Clinical Trial II

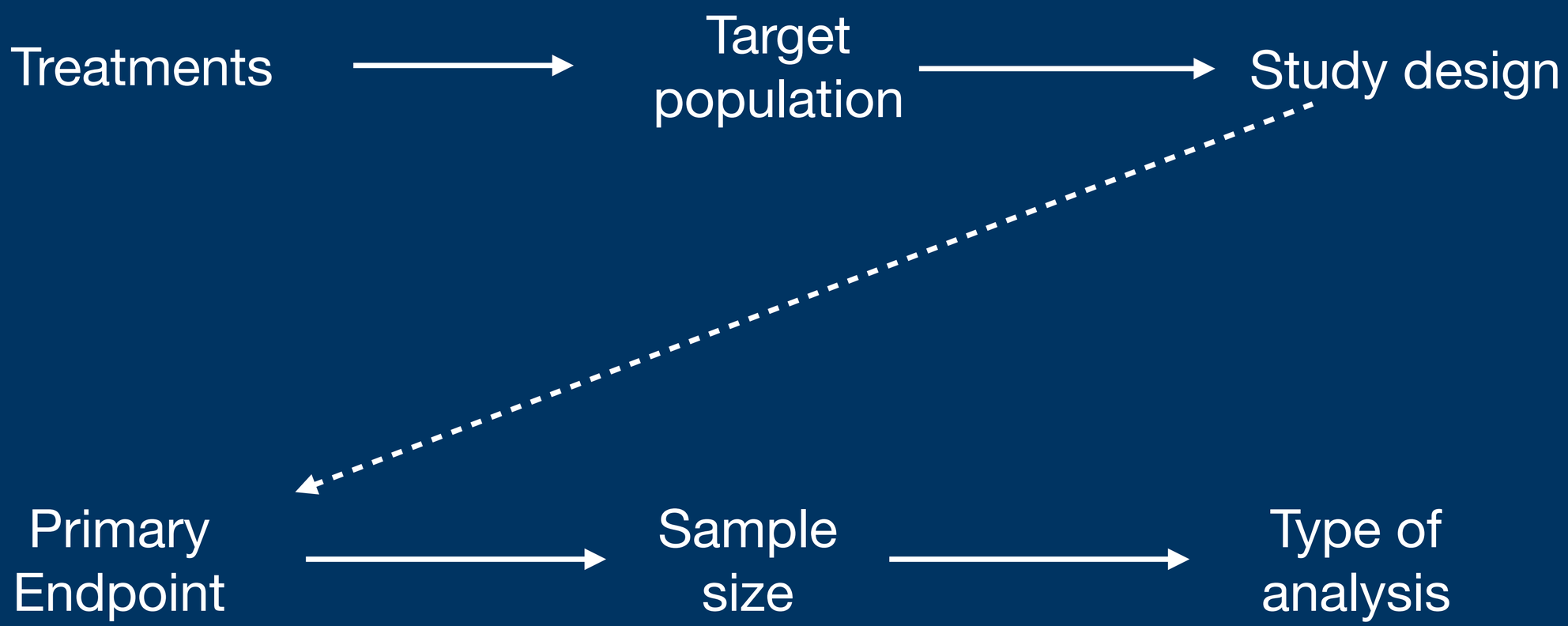
Case Studies

Nuno Sepúlveda

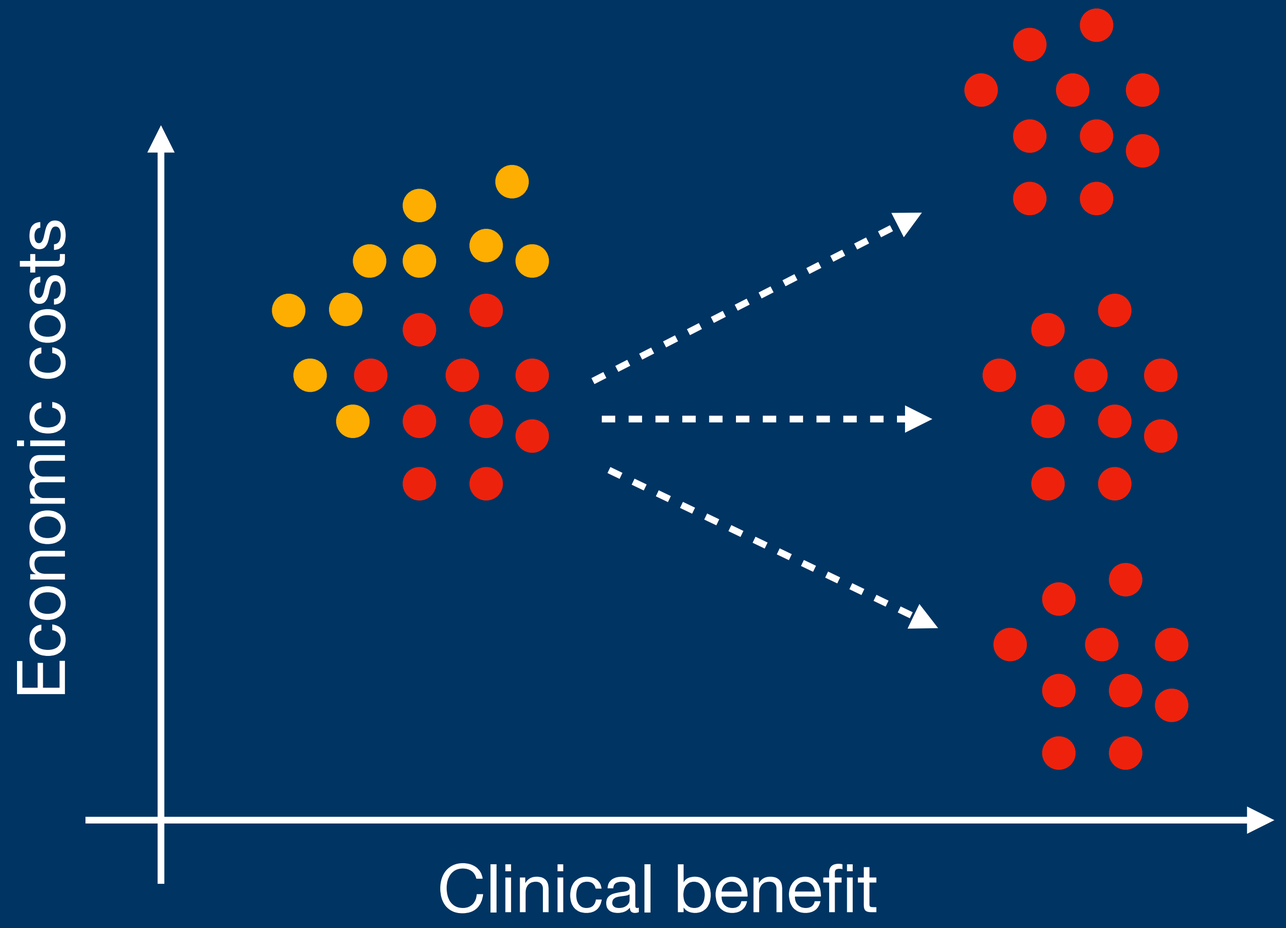
Course content

1. Basic concepts related to CTs
2. Designing/Reporting CTs/Mendelian Randomisation/Survival Analysis
3. Reporting CTs (CONSORT guidelines) Health Economics
4. Discussion on the controversial PACE trial
5. Project’s Presentations/Course Summary

