UE / ENSEIGNANT : Anglais - York

DATE : 10/10/24

GROUPE : Adélaide SALAUN, Juliette PETESCH

REMARQUES :

Confounding, Chance and Bias

Table des matières

I) Feedback on RCT presentations 2

3

I) Videos watched 4

A) NEJM Quick Take 4

B) Confounding, chance and bias 4

1) Confounding, chance and bias (Cochrane Austria video) 4
2) Socrative Quiz 5

C) Biases in Medical Research 8

1) Video: Biases in Medical Research 8

I) Feedback on RCT presentations

		1. TITLE:	2. TITLE:	3. TITLE:
content	What were the **primary and secondary endpoints (outcomes)**?			
	What are the implications for clinical practice? (focus on inclusion criteria, feasibility of intervention, size of effect/ impact on study population)			
	What are the **limitations/ drawbacks** of this RCT?			
presentation skills	Did the presenters capture and maintain your **attention**? **How**? (body language..)			
slides	Did the **1st slide** include these items?	☐ **full** article title ☐ principal **authors** ☐ **journal**: _____ ☐ publication **date**: _____ ☐ presenters' **names** ☐ slide **numbers**	☐ **full** article title ☐ principal **authors** ☐ **journal**: _____ ☐ publication **date**: _____ ☐ presenters' **names** ☐ slide **numbers**	☐ **full** article title ☐ principal **authors** ☐ **journal**: _____ ☐ publication **date**: _____ ☐ presenters' **names** ☐ slide **numbers**
	What do you remember from the main results/ **graphs/charts**? Were they **clearly explained**?			
	How did the slides help you understand the content of the presentation?			
language	What **vocabulary/ expressions** do I want to remember?			

I) Videos watched

A) NEJM Quick Take

- NEJM Quick Take: **Rifampin or Isoniazid for Latent Tuberculosis in adults**

An international open-label randomized phase 2-3 clinical trial was conducted in 6859 adults with latent TB infection.

Conclusion: 4 months of rifampicin is non-inferior in efficacy to 9 months of isoniazid.

B) Confounding, chance and bias

1) Confounding, chance and bias (Cochrane Austria video)

https://www.youtube.com/watch?v=bcfg9kcxeuU

Confounding:
Properties of confounders (= confounding factors):
- is associated with the outcome independently from the exposure
- is related to the exposure
- is not on the causal pathway between exposure and outcome

How do you deal with confounders?
The influence of known confounders can be
- … avoided in the planning phase
  - i.e., restriction
- … taken into account during analysis
  - i.e., stratification, multivariate analyses

What do you do when a confounder is unknown?
The only way to deal with confounders : RANDOMIZATION
- Study participants are randomly allocated to study arms
- Randomization leads to an equal distribution of **known** and **unknown** confounders in the study groups

Chance:
- Random deviation from the truth without specific direction
- One can minimize the influence of chance by large sample size
- In studies with fewer than 300 participants, random variability can lead to unequal distribution of patient characteristics
- Low event rates

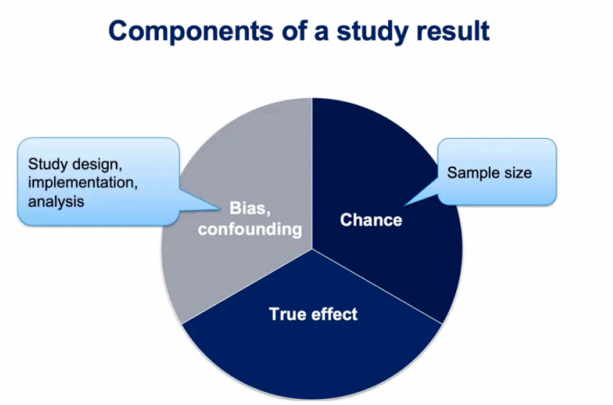
Bias = a **systematic error** in the design or execution of studies that **distort** the result

Important types of bias:
- **Selection bias**: systematic differences arise through the allocation of study participants.
- **Performance bias**: systematic differences in the treatment or care of patients.

