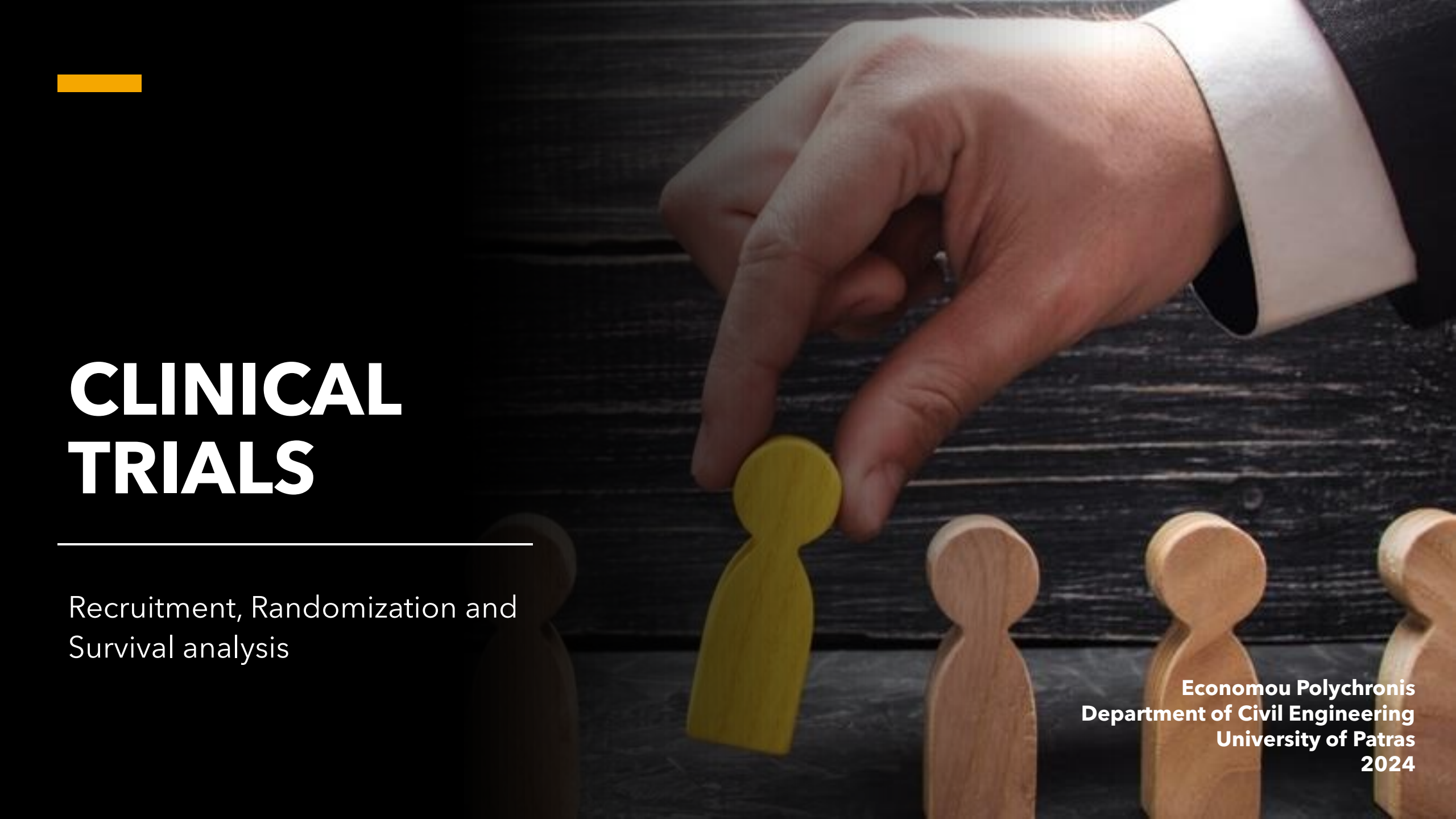
CLINICAL TRIALS

Recruitment, Randomization and Survival analysis



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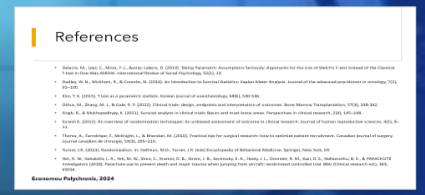
2024

Outline



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Recruitment in clinical trials

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Patient recruitment

- One of the most common problems in Clinical Trials
  - Ambitious recruitment is often misguided
  - Investigators often greatly overestimate the pool of available patients who meet the inclusion criteria

- **Recruitment rate** is influenced by both
  - patient and
  - investigator factors

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Reasons why eligible patients refuse to participate in Clinical Trials

- preference for a certain therapy patients
- did not understand the trial (trial too complex)
- did not want to be randomly assigned to a treatment
- feared a negative outcome or receiving a treatment that he/she felt was inferior for patients

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Reasons why Investigators do not recruit eligible patients to Clinical Trials

- difficulty following the study protocol
- difficulty completing the follow-up requirements
- preference for a certain therapy
- difficulties obtaining informed consent from patients.

Weak or misleading clinical trial evidences

Poor patient recruitment can lead to weak or misleading conclusions.

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Parachute use to prevent death and major trauma when jumping from aircraft

Abstract

- **Objective** To determine if using a parachute prevents death or major traumatic injury when jumping from an aircraft.
- **Design** Randomized controlled trial.
- **Setting** Private or commercial aircraft between September 2017 and August 2018.
- **Participants** 92 aircraft passengers aged 18 and over were screened for participation. 23 agreed to be enrolled and were randomized.
- **Intervention** Jumping from an aircraft (airplane or helicopter) with a parachute versus an empty backpack (unblinded).
- **Main outcome measures** Composite of death or major traumatic injury (defined by an Injury Severity Score over 15) upon impact with the ground measured immediately after landing.
- **Results** Parachute use did not significantly reduce death or major injury

Yeh R W, Valsdottir L R, Yeh M W, Shen C, Kramer D B, Strom J B et al. ***Parachute use to prevent death and major trauma when jumping from aircraft: randomized controlled trial,*** *BMJ* 2018; 363:k5094

Parachute use to prevent death and major trauma when jumping from aircraft

Abstract

Conclusions

Parachute use **did not reduce death or major traumatic** injury when jumping from aircraft in the first randomized evaluation of this intervention.

However, the trial was only **able to enroll participants on small stationary aircraft on the ground**, suggesting cautious extrapolation to high altitude jumps.

When beliefs regarding the effectiveness of an intervention exist in the community, randomized trials might selectively enroll individuals with a lower perceived likelihood of benefit, thus diminishing the applicability of the results to clinical practice.

Yeh R W, Valsdottir L R, Yeh M W, Shen C, Kramer D B, Strom J B et al. ***Parachute use to prevent death and major trauma when jumping from aircraft: randomized controlled trial,*** *BMJ* 2018; 363:k5094

Strategies to avoid common pitfalls in patients' recruitment

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STUDY PROTOCOL PHASE

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STUDY PROTOCOL PHASE

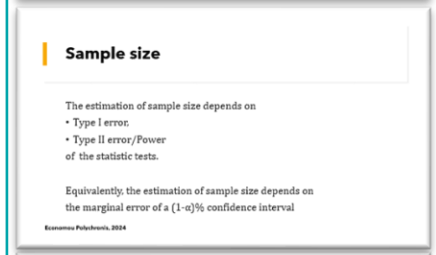
Key elements

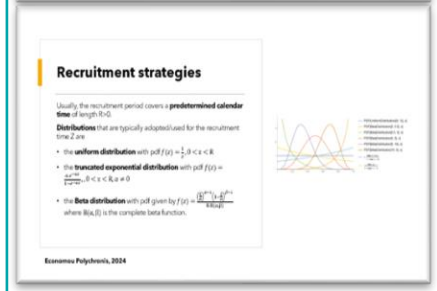
- **Type of trial (explanatory v. effectiveness)**
  Decide if the trial will be an explanatory (efficacy) or a management (effectiveness, pragmatic) trial

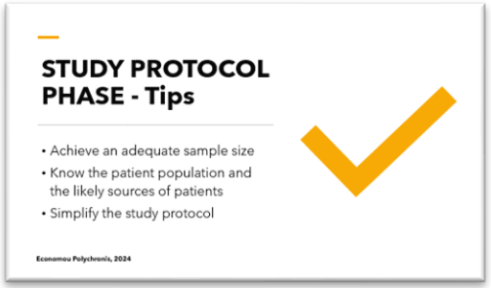
- ***Sample size***
  - Analyze power
  - Account drop out or lost to follow up rate

- **Recruitment strategies**
  - All at once at the start
  - Entering in batch mode
  - Continuously until the desire sample size
  - Until a fixed date
    - Uniformly
    - Decreasing rate
    - Increasing rate
    - …

- **Feasibility issues**
  - Determine source of patients







Efficacy vs Effectiveness trials

- **Efficacy trials (explanatory trials)** determine whether an intervention produces the expected result under **ideal circumstances.**

- **Effectiveness trials (pragmatic trials)** measure the degree of beneficial effect under **“real world” clinical settings**.