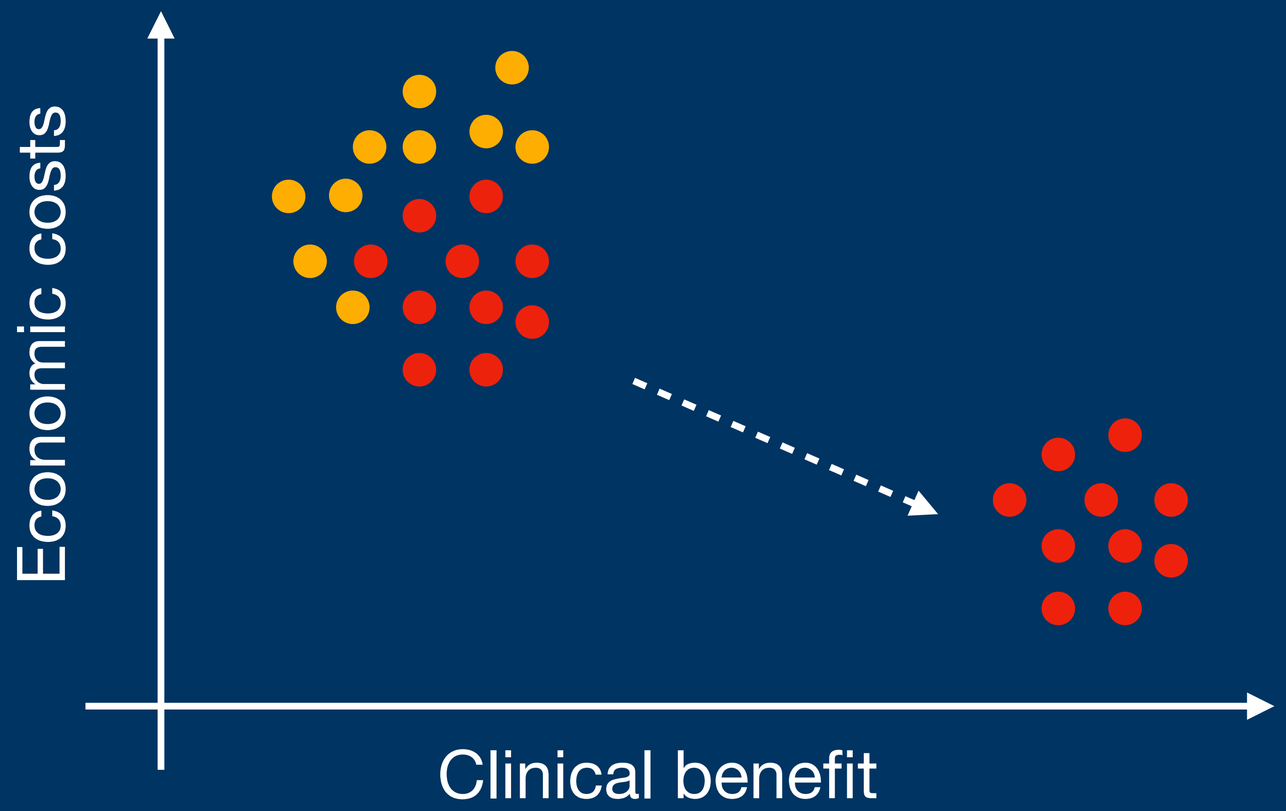
Key Elements in Clinical Trial



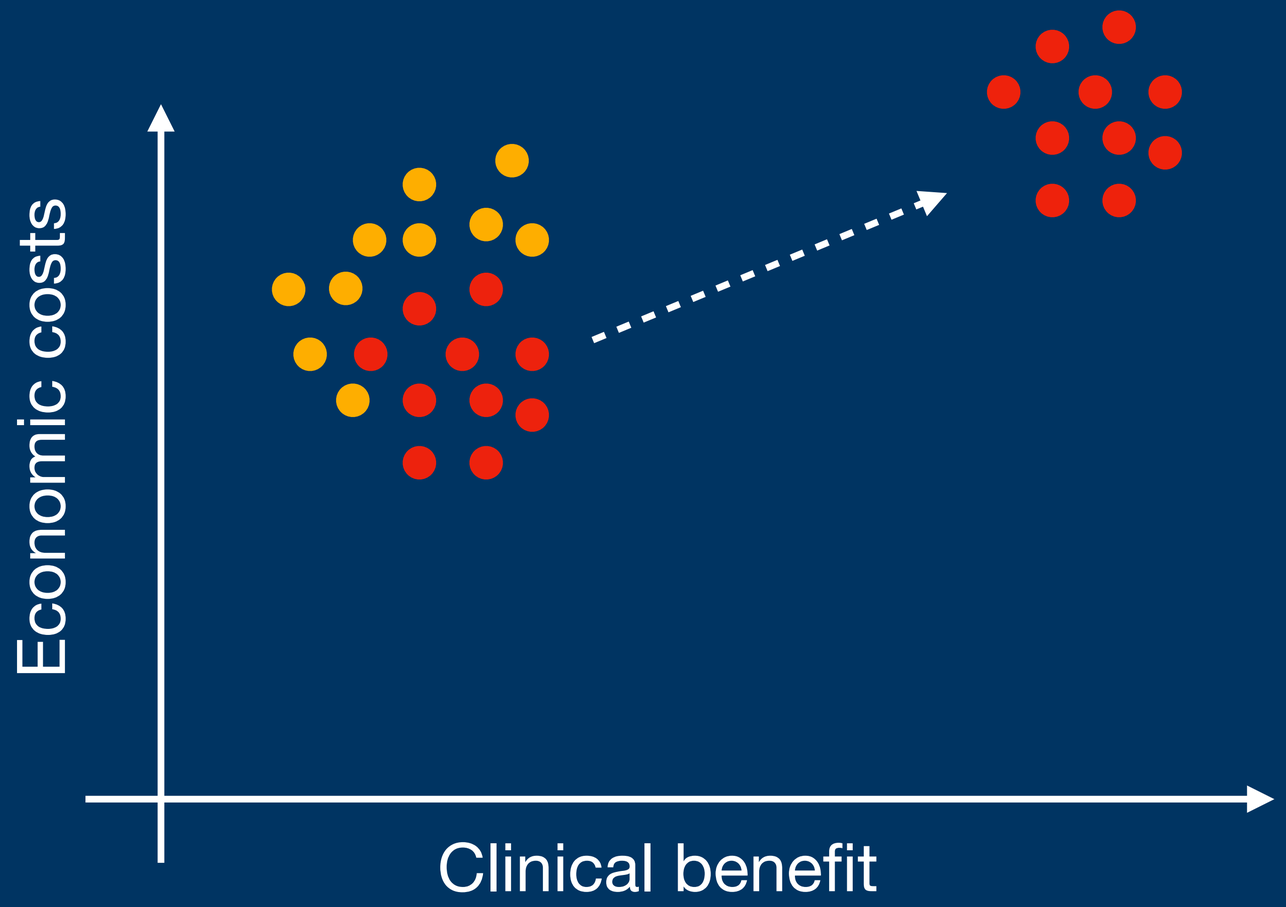
How to define the target population?



Ideal world

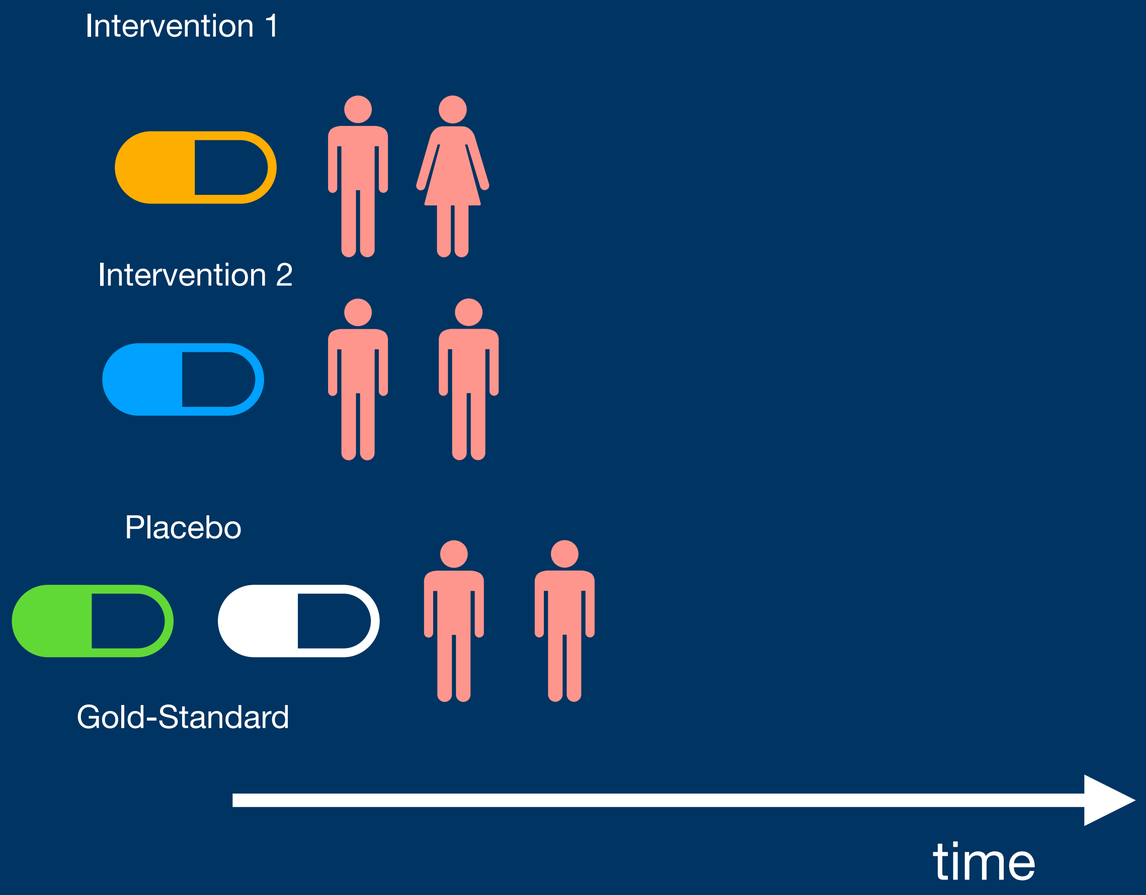


Real world (cancer)

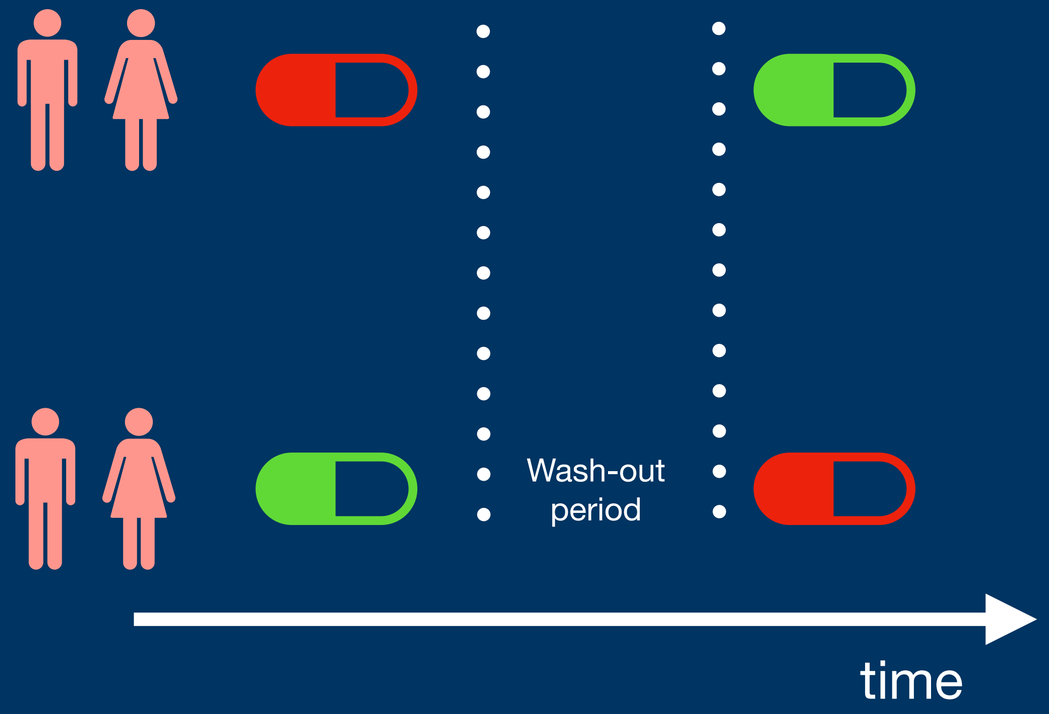


Study design

Comparator-based



Cross-Over

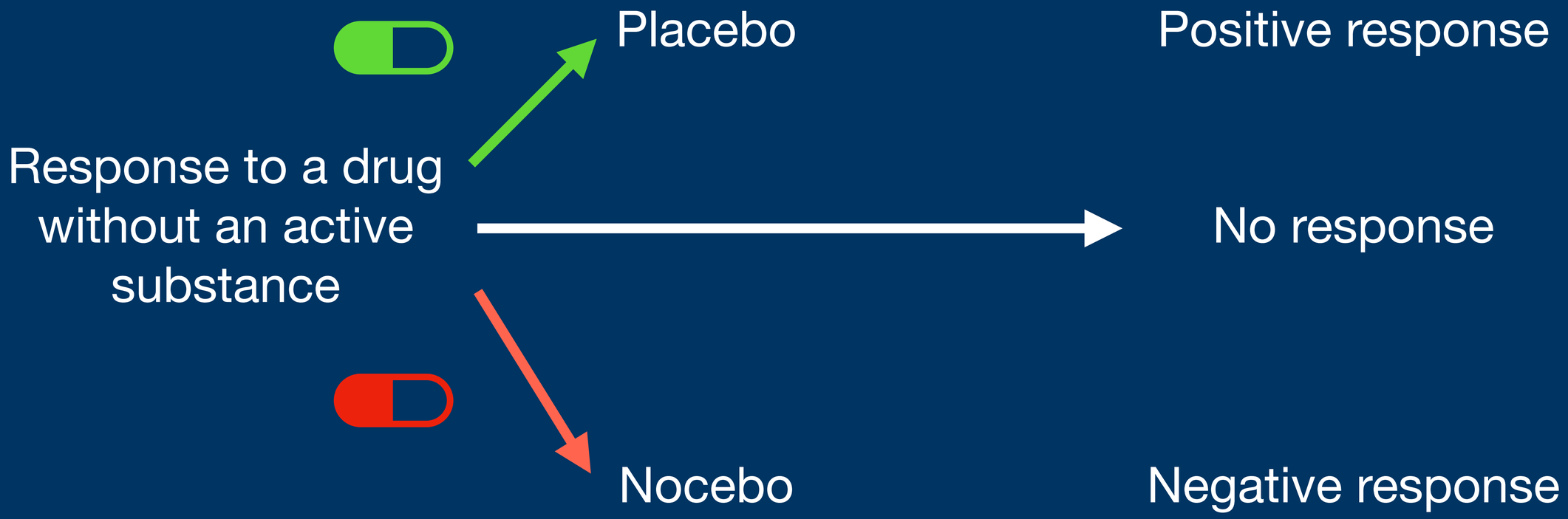


What effects can happen in the control group?

One pill makes you larger
And one pill makes you small
And the ones that mother gives you
Don't do anything at all
Go ask Alice
When she's ten feet tall

In White Rabbit by Jefferson Airplane

What effects can happen in the control group?



How to design a clinical trial?

