shaping the Future
of Drug Development

Example: TAPPAS

Background

A study of TRC105 in patients with advanced angiosarcoma

Two sub-groups

cutaneous advanced angiosarcoma

non-cutaneous advanced angiosarcoma

Indication of greater tumor sensitivity in cutaneous sub-group

Cytel

Design

- Primary endpoint of progression free survival
- Initial sample size of 124 patients
- Followed until 95 events (progression or death)
- Interim analysis after ?

Cytel

Interim Decisions

Favourable zone

Continue the study as planned

Promising zone

Increase the sample size

Enrichment zone

Recruitment continuing only in cutaneous group

Note: an unfavourable zone was also defined where the same action was taken as the favourable zone

Cytel

What happened

- Recruited 128 patients in total
- The trial continued in the full-population as planned
- TRC105 did not demonstrate activity when combined with pazopanib

EAST: Enrichment Module

East

Easy Access to the Adaptive Designs That Matter

Delivered by the Thought Leaders Behind the Methods

Software that is Faster & Easier to Use

Popular Fixed and Adaptive Designs at your Fingertips

Cytel

East ENRICH module: Design parameters

Survival Information

Input Method: Hazard Rates

Subpopulation

☐ Use Piecewise Hazard Rates

Piece #	Hazard Rates		Hazard Ratio
	Control	Treatment	
1	0.173	0.095	0.55

Complement

☐ Use Piecewise Hazard Rates

Piece #	Hazard Rates		Hazard Ratio
	Control	Treatment	
1	0.173	0.095	0.55

Full Population

Control	Treatment	Hazard Ratio
0.173	0.095	0.550

Note: Full Population parameters are approximate.

# of Accrual Periods: 1

Accrual Rate: 8

Time Lag: Coh1 and Coh2: 0

Prevalence Drives Subpopulation Accrual

Type I Error (α): 0.025

Rejection Region: Left-Tail

Subpopulation Prevalence: 0.5

Allocation Ratio (n_t/n_c): 1

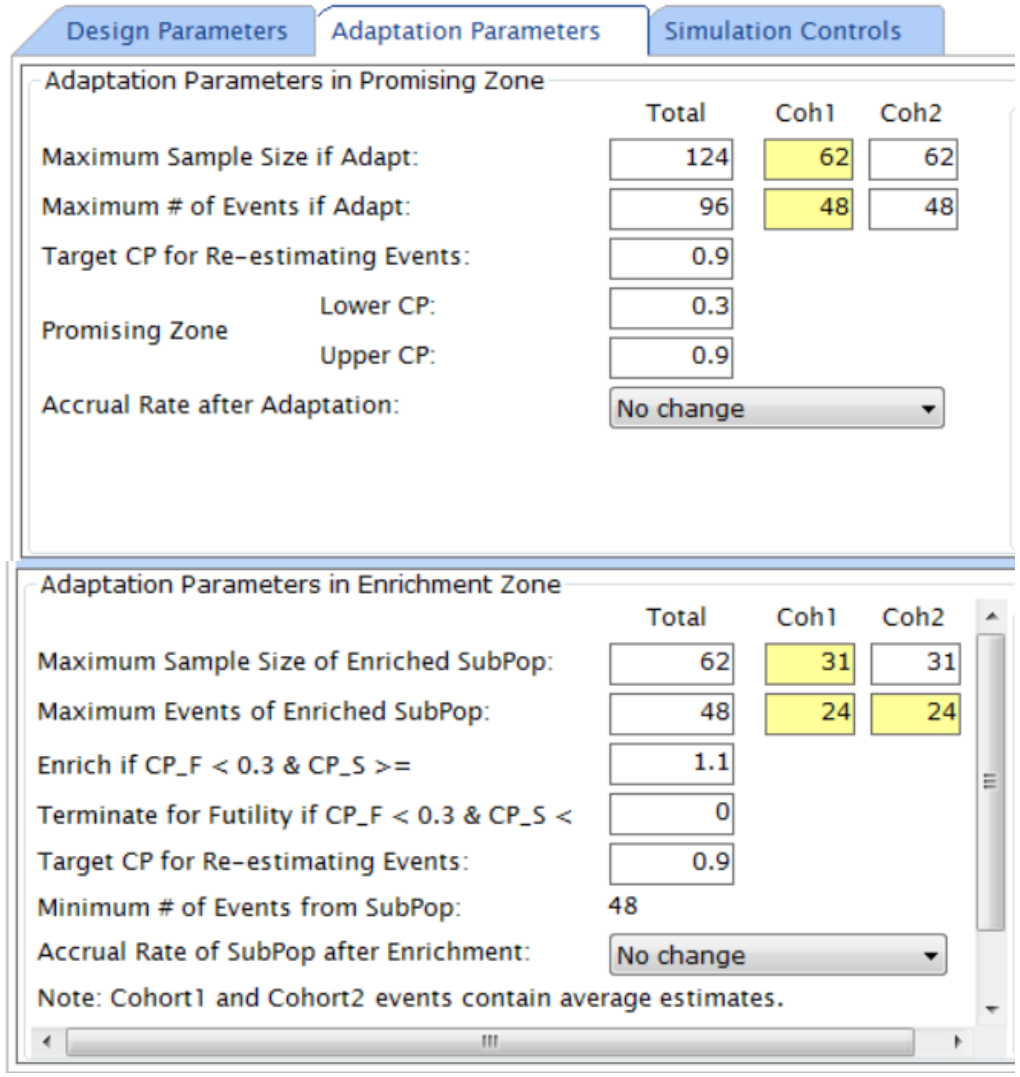
Subjects are followed: Until End of Study