Sample size

The estimation of sample size depends on

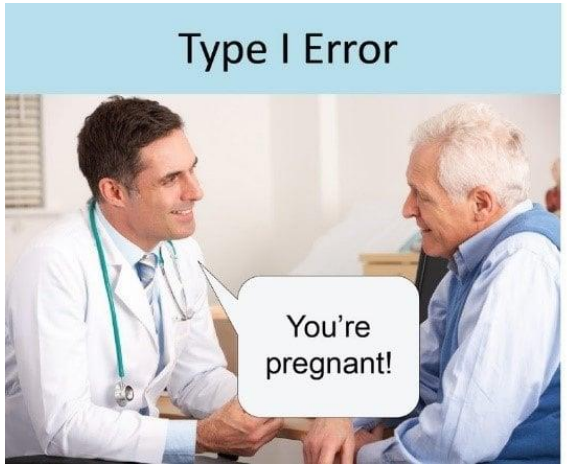
- Type I error,
- Type II error/Power

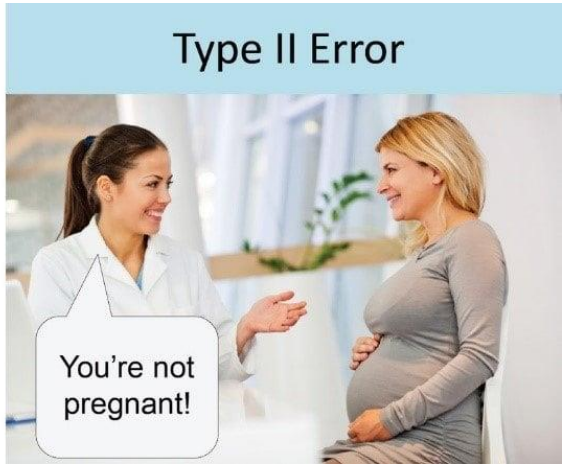
of the statistic tests.

Equivalently, the estimation of sample size depends on the marginal error of a (1-α)% confidence interval

Type I and Type II error and Power

		The truth	
		H_0 is true	**H_0 is false**
Result of the hypothesis test	**Fail to reject H_0**	Correct $1-\alpha$	Type II error (false negative) β
	Reject H_0	Type I error (false positive) size (α)	Correct power ($1-\beta$)





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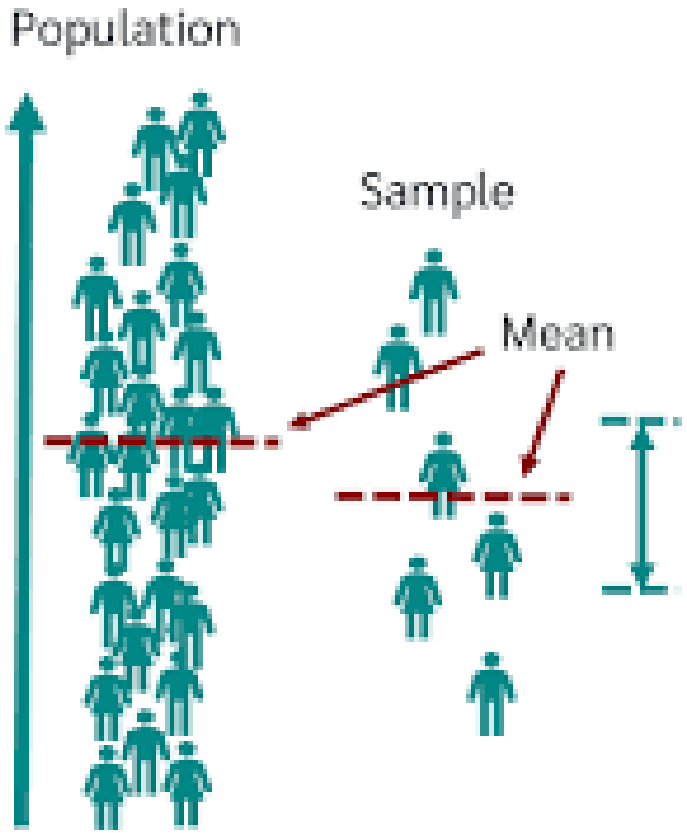
Confidence intervals



A 95% Confidence interval

Interpretation

-) Under repeated samples or experiments, 95% of the resultant intervals would contain the unknown parameter in question

-) We are 95% confident that the unknown parameter is in this interval

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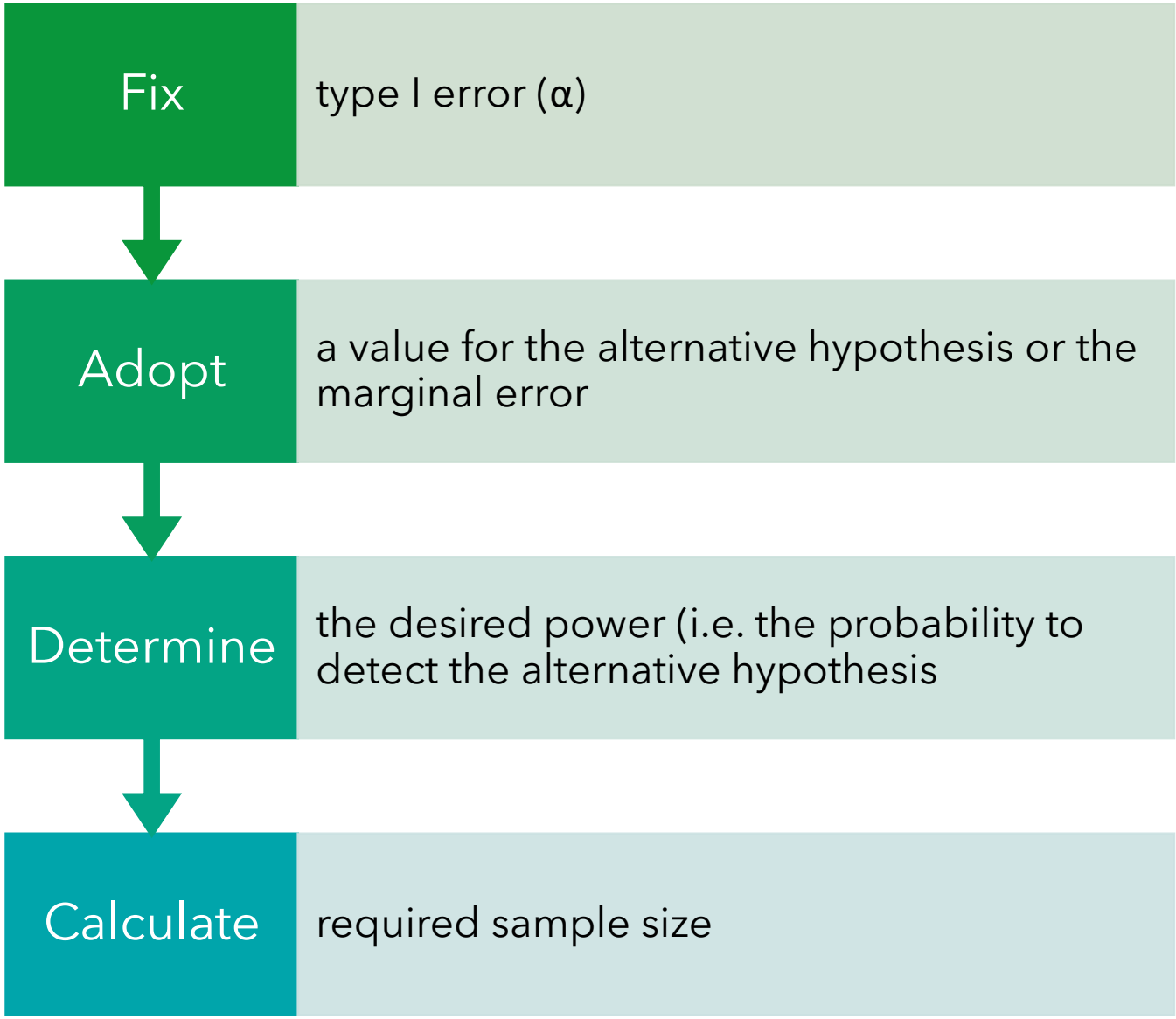
Determine sample size