Prospective

- Use of one or more comparators
- Problems of adherence/drop-outs
- Outcome/endpoints need to be observed
- Confounders controlled by randomization

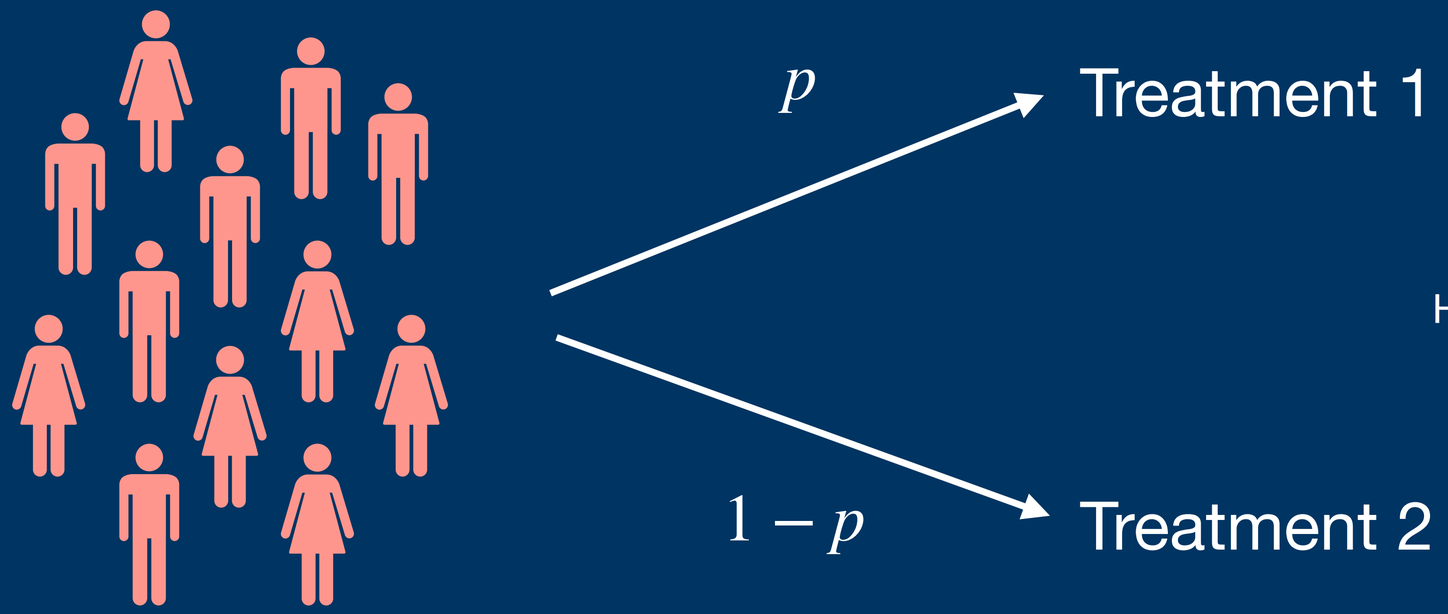
Retrospective

- Observational studies
- Outcome/endpoints already observed

How to design a clinical trial?

Randomization

Patients are assigned randomly to each arm of the study



How can you do randomization using R?

How to define an endpoint?

Endpoint
Primary Outcome
Response Variable
Dependent Variable

Use of a
Biomarker

Biomarker

A biomarker is usually measurement or a substance that indicates important facts about a living organism, usually a patient.

It provides information about:

- The biological state of the organism;
- Disease risk;
- Disease diagnosis;
- Disease progression;
- Treatments of choice;
- Monitoring responses to treatment;
- Endpoints for treatment efficacy.

Little quiz
Do you know the associated biomarker?

Longevity

Obesity

Diabetes Mellitus

Multiple sclerosis

How to define an endpoint?

Infectious Diseases

Clearance of infection
Time to clearance
Prevention of future infections

Non-communicable diseases

Diabetes - Glucose levels
Cardiovascular diseases - Blood pressure
Autoimmune diseases - Disease scores/Inflammation markers

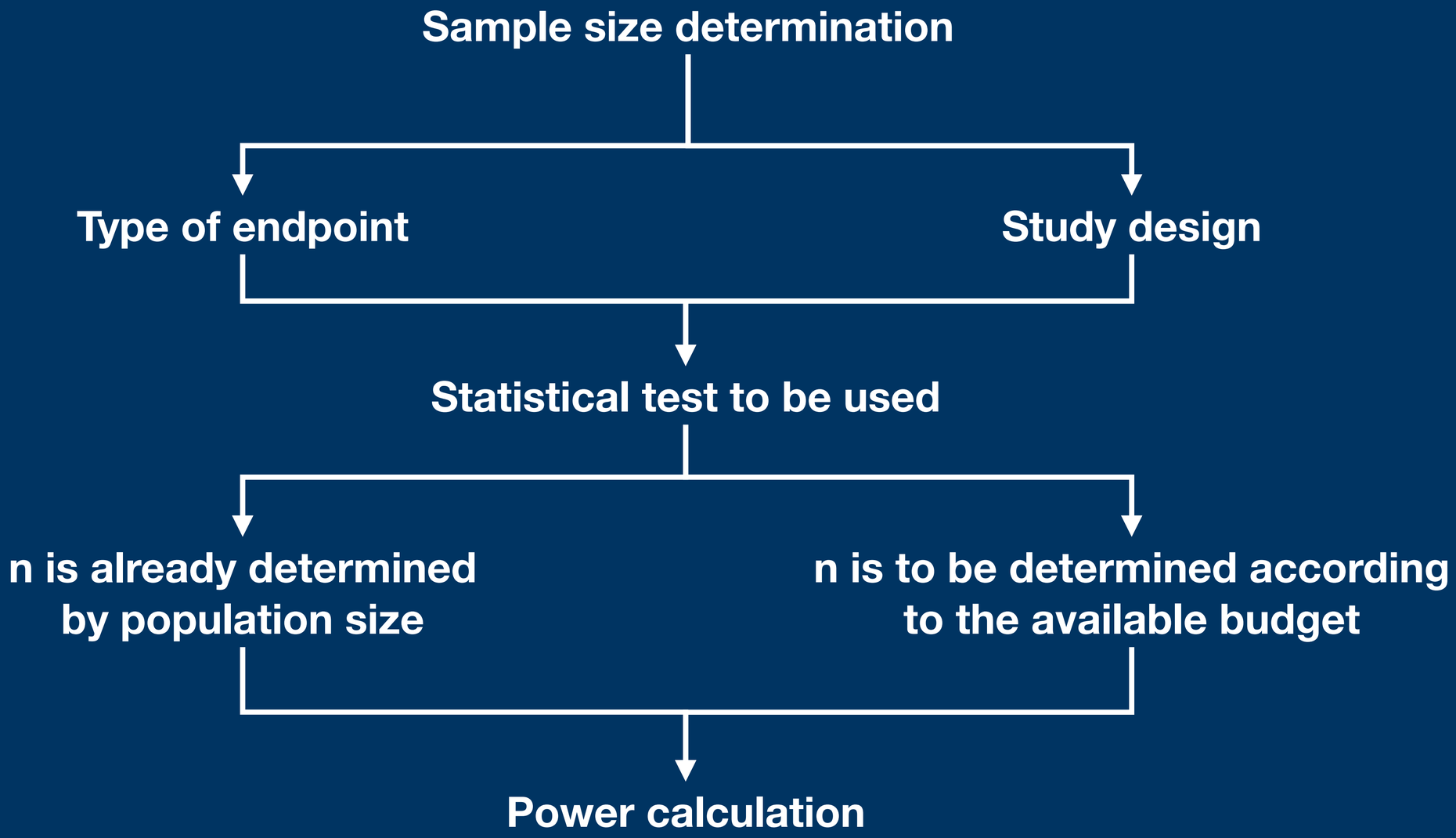
Cancer/Longevity

Time to death

Biomarkers

Survival analysis

How to define the sample size?



“Simple” sample size determination: case I

Two treatments (Placebo versus New Treatment)

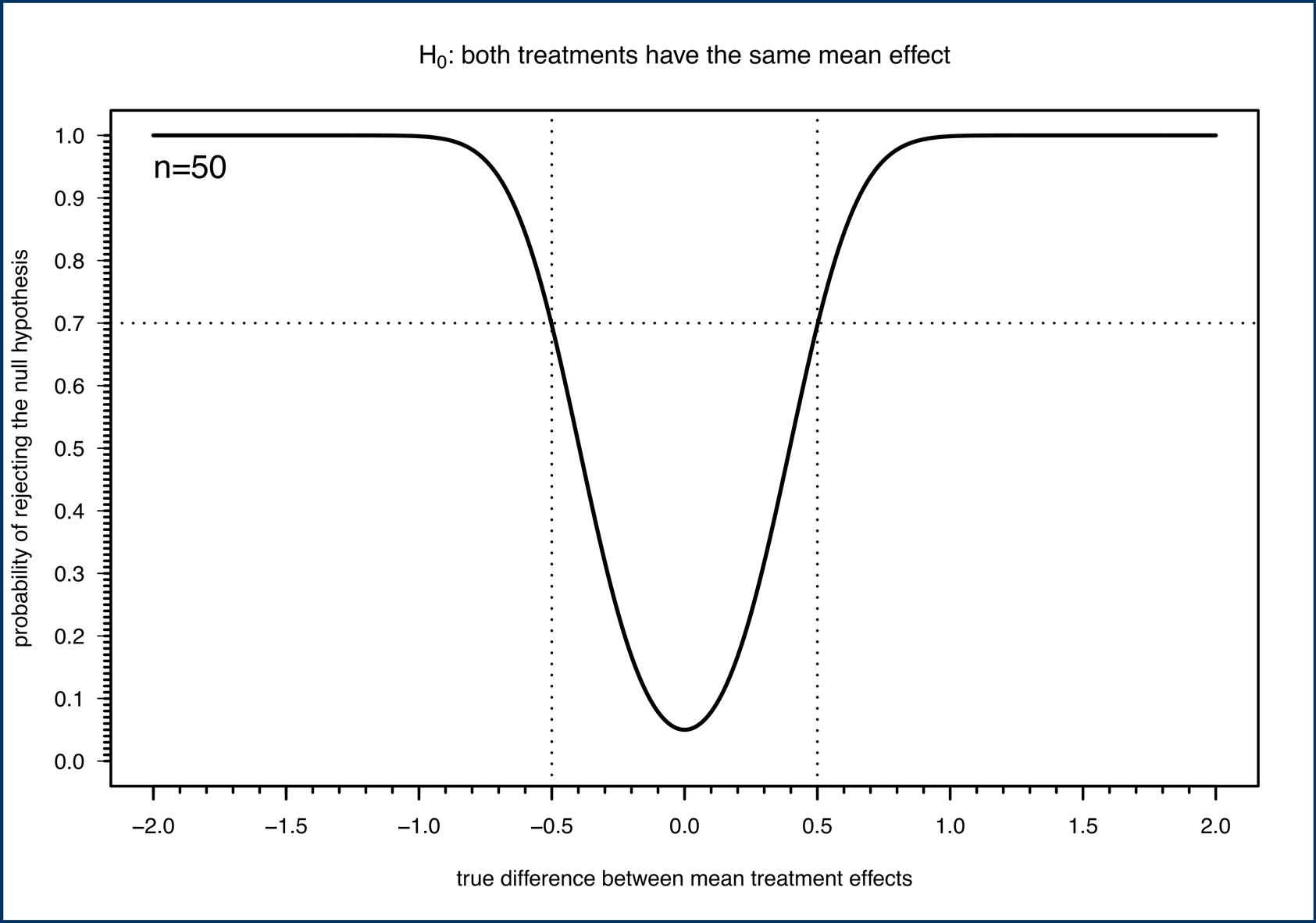
Biomarker is expected to be normally distributed in both treatments

$$H_0 : \mu_1 = \mu_2 \text{ versus } H_1 : \mu_1 \neq \mu_2$$

Which statistical test can we apply in this situation?

If n=50 patients in each treatment, what is the power to detect an absolute difference between treatment effects of at least 0.5?