Initial Sample Size

Cohort #	Sample Size	# of Events	
		Total	At IA
Cohort 1	62	48	40
Cohort 2	62	48	

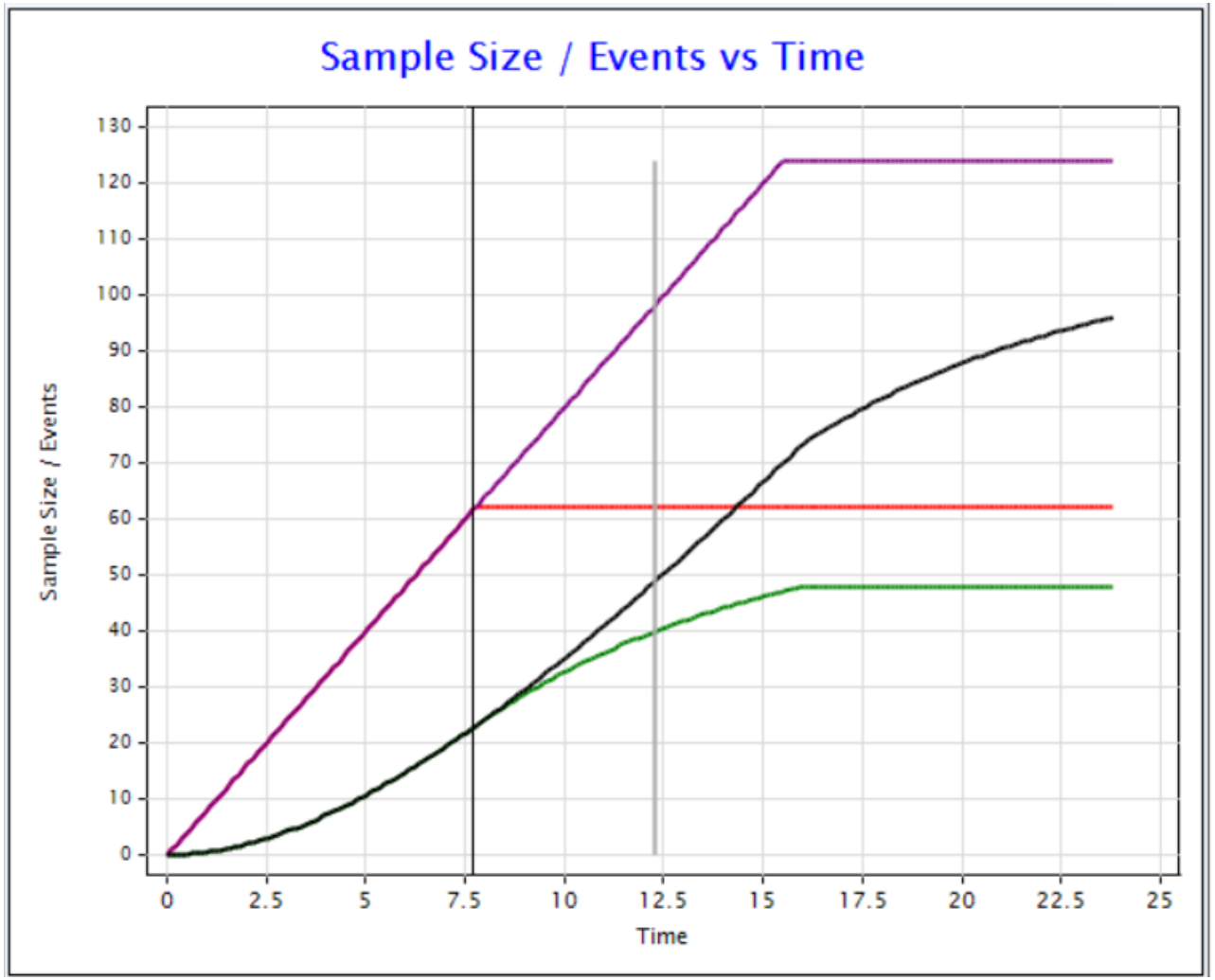
Cytel

East ENRICH module: Adaptation parameters



Cytel

East ENRICH module: Graphic



Time: 7.696 Display IA Line

Series	Y
Coh1 Sample Size	62
Coh1 Events	23
Coh1 SubPop Events	
Coh2 Sample Size	
Coh2 Events	
Coh2 SubPop Events	
Coh1&2 Sample Size	62
Coh1&2 Events	23
Coh1&2 SubPop Events	

Cytel

East ENRICH module: Simulation results

Simulation Summary

Zone		# Simulations	Reject H0_F Only	Reject H0_S Only	Reject Both	Conditional Power	Average Patients	Average Events	Average Study Duration
Unfavourable	(CP_F < 0.3)	19.300%	15.078%	1.969%	22.228%	39.275%	124	96	23.499
Promising	(0.3 <= CP_F < 0.9)	31.190%	25.136%	1.667%	43.027%	69.830%	124	96	23.482
Favourable	(CP_F >= 0.9)	49.510%	22.541%	0.364%	67.905%	90.810%	124	96	23.413
	Overall	100.000%	21.910%	1.080%	51.330%	74.320%	124	96	23.451

Overall Survival Summary

At	Count	# of Accruals	# of Events		Average Study Duration	Average Follow-Up	# of Dropouts	
			Placebo	Treatment			Placebo	Treatment
IA - Cohort 1	10000	70	22.167	17.833	10.656	3.966	0	0
Final - Cohort 1	10000	70	31.809	28.191	18.465	6.046	0	0
Final - Cohort 2	10000	90	38.041	32.777	27.125	5.374	0	0

Subpopulation Survival Summary (Enriched Simulation Only)

At	Count	# of Accruals	# of Events		Average Study Duration	Average Follow-Up	# of Dropouts	
			Placebo	Treatment			Placebo	Treatment
IA - Cohort 1	1941	70	20.977	19.023	10.644	3.956	0	0