Example

The reduction of LDL-Cholesterol levels is a major target for the prevention of cardiovascular disease.
A new drug is going to tested in patients with high levels of LDL-Cholesterol.
The main target of the study is to determine the percentage of patients that will reduce their LDL-Cholesterol more than 20 units.

How many people should be sampled so that the margin of error is (maximum) d=1% with 95% confidence?

Solution

1) Use an educated guess for the sample proportion: $\hat{p}$ = 0.3

$$n = \frac{\hat{p}(1-\hat{p})\, z_{a/2}^2}{d^2} = \frac{0.3(1-0.7)\, 1.96^2}{0.01^2} = 8067.36 \rightarrow 8067$$

2) Use a conservative approach

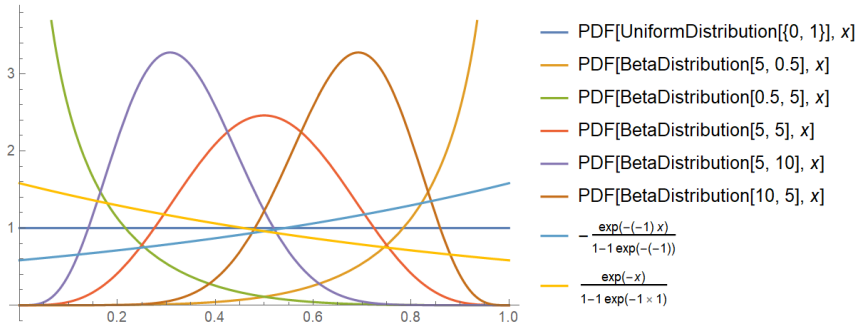
$$n = \frac{0.5(1-0.5)\, 1.96^2}{0.01^2} = 9604$$

Recruitment strategies

Usually, the recruitment period covers a **predetermined calendar time** of length R>0.

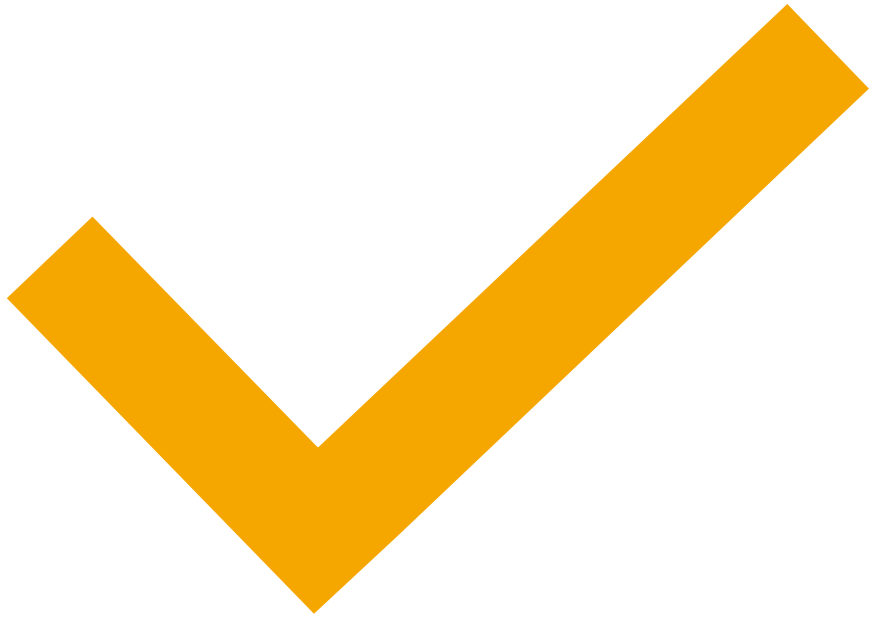
Distributions that are typically adopted/used for the recruitment time Z are

- the **uniform distribution** with pdf $f(z) = \frac{1}{z}, 0 < \mathrm{z} < \mathrm{R}$
- the **truncated exponential distribution** with pdf $f(z) = \frac{a\, e^{-az}}{1-e^{-az}}, , 0 < \mathrm{z} < \mathrm{R}, a \neq 0$
- the **Beta distribution** with pdf given by $f(z) = \frac{\left(\frac{z}{R}\right)^{\alpha-1}\left(1-\frac{z}{R}\right)^{\beta-1}}{\mathrm{R\ B}(\alpha,\beta)}$ where $\mathrm{B}(\alpha, \beta)$ is the complete beta function.



STUDY PROTOCOL PHASE - Tips

- Achieve an adequate sample size
- Know the patient population and the likely sources of patients
- Simplify the study protocol



STUDY CONDUCT PHASE

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Possible issues

Protocol- or trial-specific recruitment issues

Staff- and site-specific recruitment issues

Patient-related recruitment issues

Possible solutions

01

Re-evaluate the inclusion and exclusion criteria if recruitment is low

02

Increase the duration of recruitment or leave it open

03

Identify sites with consistently low recruitment and address the site-specific problems. Add new investigators and sites if necessary

04

Provide incentives to maintain investigator interest

05

Spend adequate time with patients and answer any questions they have about the study