Power analysis



“Simple” sample size determination: case II

Two treatments (Placebo versus New Treatment)

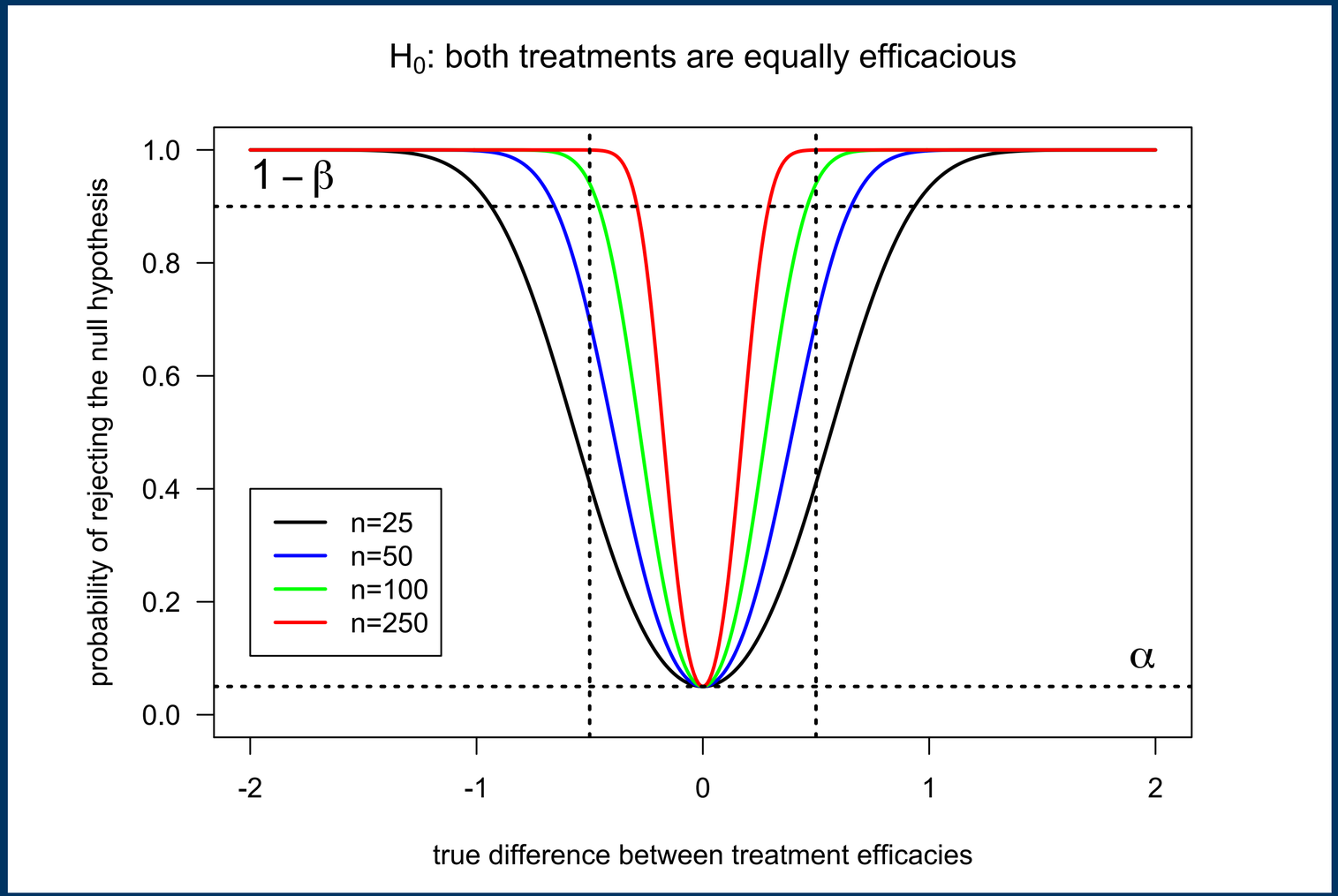
Biomarker is expected to be normally distributed in both treatments

$$H_0 : \mu_1 = \mu_2 \text{ versus } H_1 : \mu_1 \neq \mu_2$$

Which statistical test can we apply in this situation?

What is the sample size to detect an absolute difference between treatment effects of at least 0.5 with a minimum probability of 0.90?

Power analysis



Let’s go practical

PLOS ONE

RESEARCH ARTICLE

B-Lymphocyte Depletion in Myalgic Encephalopathy/ Chronic Fatigue Syndrome. An Open-Label Phase II Study with Rituximab Maintenance Treatment

Øystein Fluge[1]*, Kristin Risa[1], Sigrid Lunde[1], Kine Alme[1], Ingrid Gurvin Rekeland[1], Dipak Sapkota[1,2], Einar Kleboe Kristoffersen[3,4], Kari Sørland[1], Ove Bruland[1,5], Olav Dahl[1,4], Olav Mella[1,4]*

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2 Department of Clinical Medicine, University of Bergen, Haukeland University Hospital, Bergen, Norway,
3 Department of Immunology and Transfusion Medicine, Haukeland University Hospital, Bergen, Norway,
4 Department of Clinical Science, University of Bergen, Haukeland University Hospital, Bergen, Norway,
5 Department of Medical Genetics and Molecular Medicine, Haukeland University Hospital, Bergen, Norway

Abstract

Background

Myalgic Encephalopathy/Chronic Fatigue Syndrome (ME/CFS) is a disease of unknown etiology. We previously reported a pilot case series followed by a small, randomized, placebo-controlled phase II study, suggesting that B-cell depletion using the monoclonal anti-CD20 antibody rituximab can yield clinical benefit in ME/CFS.

Methods

In this single-center, open-label, one-armed phase II study (NCT01156909), 29 patients were included for treatment with rituximab (500 mg/m^2) two infusions two weeks apart, followed by maintenance rituximab infusions after 3, 6, 10 and 15 months, and with follow-up for 36 months.

Findings

Major or moderate responses, predefined as lasting improvements in self-reported *Fatigue score*, were detected in 18 out of 29 patients (intention to treat). Clinically significant responses were seen in 18 out of 28 patients (64%) receiving rituximab maintenance treatment. For these 18 patients, the mean response durations within the 156 weeks study period were 105 weeks in 14 major responders, and 69 weeks in four moderate responders. At end of follow-up (36 months), 11 out of 18 responding patients were still in ongoing clinical remission. For major responders, the mean lag time from first rituximab infusion until start of clinical response was 23 weeks (range 8–66). Among the nine patients from the placebo group in the previous randomized study with no significant improvement during 12

Determine the sample size of phase III trial

Phase I - Pilot study (optimal doses)

Phase II - Randomised clinical trials (Fluge et al)

Phase III - Pre-marketing (evaluation in clinical practice)

Phase IV - Post-marketing

Previous Lecture

Probability of clinical remission 11/29 (0.38; 38%)

95% CI = (0.20;0.58) Binom.test (0.21; 0.58) Prop.test

Question 1:

Probability of clinical remission 11/29 (0.38; 38%)

95% CI = (0.20;0.58) Binom.test (0.21; 0.58) Prop.test

What is the standard error of the sample proportion?

Question 1:

Probability of clinical remission 11/29 (0.38; 38%)

95% CI = (0.20;0.58) Binom.test (0.21; 0.58) Prop.test

What is the standard error of the sample proportion?

$$se(\hat{p}) = \sqrt{\frac{p \times (1-p)}{n}}$$

$$se(\hat{p}) = ?$$

Question 1:

Probability of clinical remission 11/29 (0.38; 38%)

95% CI = (0.20;0.58) Binom.test (0.21; 0.58) Prop.test

What is the standard error of the sample proportion?

$$se(\hat{p}) = \sqrt{\frac{p \times (1-p)}{n}}$$

$$se(\hat{p}) = 0.09$$

Why is the standard error so important?

Wald's confidence interval

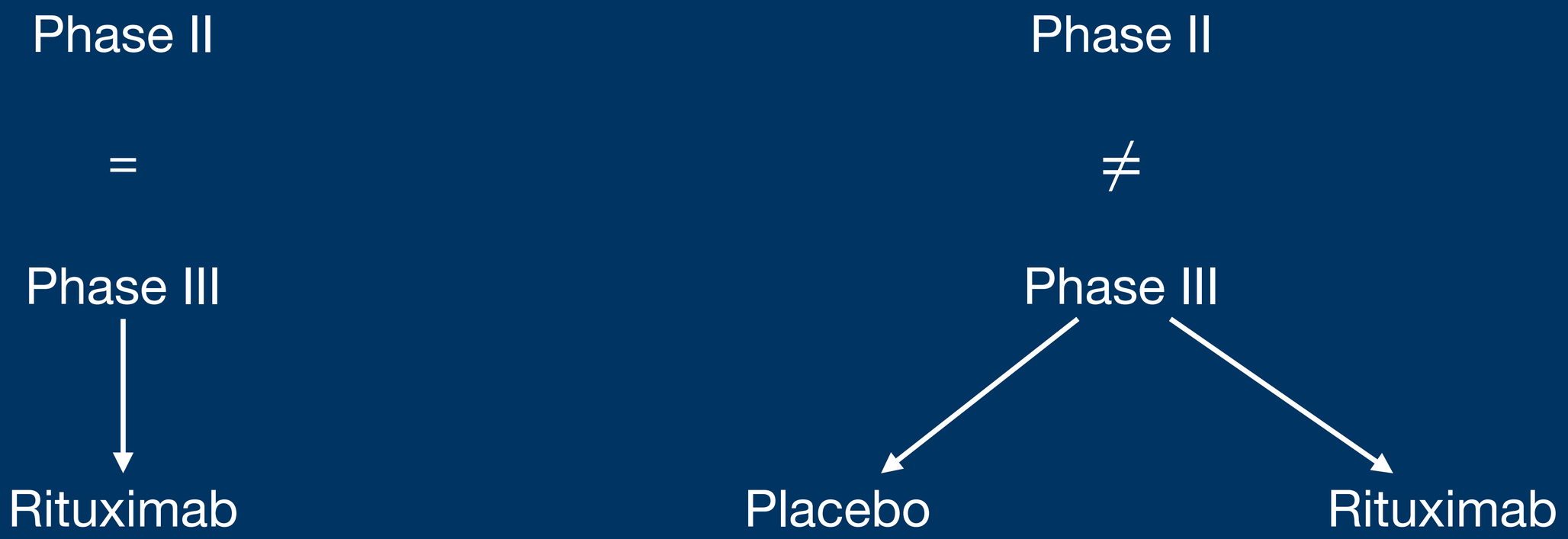
$$95\,\%\ CI(\hat{p}) = \hat{p} \pm 1.96 \times se(\hat{p})$$

$$95\,\%\ CI(\hat{p}) = 0.38 \pm 1.96 \times 0.09 = (0.20; 0.56)$$

$$\text{length of 95\% CI } (\hat{p}) = 2 \times 1.96 \times se(\hat{p}) = 2 \times 1.96 \times 0.09 = 0.35$$

"Precision"

Two possible study designs



Study design 1

Phase II

=

Phase III

Rituximab

Question:

What should be the statistical (or inferential) objective in this design?

Study design 1

Phase II

=

Phase III

Rituximab

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Possible objective:

What is the sample size that ensures the “precision” is less than 0.05?

Study design 1

Phase II

=

Phase III

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Can you translate this question in terms of standard error?