Final - Cohort 1	1941	70	31.505	28.495	18.438	6.034	0	0
Final - Cohort 2	1941	97	41.816	34.713	36.061	6.205	0	0

Cytel

Summary

- Adaptive Enrichment introduces flexibility to sub-group selection
- This flexibility can be accounted for in hypothesis testing
- Decision making at the interim analysis is key
- Several methods available for decision making
- Used appropriately it can be a powerful tool

Cytel

Global Products and Services

Statistical Software

Industry standard for trial design, including CID adaptive (East, EOD)

Leader in exact statistical solutions (Xact: StatXact, LogXact, Procs)

Operations software (e.g. ACES, EnForeSys, FlexRandomizer)

All 25 top biopharma companies, the FDA, EMA & PMDA use our software

Strategic Consulting

PhD statisticians expert in innovative design & complex statistical questions

Experts in Data Science, PK/PD, Enrolment & Event Forecasting, Portfolio/Program Optimization (NPV)

Project-Based Services

Reliable Biometrics service provider delivering high quality, on time

Lead staff with over 15 years industry experience on average

Including biostatistics & programming, ISC, data management, PK/PD analysis, medical writing

Functional Services Provision (FSP)

Creation of dedicated teams operating within/as an extension of the client's own biostatistics & programming, data management and PK/PD teams

Leader in offshoring of Biometrics competencies

Cytel

Cytel
Shaping the Future
of Drug Development

Q&A