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STUDY FOLLOW-UP PERIOD

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STUDY FOLLOW-UP PERIOD

Loss to follow-up

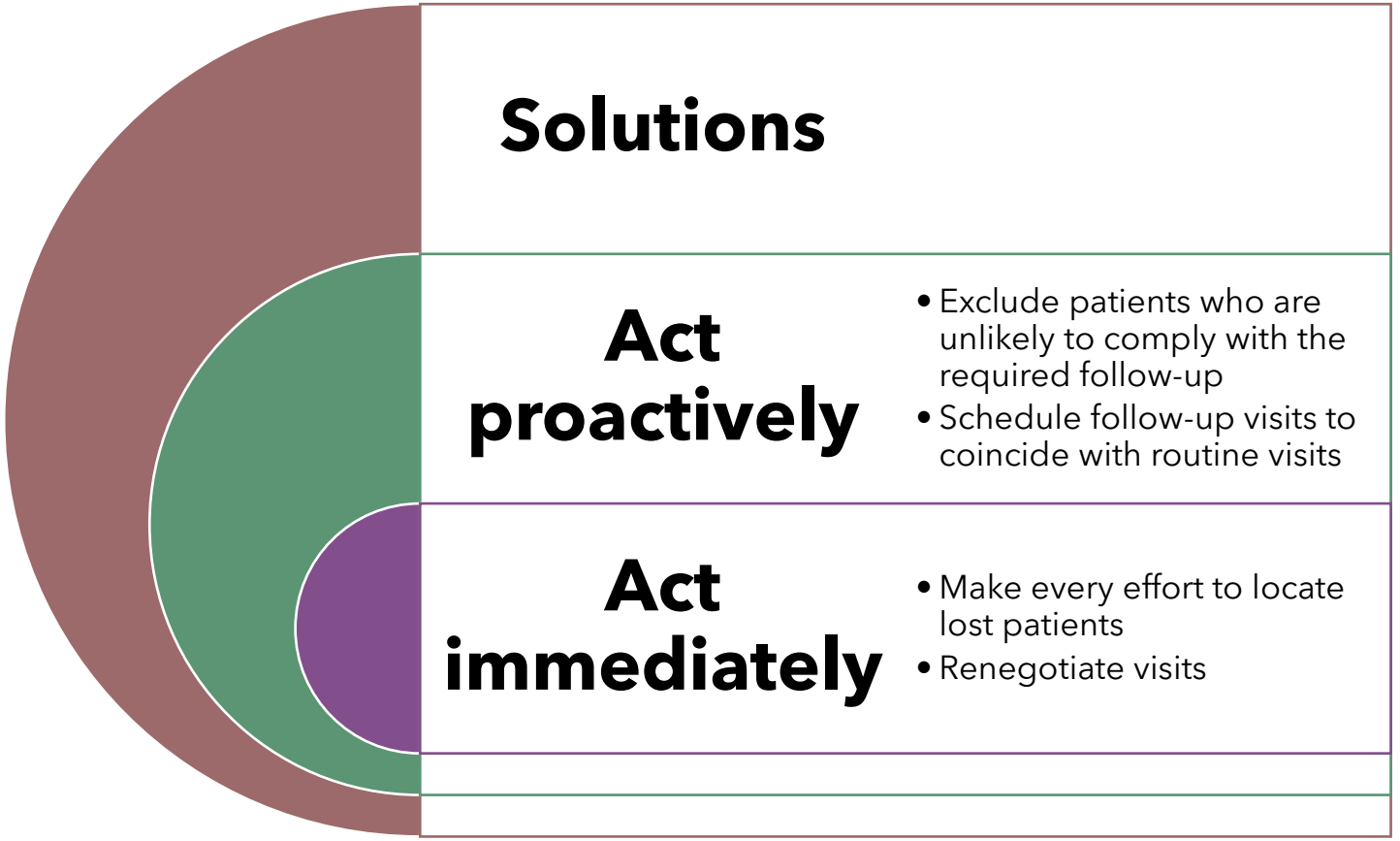
Reasons

- opt to withdraw from the clinical trial
- move away from the particular study site
- become ill and unable to communicate
- are deceased

Results

- reduce the effective sample size
- introduce bias

STUDY FOLLOW-UP PERIOD



Randomization in clinical trials

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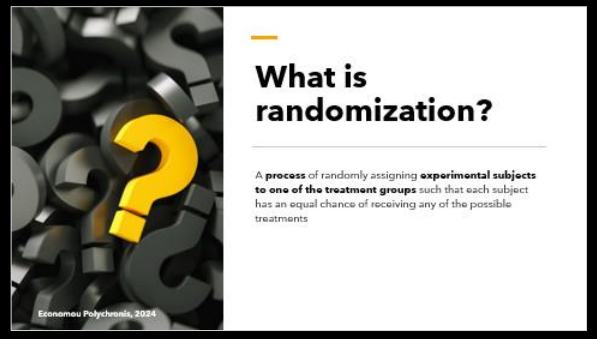
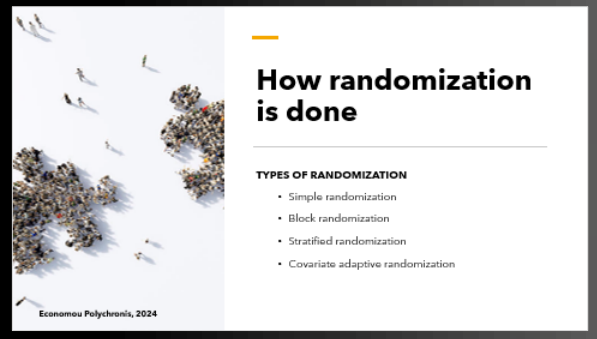
What
Why
When
How





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What is randomization?

A **process** of randomly assigning **experimental subjects to one of the treatment groups** such that each subject has an equal chance of receiving any of the possible treatments

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Why randomization is important

1) **Avoids selection bias** in subject assignment

2) **Controls any lurking variable** and establish a cause-and-effect relationship.

Lurking variable: Potential influences that

- cannot be controlled (e.g., height, weight) or
- cannot be determined by observation (e.g., specific metabolic pathway that influences in pharmaceutical clinical trials)

When randomization is adopted, these variables are likely to have the same distribution in one treatment group as they have in the other.

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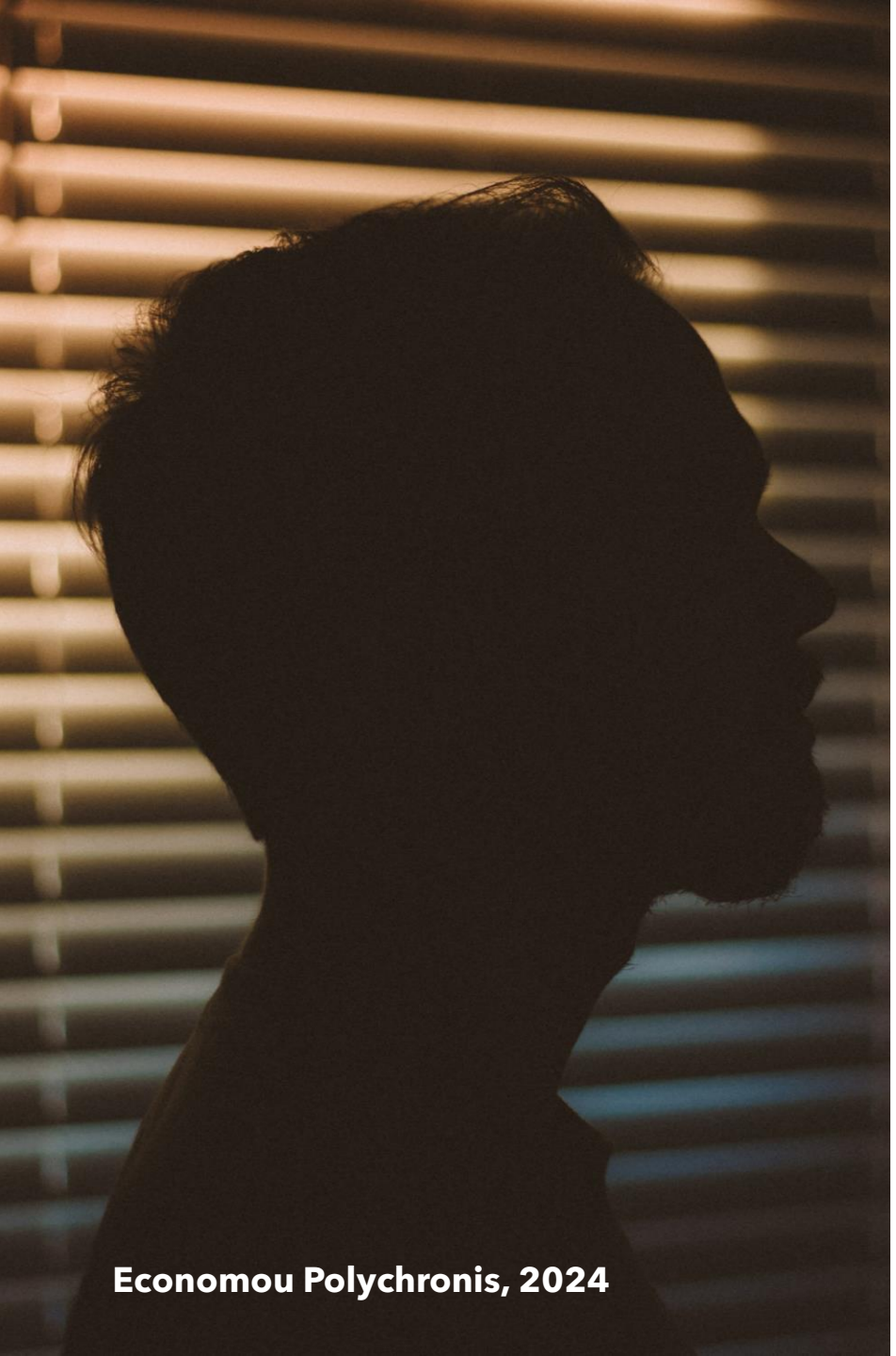
When randomization is applied

After a subject's eligibility for a clinical trial has been determined

Before any experimental data are collected



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Randomization and Blinding

Blinding refers to the concealment of group allocation from one or more individuals involved in a clinical research study

Blind as many individuals as possible in the trial

- Participants (patients)
- Practitioners (doctors, nurses, dieticians, etc.)
- Data collectors

For example, double-blind studies, i.e. studies in which the participant and trial facilitator are unaware of assigned interventions, are an excellent example of clinical trials that results to bias reduction.