Study design 1

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=

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Study design 1

Phase II

=

Phase III

Rituximab

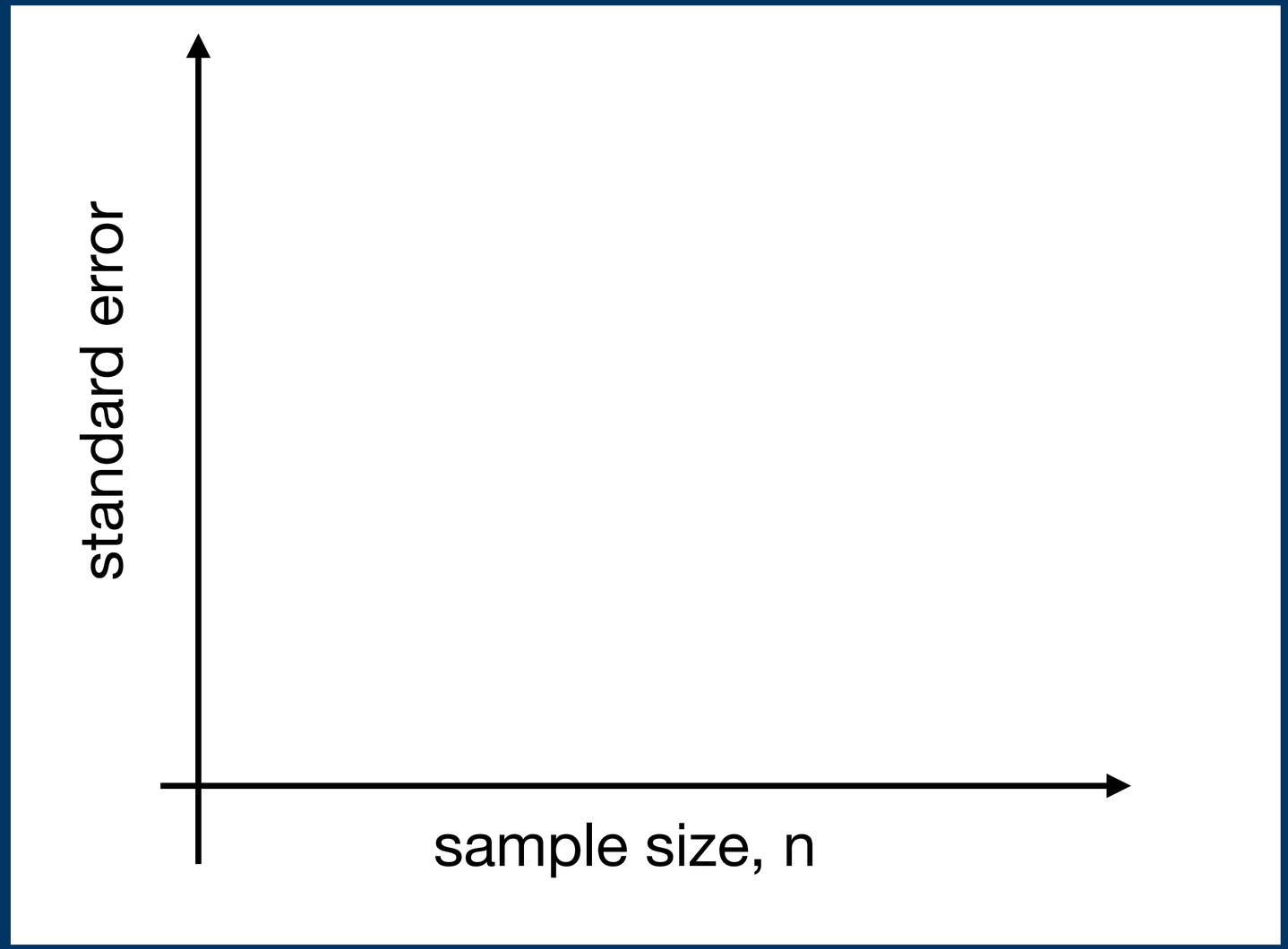
Question:

What should be the statistical (or inferential) objective in this design?

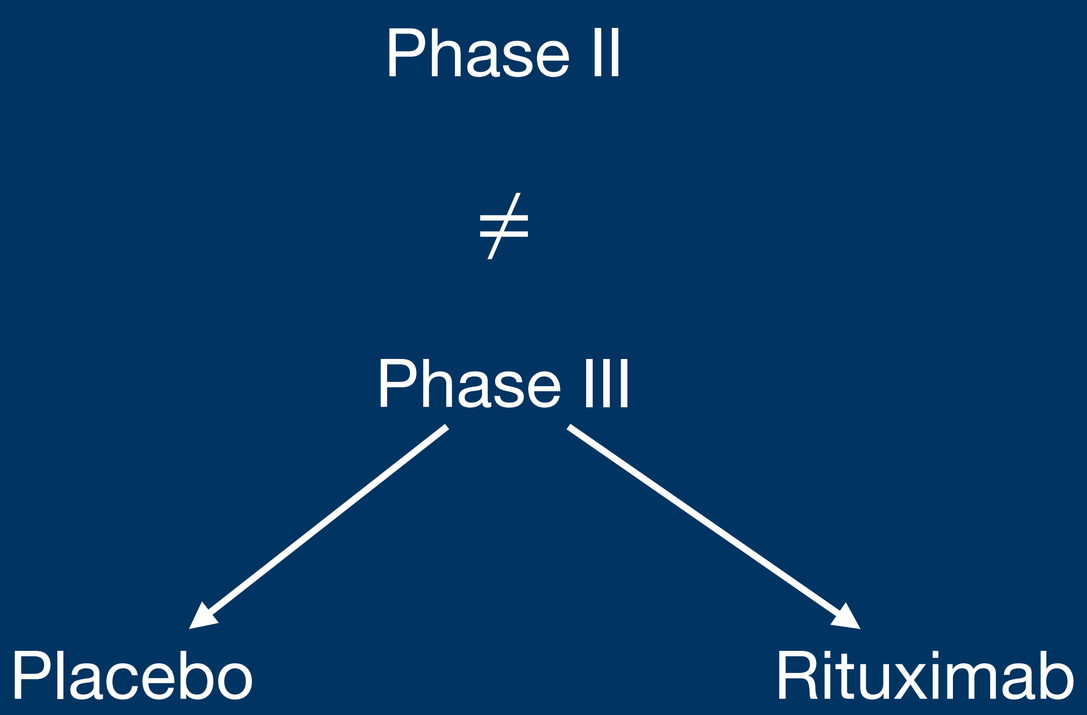
Possible objective:

What is the sample size that ensures the “standard error” is less than 0.013?

Go to R and construct this plot

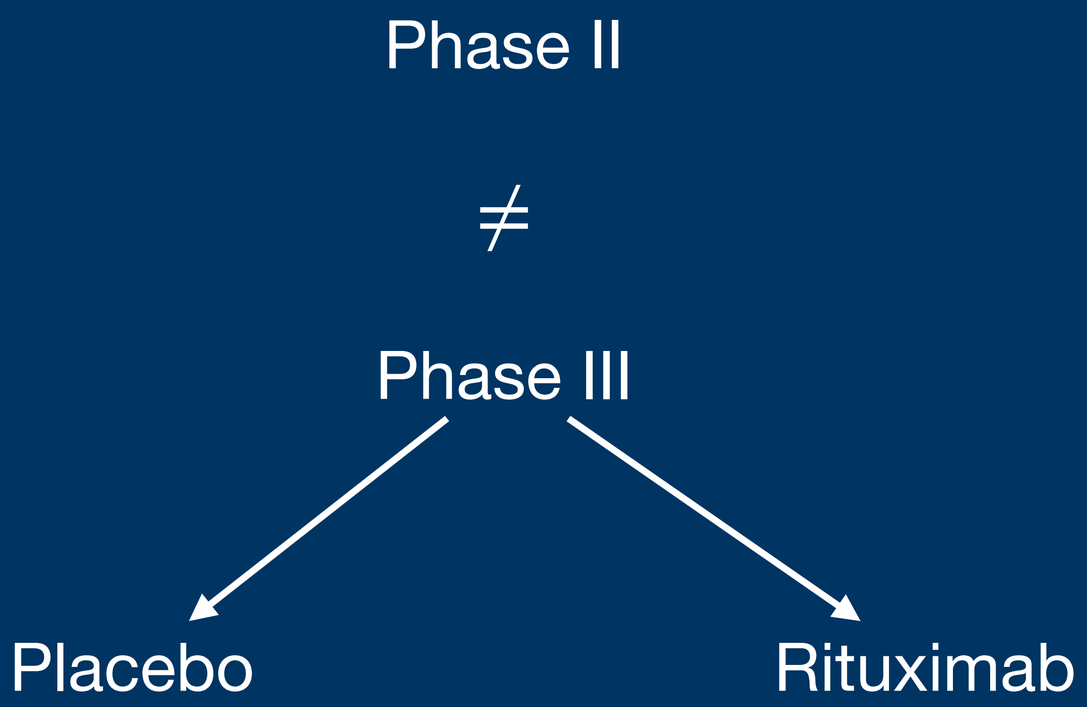


Study design 2



What is the null hypothesis under testing?

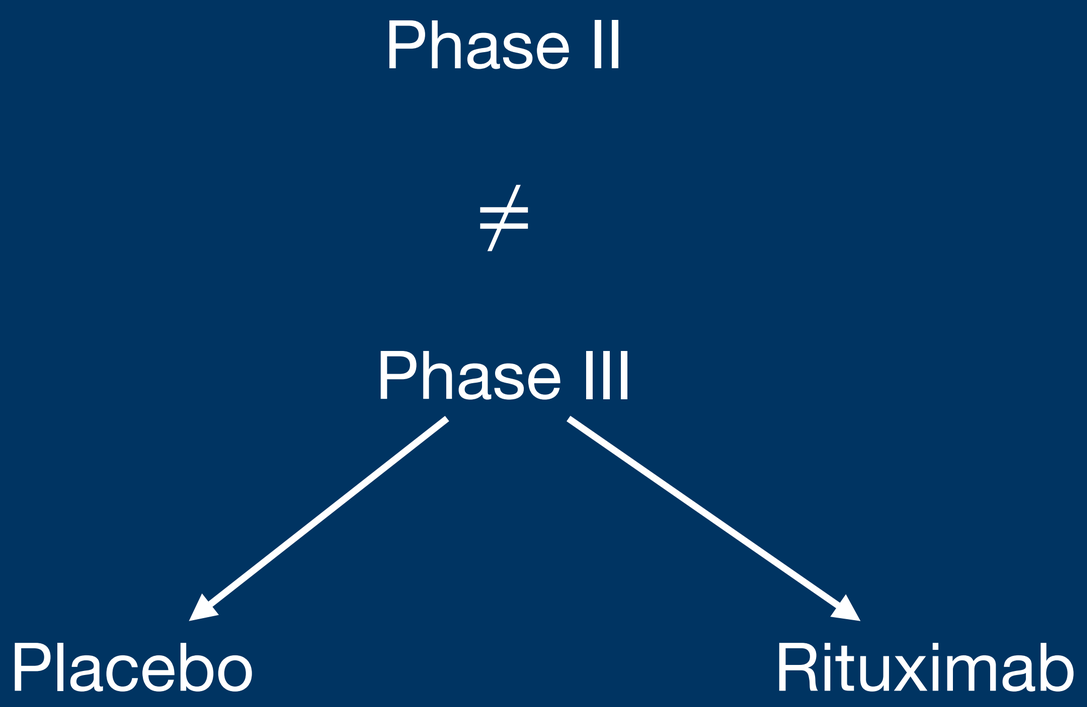
Study design 2



What is the null hypothesis under testing?

$$H_0 : \pi_{Rituximab} = \pi_{Placebo}$$

Study design 2



What is the null hypothesis under testing?

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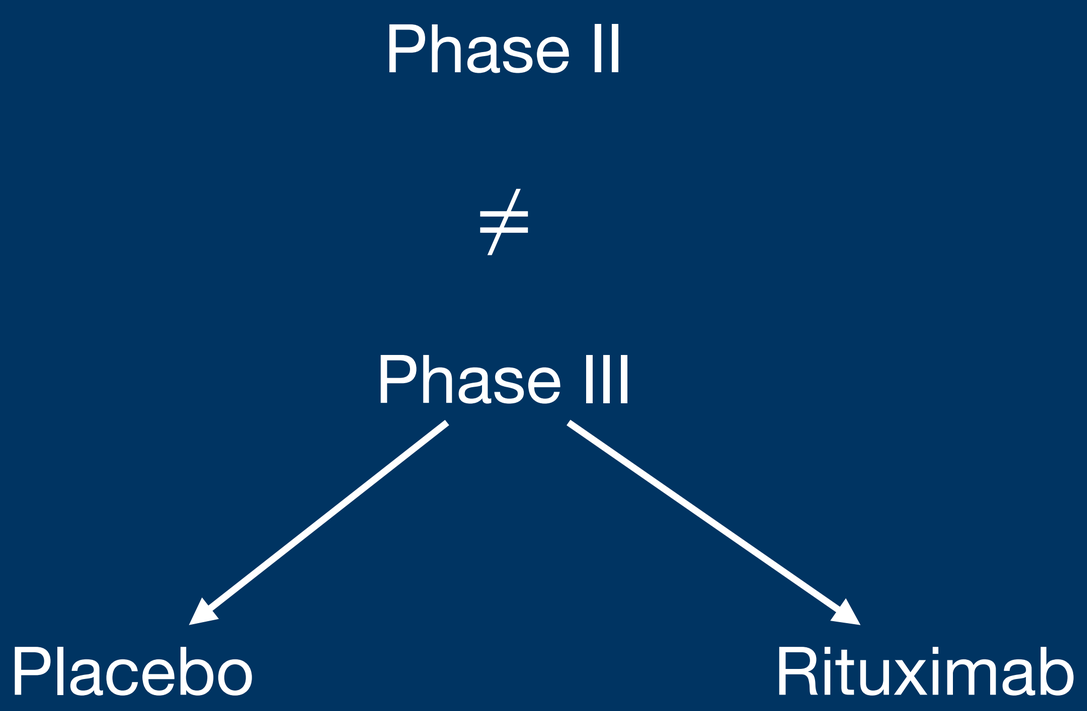
What is the alternative hypothesis?

Study design 2



What is the null hypothesis under testing?

$$H_0 : \pi_{Rituximab} = \pi_{Placebo}$$

What is the alternative hypothesis?

$$H_1 : \pi_{Rituximab} > \pi_{Placebo}$$

Sample size determination via power analysis

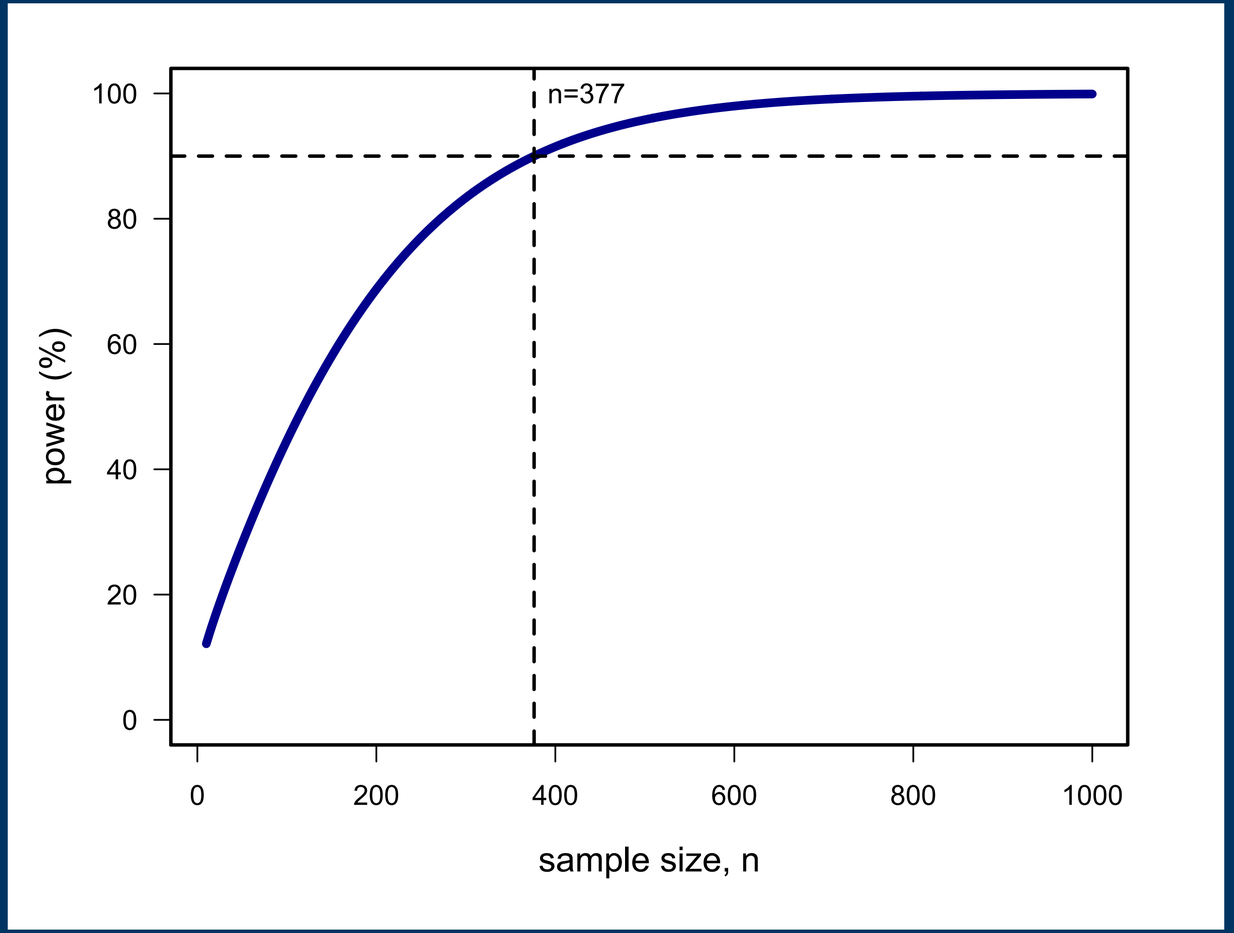
What is the sample size that ensure a power of at least 90% for the difference between success probabilities of Rituximab and placebo of at least 0.10?

$$H_0 : \pi_{Rituximab} - \pi_{Placebo} = 0 \text{ versus } H_1 : \pi_{Rituximab} - \pi_{Placebo} > 0.1$$

Go to R and use the function “pwr.2p.test” of the package “pwr”

What are the assumptions?

$$n_{Rituximab} = n_{Placebo}$$



total sample size=
377 + 377 = 754

Sample size determination via power analysis

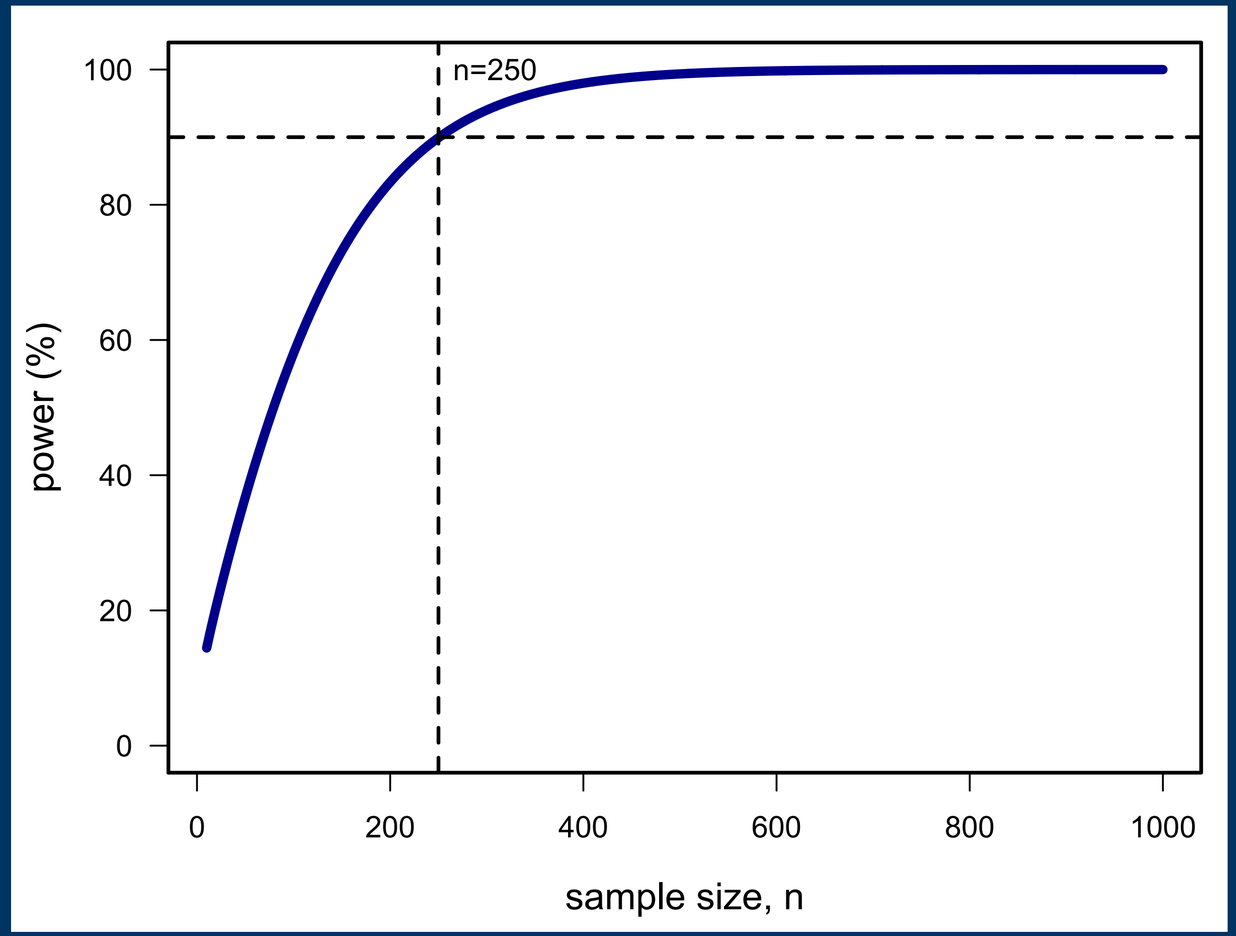
What is the sample size that ensure a power of at least 90% for the difference between success probabilities of Rituximab and Placebo of at least 0.10?

$$H_0 : \pi_{Rituximab} - \pi_{Placebo} = 0 \text{ versus } H_0 : \pi_{Rituximab} - \pi_{Placebo} > 0.1$$

Go to R and use the function “pwr.2p2n.test” of the package “pwr”