How randomization is done

TYPES OF RANDOMIZATION

- Simple randomization
- Block randomization
- Stratified randomization
- Covariate adaptive randomization

Simple randomization

A method of assigning participants to different treatment groups in a way that is entirely random and unbiased.

- The gold standard for assigning participants in clinical trials
- Widely used to minimize the risk of bias and ensure the validity of the study results.
- Each participant has an equal chance of being assigned to any of the treatment groups.
- Groups are comparable at the start of the study and any differences observed in the outcomes can be attributed to the treatment and not to the selection bias.
- Simple randomization is often conducted using a random number generator or a coin toss.

Simple randomization

Example

A **pharmaceutical company** is conducting a clinical trial to evaluate the effectiveness of a new drug in reducing blood pressure.

Aim: to compare the effects of the drug against a placebo control group.

The company randomly selects **100 participants** from a pool of **eligible patients** with hypertension and assigns them to one of the two groups: **treatment or control**.

Simple randomization

Example (cont.)

To ensure the randomization is **unbiased**, the company uses a computer-generated **list of random numbers** to assign participants to the two groups.

Random numbers

101101110111000011011101111110111001011011100001001111110101011101000011011011111100100001001000100110101011111000110111000110000010001100100001001110111101111011100011101101000111110010101110111010111010

- Each participant has an equal chance of being assigned to either the treatment or control group, thereby minimizing the risk of selection bias.
- The treatment group (1) receives the new drug, while the control group (0) receives a placebo.

The study can then evaluate the effect of the drug on blood pressure by comparing the outcomes between the two groups.

Block randomization

use predetermined sizes blocks, and then randomly assigning participants to the treatment groups within each block

Goal

Ensure a balanced distribution of participants across the treatment groups over time.

Reduce the potential for confounding due to chance imbalances in the assignment of participants to the treatment groups.

Key elements

Block size: Number of participants assigned to each block.

Predetermined and fixed (a multiple of the number of treatment groups)

Treatment allocation: Within each block, participants are randomly allocated to treatment groups in a predetermined ratio

Example: 2 groups
Treatment, Control
Ratio 1:1
Block 1: T T C C T C
Block 2: C T T C T C
Block 3: C T T C C T
Block 4: T C C T T C
Block 5: T C C T C T
Block 6: C C T T C T

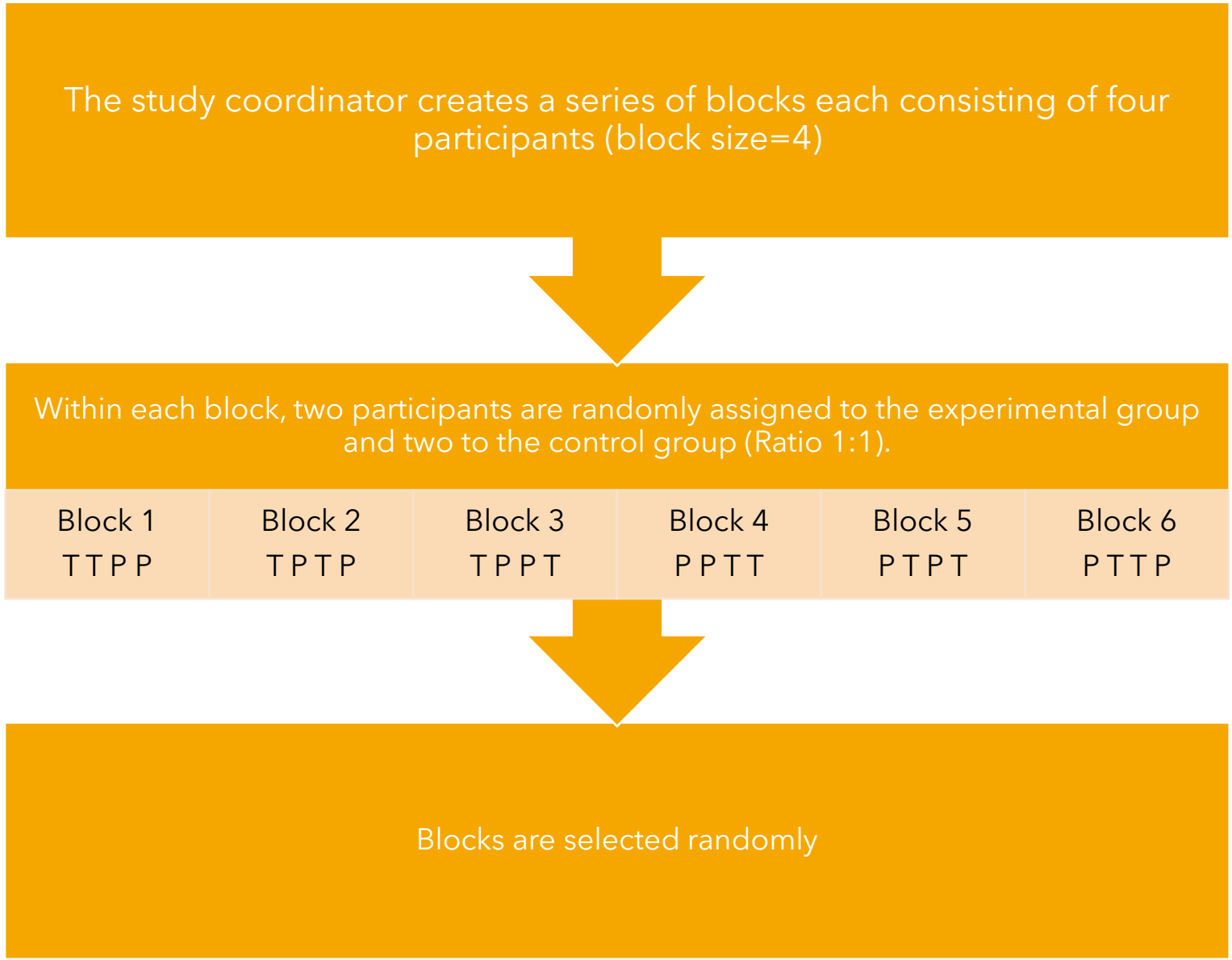
Randomization sequence: The blocks are allocated randomly to minimize the risk of bias.

Block randomization

Example

A clinical trial is being conducted to evaluate a new medication for the treatment of high blood pressure, with two treatment groups:

1. the experimental group (T) receiving the new medication and
2. the control group receiving a placebo (P).



Stratified randomization

1. Divide participants into subgroups (strata) based on their characteristics (age, gender, disease severity, etc)

2. Randomize the participants within each stratum to ensure that treatment groups are balanced for these characteristics.

Minimizes the potential for confounding variables that may affect treatment outcomes

The power and accuracy of the study increases

Stratified randomization

Example

Clinical trial to evaluate the efficacy of a new treatment for patients with lung cancer.

Aim: to compare the effects of the new treatment against a standard treatment.

Two strata based on the stage of their cancer

- early-stage
- late-stage.

Stratification is necessary because patients with early-stage cancer may **respond differently** to treatment than those with late-stage cancer.

Within each stratum, the patients are then randomized to either the new treatment or the standard treatment, using **simple randomization**.

Early-stage stratum

20 patients receive the new treatment
20 patients receive the standard treatment

Late-stage stratum

25 patients receive the new treatment
25 patients receive the standard treatment

.