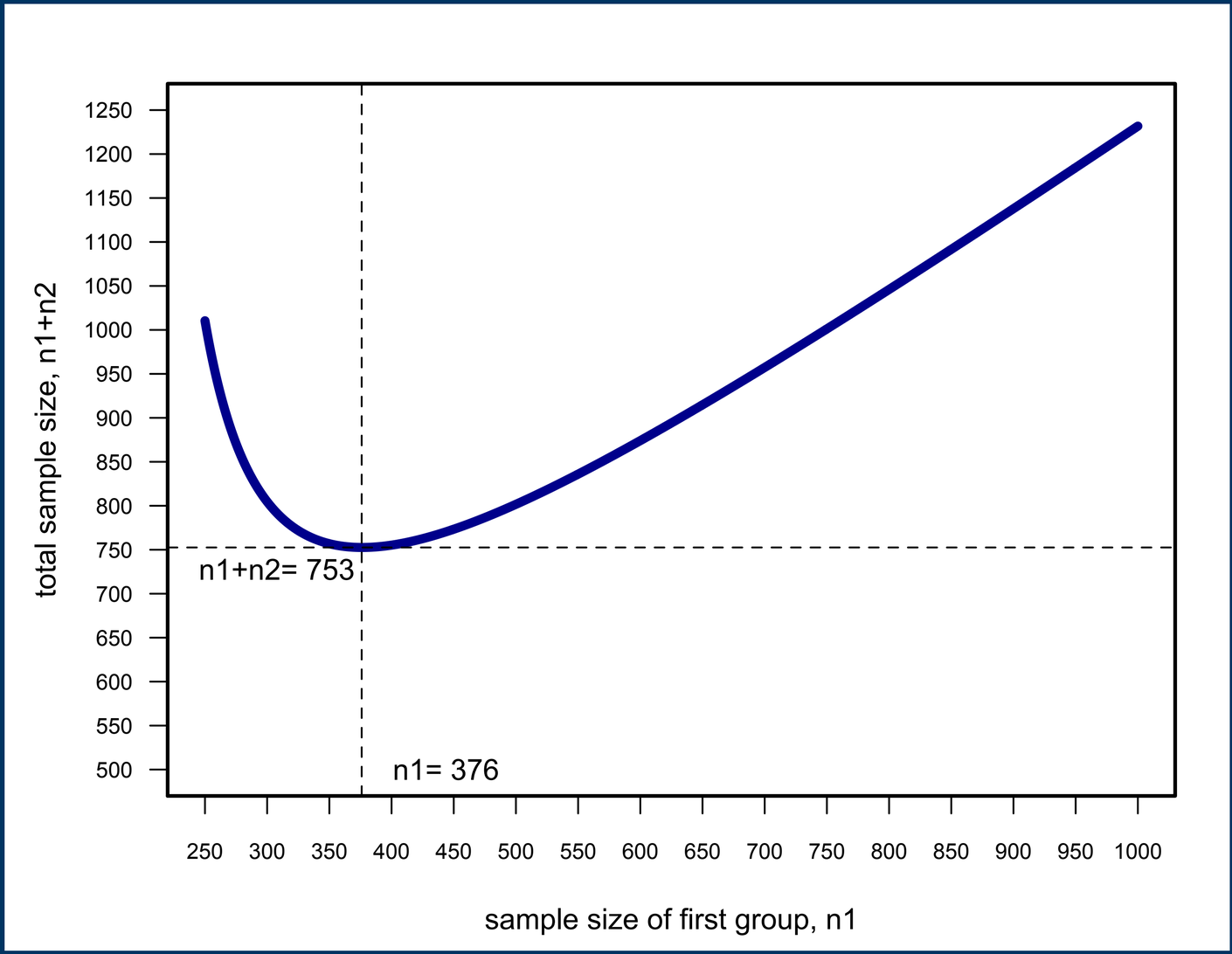
$$n_{Rituximab} = 3 \times n_{Placebo}$$

$$n_{Rituximab} = 3n_{Placebo}$$



total sample size=
750 + 250 = 1000

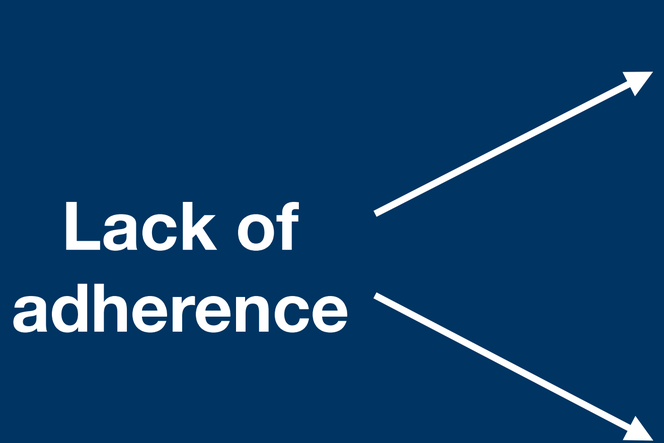
Optimal design



What are the different CT phases doing to the statistical power?

In practice

The theoretical sample size needs to be corrected (increased) for lack of adherence



Missing data

Endpoint is not observed

Censored data

Endpoint is partially observed

Time-to-event clinical trials

Type of analysis

Intention-to-treat

Statistical analysis following the study protocol

What do you think about the success rate for a new drug/ intervention being approved by FDA or similar entity?

Research

JAMA Internal Medicine | Original Investigation

Failure of Investigational Drugs in Late-Stage Clinical Development and Publication of Trial Results

Thomas J. Hwang, AB; Daniel Carpenter, PhD; Julie C. Lauffenburger, PharmD, PhD; Bo Wang, MD, PharmD; Jessica M. Franklin, PhD; Aaron S. Kesselheim, MD, JD, MPH

Table 1. Characteristics of Novel Drugs and Biologics Entering Pivotal Trials, 1998-2008

Novel Drugs and Biologics (n = 640)	No. (%)
Approval status	
Approved in United States	230 (35.9)
Approved in the Europe, Japan, Canada, or Australia but not in United States	49 (7.6)
Approved in other countries but not in the United States, Europe, Japan, Canada, or Australia	17 (2.7)
Unapproved	344 (53.8)

Table 2. Reasons for Failure of Late-Stage Clinical Development of Experimental Agents, Stratified by Agent Characteristics

Characteristic	Reason for Failure, No. (%)				Failures From Any Cause, No. (%)
	Efficacy	Safety	Commercial	Unknown	
All (n = 344)	195 (56.7)	59 (17.2)	74 (21.5)	16 (4.7)	344 (100)
ATC therapeutic area					
Alimentary	21 (46.7)	11 (24.4)	10 (22.2)	3 (6.7)	45 (13.1)
Cardiovascular	24 (45.3)	14 (26.4)	11 (20.8)	4 (7.5)	53 (15.4)
Genitourinary	4 (30.8)	3 (23.1)	5 (38.5)	1 (7.7)	13 (3.8)
Infectious disease	18 (50.0)	8 (22.2)	10 (27.8)	NA	36 (10.5)
Cancer	65 (63.7)	12 (11.8)	24 (23.5)	1 (1.0)	102 (29.7)
Musculoskeletal	9 (45.0)	2 (10.0)	4 (20.0)	5 (25.0)	20 (5.8)
Neurologic	37 (71.2)	6 (11.5)	7 (13.5)	2 (3.8)	52 (15.2)
Respiratory	10 (83.3)	1 (8.3)	1 (8.3)	NA	12 (3.5)
Sensory and other	7 (63.6)	2 (18.2)	2 (18.2)	NA	11 (3.2)
Agent type					
Biologic	59 (55.7)	14 (13.2)	29 (27.4)	4 (3.8)	106 (30.8)
Pharmacologic	136 (57.1)	45 (18.9)	45 (18.9)	12 (5.0)	238 (69.2)
Sponsor firm					
Small, <US$1B	87 (52.1)	18 (10.8)	53 (31.7)	9 (5.4)	167 (48.5)
Large, ≥US$1B	108 (61.0)	41 (23.2)	21 (11.9)	7 (4.0)	177 (51.5)
Orphan designation					
Yes	43 (70.5)	6 (9.8)	12 (19.7)	NA	61 (17.7)
No	152 (53.7)	53 (18.7)	62 (21.9)	16 (5.7)	283 (82.3)
Regulatory fast track					
Yes	39 (67.2)	9 (15.5)	10 (17.2)	NA	58 (16.9)
No	156 (54.5)	50 (17.5)	64 (22.4)	16 (5.6)	286 (83.1)
Novel pathway					
Yes	128 (59.8)	33 (15.4)	45 (21.0)	8 (3.7)	214 (62.2)
No	67 (51.5)	26 (20.0)	29 (22.3)	8 (6.2)	130 (37.8)

Many clinical trials fail!!!
In which phase?

An Example from the Real World

High Selenium Levels

Protection against Prostate Cancer

SELECT trial

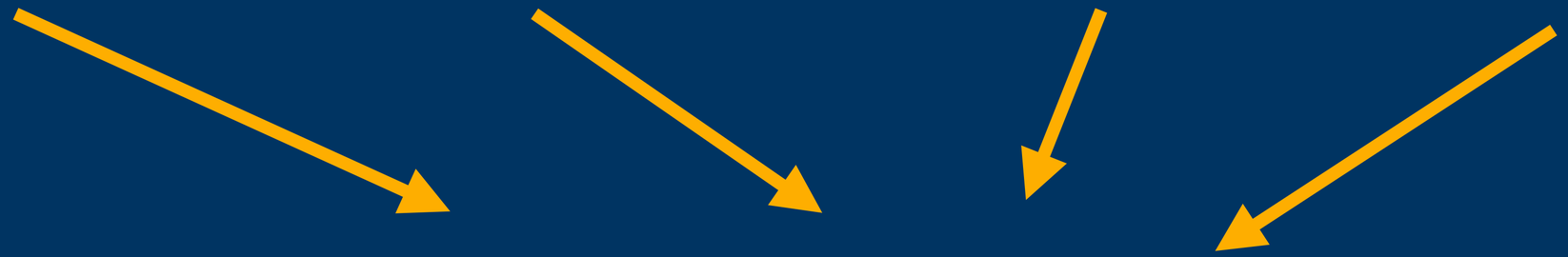
427 participating sites

Placebo
n=8696

Vitamin E
n=8737

Selenium
n=8752

Vitamin E + Selenium
n=8703



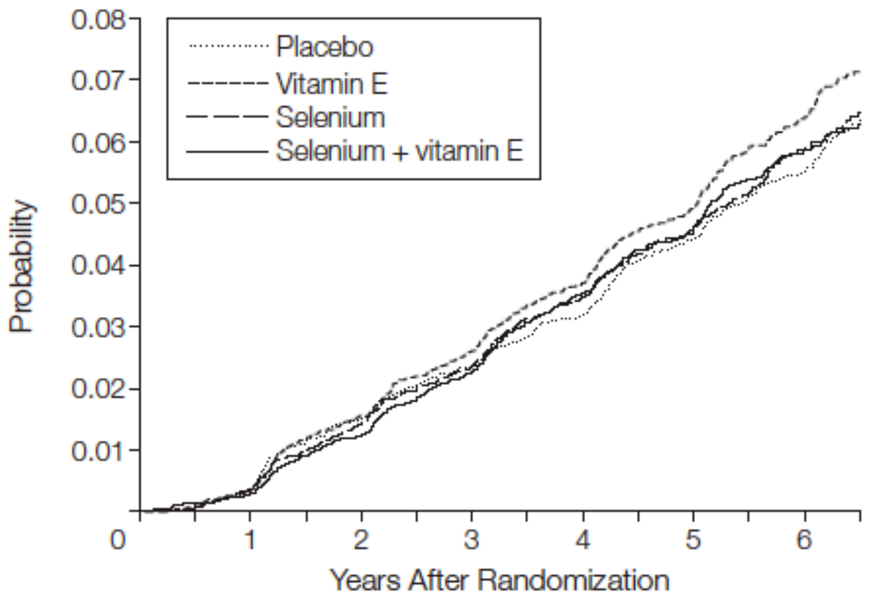
Follow-ed up 7 to 12 years

Developed or not Prostate Cancer

Lippman et al (2009), JAMA 301:39

Disappointment!

Figure 2. Cumulative Incidence of Prostate Cancer Detected Each Year by Intervention Group



No. at risk							
Placebo	8689	8553	8328	8039	7389	4892	2516
Vitamin E	8732	8610	8373	8098	7401	4867	2537
Selenium	8750	8597	8341	8083	7393	4848	2558
Selenium + vitamin E	8700	8585	8371	8097	7428	4894	2580

Compared with placebo, there was a statistically nonsignificant increase in prostate cancer in the vitamin E group (P=.06) and not in the selenium + vitamin E group (P=.52) or the selenium group (P=.62).