Covariate adaptive randomization

A method of randomization that involves using information about certain baseline characteristics (covariates) of the participants to adjust the probability of assignment to the different treatment groups.

Baseline characteristics (covariates, for example age, gender, disease severity) are used to stratify the participants into subgroups,

Allocation of participants to treatment groups is adjusted based on the imbalance of the covariates within each stratum.

- The probability of assigning a participant to a particular treatment group is adjusted to achieve a balance in the distribution of the covariates within each stratum.

Covariate adaptive randomization

Example

Clinical trial to evaluate the efficacy of a new treatment for patients with chronic pain.

Aim: to compare the effects of the new treatment against a placebo.

Pain severity can be used as a covariate for covariate adaptive randomization as it is an important predictor of treatment response.

Participants are **stratified into two subgroups** based on pain severity

- high severity
- low severity.

Probability of assignment to the treatment or placebo group **is adjusted** based on the **imbalance of pain severity**.

For example, if

- the **first 5** patients who were randomized had **high pain severity** and
- **3 of these** patients were assigned to the **treatment** group

then the **probability** of assigning the **next high-severity** patient to the **treatment group** would be **reduced**, to increase the chances of balancing the treatment groups with respect to pain severity.

Endpoints analysis in clinical trials

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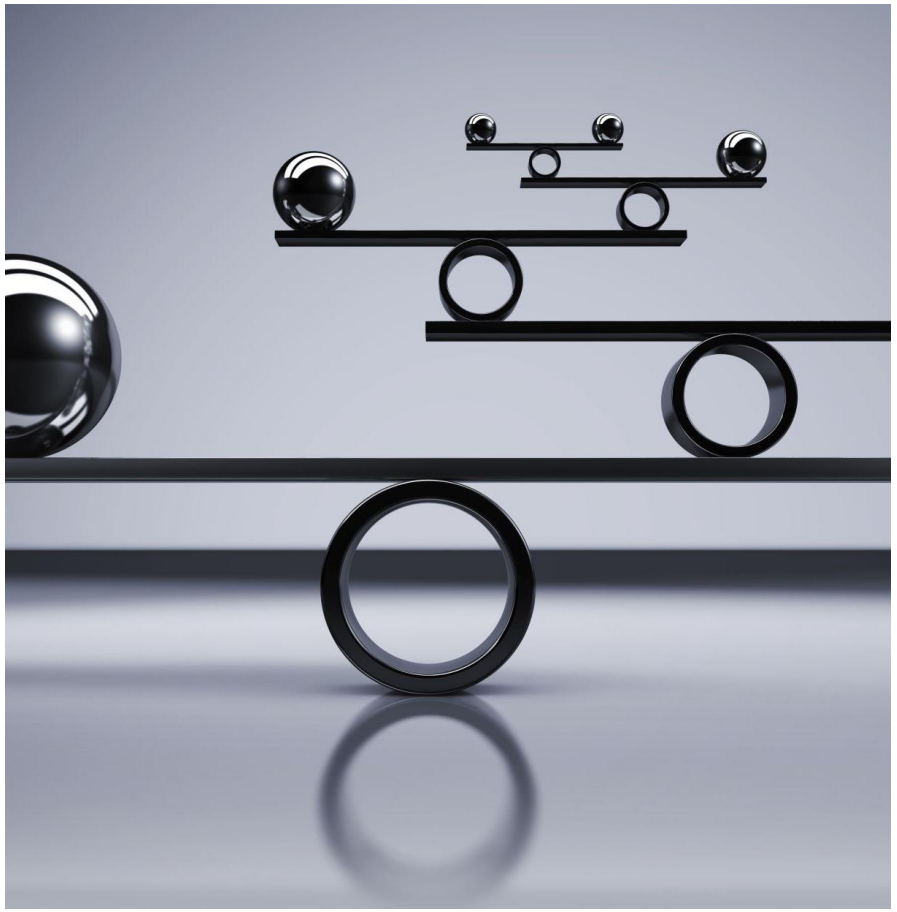
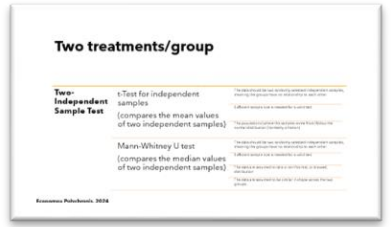


Comparison of treatments/groups

- **mean, response rate, etc**



- **Survival/hazard rate**

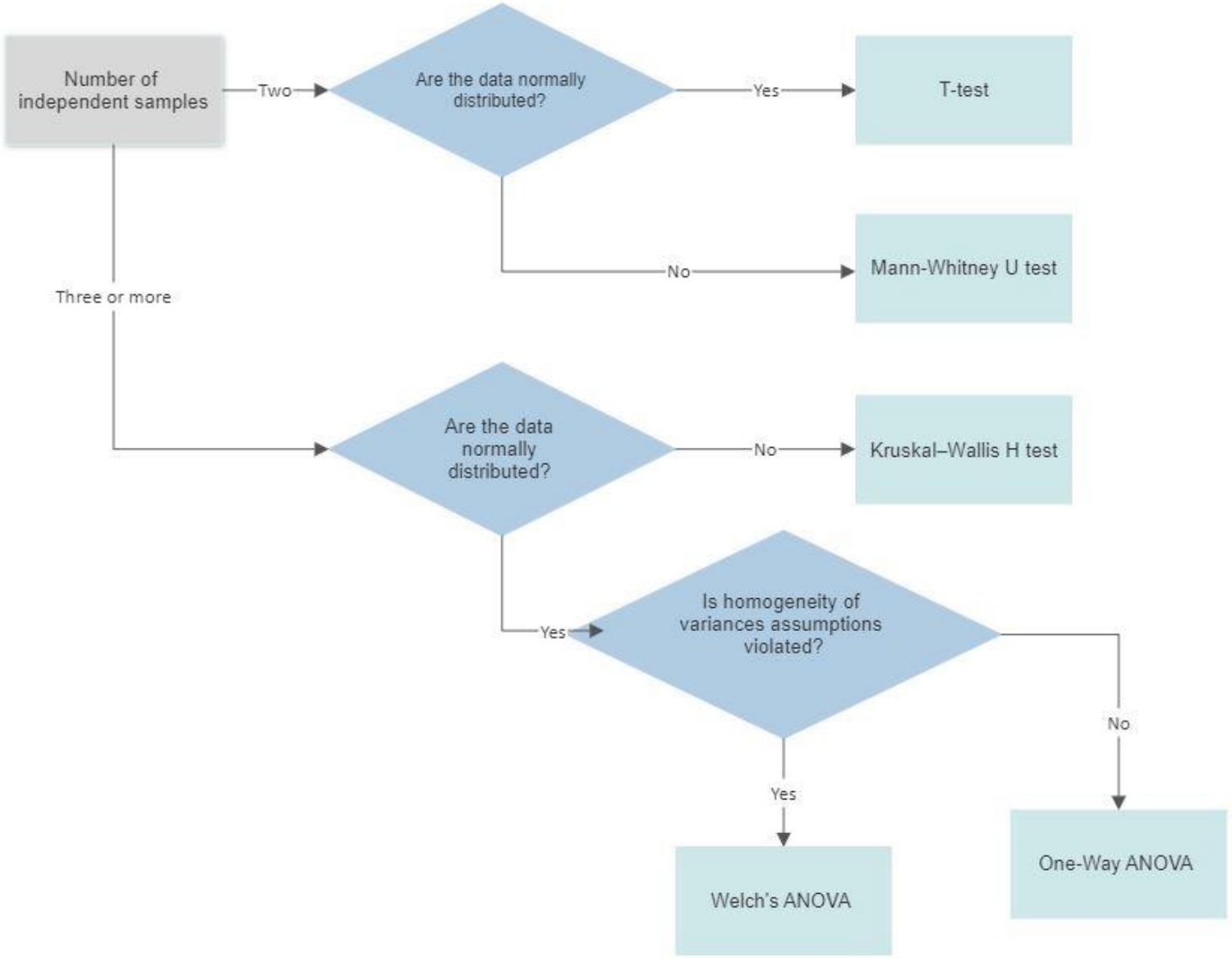
Two treatments/group

Two-Independent Sample Test	t-Test for independent samples (compares the mean values of two independent samples)	The data should be two randomly selected independent samples, meaning the groups have no relationship to each other.
		Sufficient sample size is needed for a valid test
		The populations (where the samples come from) follow the normal distribution (normality criterion)
	Mann-Whitney U test (compares the median values of two independent samples)	The data should be two randomly selected independent samples, meaning the groups have no relationship to each other.
		Sufficient sample size is needed for a valid test
		The data are assumed to take a non-Normal, or skewed, distribution
		The data are assumed to be similar in shape across the two groups.

K treatments/group

K-Independent Samples	One-Way ANOVA (One Way Analysis Of Variance) (Tests differences of means)	The data should be two randomly selected independent sample Sufficient sample size is needed for a valid test The populations (where the samples come from) follow the normal distribution (normality criterion) All input samples are from populations with equal variances
	Welch's ANOVA (Alternative to the Classic ANOVA when the assumption of homogeneity of variances is violated)	The data should be two randomly selected independent samples Sufficient sample size is needed for a valid test The populations (where the samples come from) follow the normal distribution (normality criterion) All input samples are from populations with unequal variances
	Kruskal–Wallis H test (Non-parametric for testing whether samples originate from the same distribution)	The data should be two randomly selected independent samples The measurement scale is at least ordinal, and the variable is continuous it has no distributional assumptions

Flow chart



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Example
New Depression Drug

A pharmaceutical company is conducting a clinical trial to test the efficacy of a new drug for treating depression.

- **Recruitment**: 150 patients over a year
- **Simple randomization:** three groups of participants
  - 1st group receives a placebo
  - 2nd group receives a standard treatment
  - 3rd group receives the new drug

The researchers measure the **depression scores** of each participant at the **beginning** and **end** of the study and they are interested in the change of these scores, DS.

Goal: To test if there are statistically significant differences in mean DS.

	A	B	C	D
1	ID	group	Start	End
2	1	3	48.6	31.7
3	2	2	33.5	25.2
4	3	3	31.9	20.1
5	4	2	47.7	37.1
6	5	3	48.7	29.8
7	6	3	31.5	16.2
8	7	2	31.9	25
9	8	3	46.3	35.6
10	9	1	32.4	26.1
11	10	3	30	16.8
12	11	1	46.9	42

Descriptive statistics

Treatments	3	2	1
Number of patients	N=50	N=49	N=51
Start	38.536 (6.004)	39.853 (5.833)	39.935 (5.63)
End	23.02 (6.252)	29.971 (5.685)	34.935 (5.876)
Change from baseline	-15.516 (2.597)	-9.882 (1.892)	-5.0 (1.059)

Normality test Shapiro-Wilks

Measurements	Test Statistic	Sample length	p-value
3	0.99	50	0.94
2	0.986	49	0.832
1	0.981	51	0.578

Homogeneity test
Levene’s test

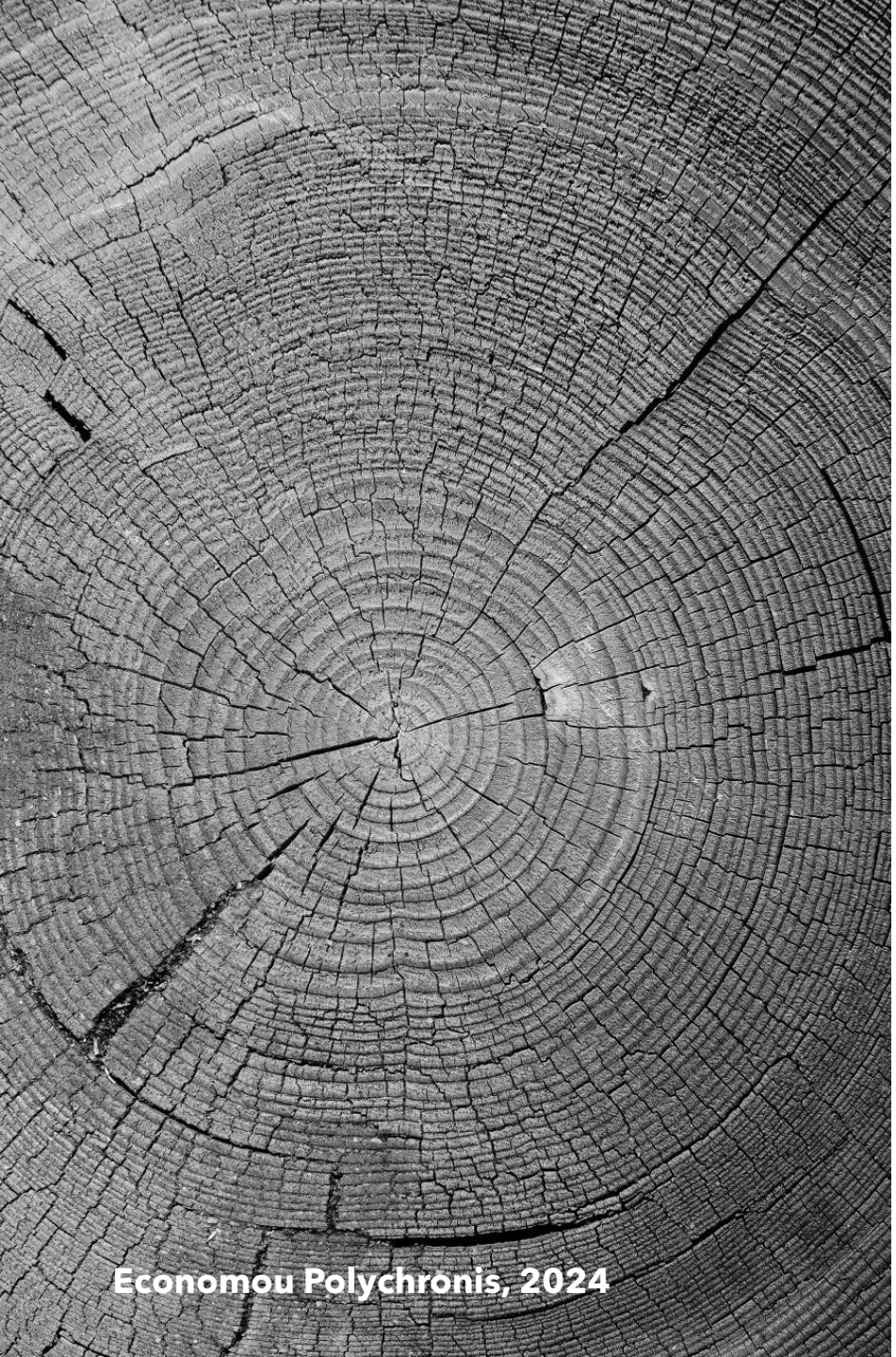
Homogenity of Variances	Value
Levene's test	11.576
p-value	<0.001

Welch's ANOVA

Source	df1	df2	F	p-value
group	2	85.261896	412.400229	1.451801e-44

Extra
Post-hoc comparisons

A	B	mean(A)	mean(B)	diff	se	T	df	p-value
1	2	-5.000	-9.882	4.882	0.308	15.834	74.727	0.001
1	3	-5.000	-15.516	10.516	0.396	26.550	64.586	0.001
2	3	-9.882	-15.516	5.634	0.456	12.355	89.617	0.001



Survival Analysis

Time to event data

- Many clinical trials involve following patients for a **long time**.

- The **major events** that the trial subjects suffer are death, development of an adverse reaction, relapse from remission, and development of a new disease entity

- **Survival Analysis** typically focuses on **time to event data**, i.e. the time until the occurrence of the event of interest.

Why we need the survival analysis?

In survival analysis subjects are usually followed over a specified time period and the focus is on the time at which the event of interest occurs.