How to increase clinical trial reproducibility?

The use of Mendelian Randomisation in clinical trials

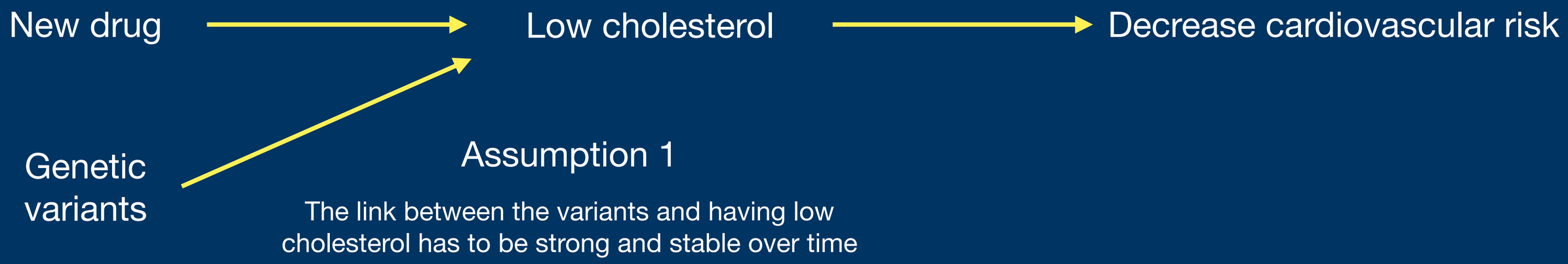
Use of genetic variants as instrumental variables or covariates

The use of Mendelian Randomisation in clinical trials

Use of genetic variants as instrumental variables or covariates

The use of Mendelian Randomisation in clinical trials

Use of genetic variants as instrumental variables or covariates



The use of Mendelian Randomisation in clinical trials

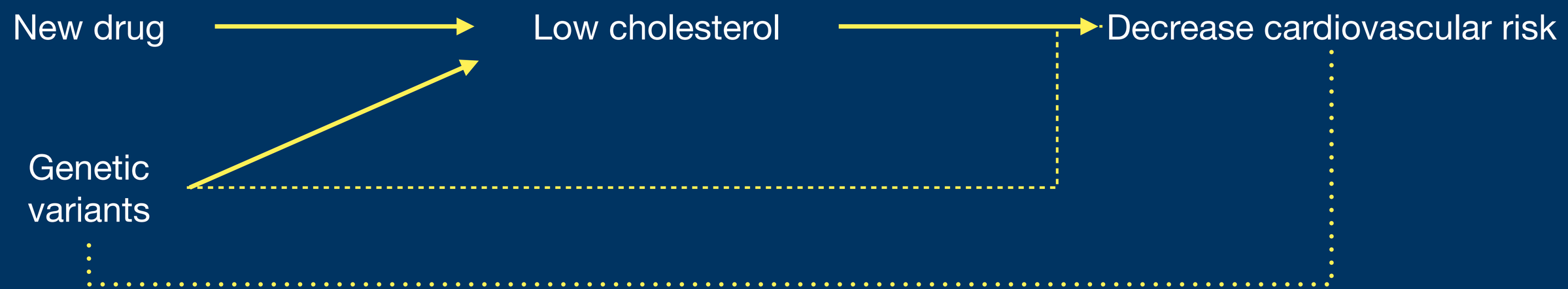
Use of genetic variants as instrumental variables or covariates

Assumption 2

The variants must not influence variables that might affect both cholesterol levels and CVD risk

The use of Mendelian Randomisation in clinical trials

Use of genetic variants as instrumental variables or covariates

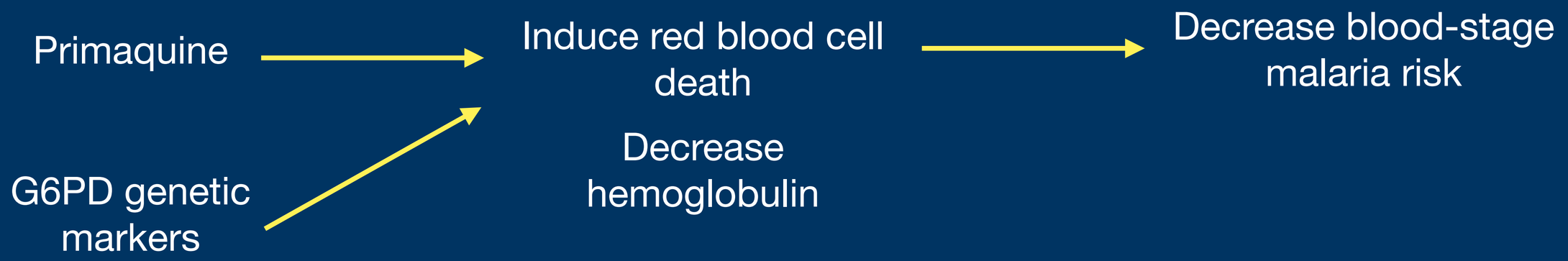


Assumption 3

The variants must not be associated with CVD risk in any other way than through the relationship to cholesterol

Primaquine and Malaria

Use of genetic variants as instrumental variables or covariates



G6PD = glucose-6-phosphate dehydrogenase

Single dose primaquine for clearance of *Plasmodium falciparum* gametocytes in children with uncomplicated malaria in Uganda: a randomised, controlled, double-blind, dose-ranging trial

Alice C Eziefula, Teun Bousema, Shunmay Yeung, Moses Kamya, Asiphas Owaraganise, Grace Gabagaya, John Bradley, Lynn Grignard, Kjerstin H W Lanke, Humphrey Wanzira, Arthur Mpimbaza, Samuel Nsobya, Nicholas J White, Emily L Webb, Sarah G Staedke, Chris Drakeley

Let’s go to R

Variables

Treatment = Primaquine Dose (in mg/kg) - 0, 0.1, 0.4, 0.75

Age (in years)

Gender (1= male, 2= female)

rs1050828 (G6PD genetic variant 1, CC, TC, TT)

rs1050829 (G6PD genetic variant 2, CC, TC, TT)

pf.d0 = parasite density at day 0

clear.inf.d7 = clearance of infection at day 7 (0=No, 1=Yes)

Let’s go to R

Is Primaquine efficacious under a Mendelian randomisation using G6PD deficiency variants?

Project 1

The effect of metformin on SIRT1 activation for increasing longevity using a phase 0 trial (proof-of-concept)

nature COMMUNICATIONS

ARTICLE

Received 2 Nov 2012 | Accepted 26 Jun 2013 | Published 30 Jul 2013

DOI: 10.1038/ncomms3192

Metformin improves healthspan and lifespan in mice

Alejandro Martin-Montalvo[1,*], Evi M. Mercken[1,*], Sarah J. Mitchell[1,2,3], Hector H. Palacios[1], Patricia L. Mote[4], Morten Scheibye-Knudsen[5], Ana P. Gomes[6], Theresa M. Ward[1], Robin K. Minor[1], Marie-José Blouin[7], Matthias Schwab[8], Michael Pollak[7], Yongqing Zhang[9], Yinbing Yu[10], Kevin G. Becker[9], Vilhelm A. Bohr[5], Donald K. Ingram[11], David A. Sinclair[6], Norman S. Wolf[12], Stephen R. Spindler[4], Michel Bernier[1] & Rafael de Cabo[1]

GEO dataset: GSE40936

Project 2

The effect of diet/lifestyle intervention on ageing

www.aging-us.com AGING 2021, Vol. 13, No. 7

Research Paper

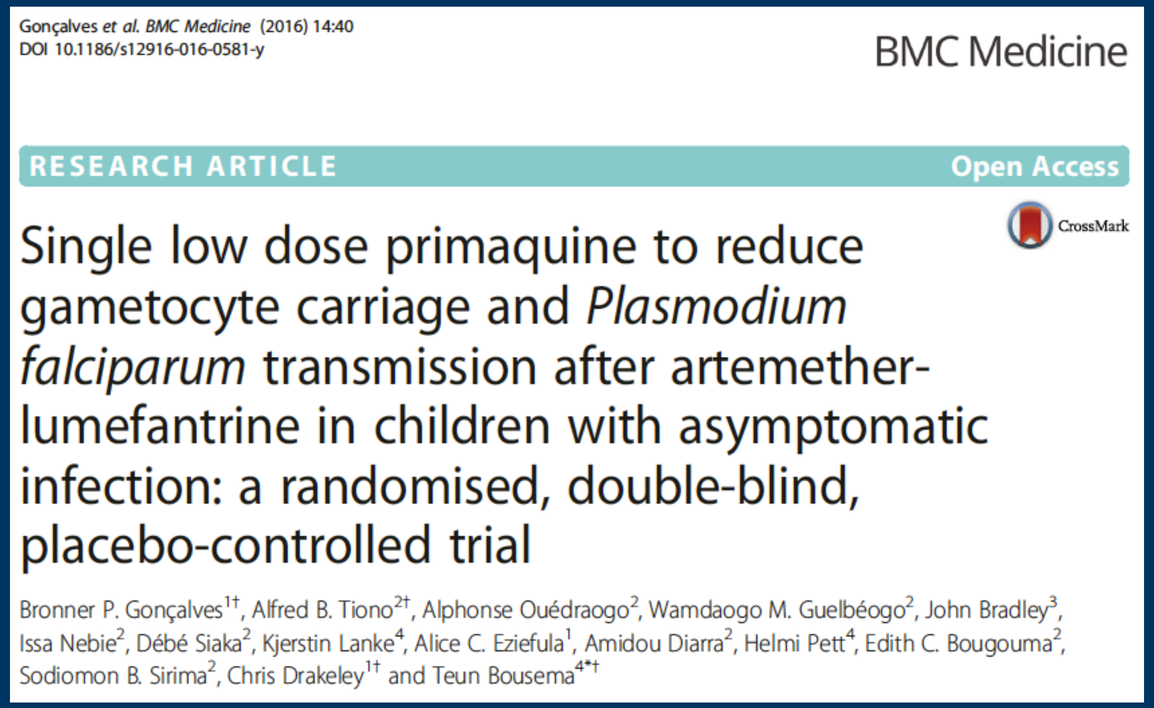
Potential reversal of epigenetic age using a diet and lifestyle intervention: a pilot randomized clinical trial

Kara N. Fitzgerald[1], Romilly Hodges[2], Douglas Hanes[3], Emily Stack[4], David Cheishvili[5], Moshe Szyf[6], Janine Henkel[7], Melissa W. Twedt[7], Despina Giannopoulou[7], Josette Herdell[7], Sally Logan[7], Ryan Bradley[7,8]

GEO dataset: GSE149747

Project 3

Malaria and the efficacy and safety of low-dose primaquine.



Gonçalves *et al. BMC Medicine* (2016) 14:40
DOI 10.1186/s12916-016-0581-y

BMC Medicine

RESEARCH ARTICLE Open Access

Single low dose primaquine to reduce gametocyte carriage and *Plasmodium falciparum* transmission after artemether-lumefantrine in children with asymptomatic infection: a randomised, double-blind, placebo-controlled trial

Bronner P. Gonçalves[1†], Alfred B. Tiono[2†], Alphonse Ouédraogo[2], Wamdaogo M. Guelbéogo[2], John Bradley[3], Issa Nebie[2], Débé Siaka[2], Kjerstin Lanke[4], Alice C. Eziefula[1], Amidou Diarra[2], Helmi Pett[4], Edith C. Bougouma[2], Sodiomon B. Sirima[2], Chris Drakeley[1†] and Teun Bousema[4*†]