As a result, the time to event data often present a characteristic feature, known as **censoring**, which broadly speaking is when the time to event (lifetime) is incompletely determined for some subjects, i.e., for some subjects we may know that their survival

- time have occurred within certain intervals, whereas, for other
- subjects, we will know their exact time of event.

Another feature of time to event data that may be present in some survival studies is that of **truncation**. Truncation occurs when only individuals who experience some event can be observed by the investigator.

Censoring

Right

A right censored observation is one that is known only to be larger than some value (for example lifetime>70 years).

Left

A left censored observation is one that is known only to be less than some value (for example I start smoking at some age earlier than 15 but I can not remember exactly)

Interval

An interval censored observation is reported as being within a specified interval (for examples a tumor recurrence in a patient may be known to fall only the interval between visits).

Truncation

- **Truncation** is similar to but distinct from the concept of censoring.

- Truncation occurs when the subjects have been at risk before entering the study.

- This means that for a portion of the population **the event of interest may have occurred but could not be observed** and as result is unknown if or not has occurred.

- Consequently, the investigator is not aware of the existence of these individuals.

- There are mainly two types of truncation
  - left and
  - right

Main target of Survival Analysis

The main target of survival analysis is the estimation of the so-called **survival function**

$$S(t) = P(T > t)$$

Survival function gives the **probability** that an individual will **survive** beyond a specified time t.

The survivor function is often estimated by the **Kaplan-Meier** curve.

Other important functions

Hazard function h(t) (also known as the failure rate, hazard rate, or force of mortality)

the instantaneous rate of failure (experiencing the event) **at time t given that an individual is alive at time t**.

Cumulative hazard H(t)

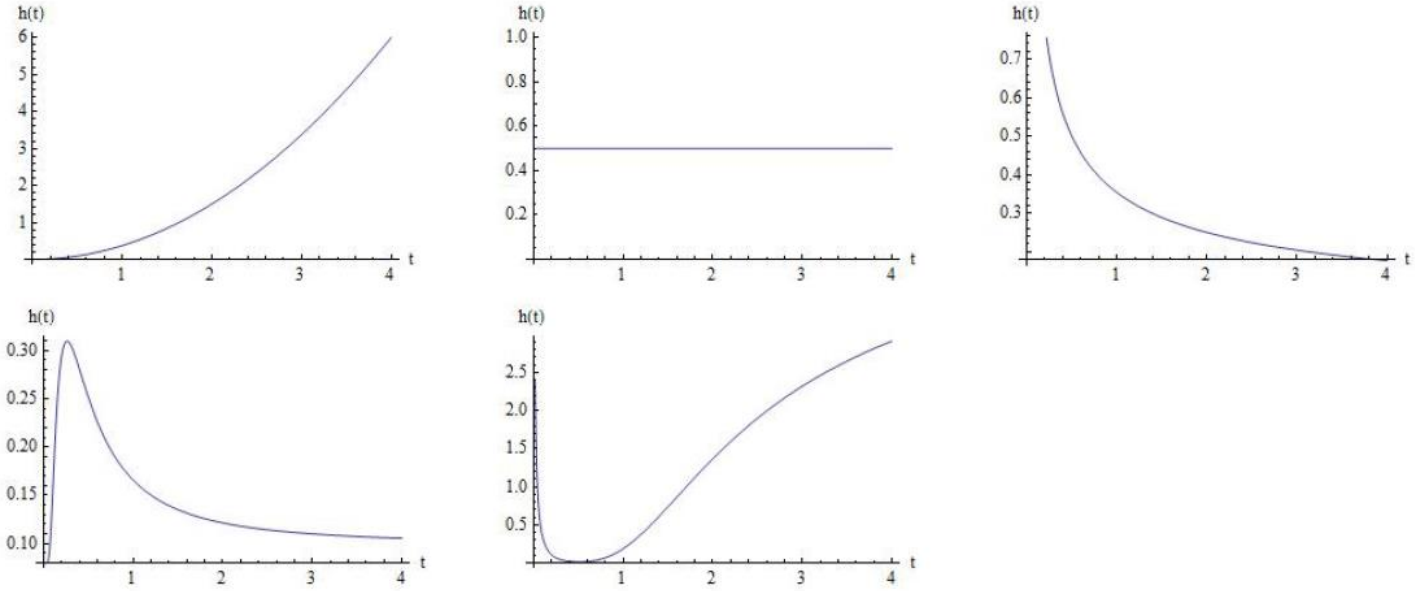
The accumulated risk up to time t.

Mean residual life function

as the expected value of the remaining lifetimes after a fixed time point t

Hazard function patterns

The greater the hazard between times t1 and t2, the greater the risk of failure in this time interval



Example

The table shows the survival times of two groups of 45 patients suffering from gastric cancer. Group 1 received chemotherapy and radiation. Group 2 just received chemotherapy. An asterisk indicates censoring.

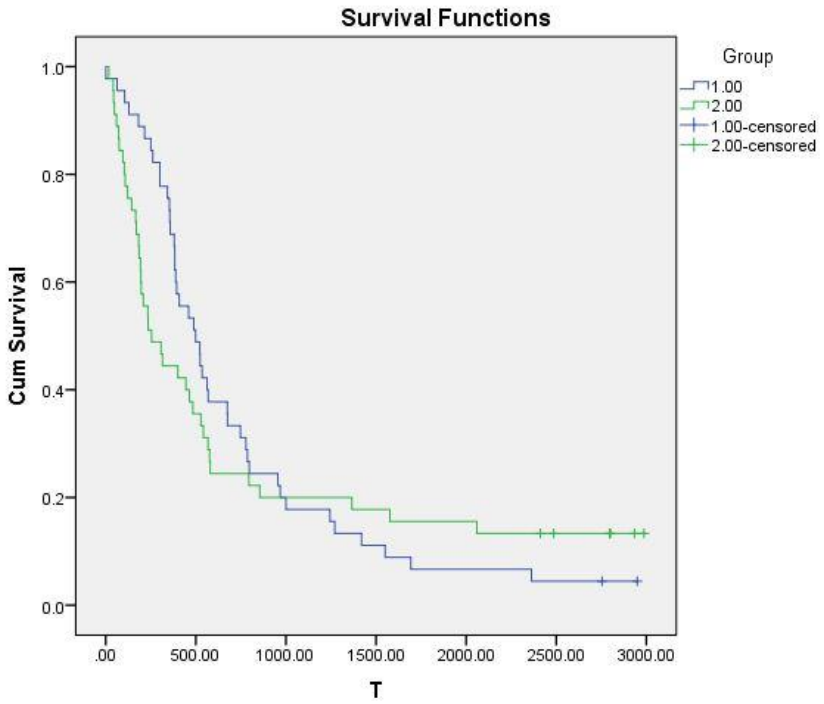
Group 1								
1	63	105	129	182	216	250	262	301
301	342	354	356	358	380	383	383	388
394	408	460	489	499	523	524	535	562
569	675	676	748	778	786	797	955	968
1000	1245	1271	1420	1551	1694	2363	2754*	2950*

Group 2								
17	42	44	48	60	72	74	95	103
108	122	144	167	170	183	185	193	195
197	208	234	235	254	307	315	401	445
464	484	528	542	567	577	580	795	855
1366	1577	2060	2412*	2486*	2796*	2802*	2934*	2988*

	T	D	group
1	1.00	1.00	1.00
2	63.00	1.00	1.00
3	105.00	1.00	1.00
4	129.00	1.00	1.00
5	182.00	1.00	1.00
6	216.00	1.00	1.00
7	250.00	1.00	1.00
8	262.00	1.00	1.00
9	301.00	1.00	1.00
10	301.00	1.00	1.00
11	342.00	1.00	1.00
42	1694.00	1.00	1.00
43	2363.00	1.00	1.00
44	2754.00	.00	1.00
45	2950.00	.00	1.00
46	17.00	1.00	2.00
47	42.00	1.00	2.00
48	44.00	1.00	2.00
49	48.00	1.00	2.00
50	60.00	1.00	2.00

Compare survival functions

Kaplan-Meier
log-rank test



Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	.225	1	.635

Test of equality of survival distributions for the different levels of Group.

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