- **Measurement bias**: systematic differences in measuring outcomes.
  - Relevant criteria: **blinding** the participants and the people measuring outcomes.
- **Attrition bias**: systematic differences between study groups in case of premature withdrawal from the study.
  - Relevant criteria: - intention-to-treat analysis
    - complete description of dropouts from the study

Risk of bias:

- Bias can not be measured directly.
- The risk of bias can only be assessed indirectly through the evaluation of the study design and the execution of studies.
- Risk of bias may vary between outcomes.



2) Socrative Quiz

1.

The goal of clinical trials is to investigate the _____ and _____ of treatments.

efficacy and safety

2.

Confounders:

A confuse us in interpreting study results

B lead us to infer correct conclusions

C deal with cause and effect relationships

D all of the above

Answer: AC

3.

Smokers are at increased risk of developing coronary heart disease because they drink coffee.

T True F False

Answer: False

4.

Choose the correct statement(s) on confounding:

A confounders are related to exposure

B confounders can be avoided thanks to inclusion criteria

C specific analyses can limit the influence of confounders

D stratification leads to confounding

E all of the above

Answer: ABC

5.

Restriction is a method to limit confounders in a study, by limiting them before randomization

T True

F False

Answer: True

6.

In a randomized study, participants are allocated to study _____.

arms
= study groups

7.

Chance is also called _____.

random error

8.

Large sample size increases the risk of chance.

T True

F False

Answer: False, it is minimized

9.

Randomisation protects against the influence of chance.

T True

F False

Answer: False

10.

Low event rates make it more likely to have random error.

T True

F False

Answer: True

11.

Bias:

A is a type of random error

B is caused by confounders

C is a systematic error in study design

D always distorts results

E is a systematic error in study analysis

F is found only in interventional studies

G has many different subcategories

Answer: CDEG
⇒ To distort = to skew results

TIPS : Comment prononcer le mot “bias” selon Mrs. YORK ⇒ *‘by ass*🍑’

II - Biases in Medical Research

1) *Research groups*

In groups, research one of the following biases: performance, selection, attrition, measurement, reporting, publication, sponsorship.

Summarize essential information in some slides ⇒ oral presentations.

Student’s presentations by groups :

A) Reporting bias

Reporting bias refers to the systematic distortion that occurs when the dissemination or publication of research findings is influenced by factors other than the quality or relevance of the study. It happens when certain results are selectively reported or emphasized, while others are downplayed, hidden, or excluded. This can lead to a skewed understanding of evidence and misinform decisions, especially in fields like medicine, social sciences, and public policy.

Types :

- Publication bias : The publication or non-publication of research findings, depending on the nature and direction of the results
- Time lag bias : The rapid or delayed publication of research findings, depending on the nature and direction of the results (something positive is mentioned more rapidly than something negative)

- Multiple (duplicate) publication bias
- Location bias
- Citation bias
- Language bias
- Outcome reporting bias : The selective reporting of some outcomes but not others, depending on the nature and direction of the results

How to prevent it ?

- transparency ++: to guarantee objectivity of medical research
- before the study : register the study because the results of prospectively registered trials are very more likely to be published than those of unregistered trials
- during the study: Open science practices, aids reproducibility, prevents duplication, reduces waste, accelerates innovation, identifies errors, and prevents reporting biases
- after the study: Reporting guidelines can help guide researchers to improve their reporting of randomized trials

B) Measurement bias

Bias of measurement refers to systematic errors that consistently skew results in a particular direction, affecting the accuracy and validity of data.

Different types:

- recall bias (ex : patients suffering from a heart attack are more likely to recall and report lack of exercise in the past than controls)
- observal bias
- attention bias
- expectation bias
- replication
- intensive measurement bias
- lead time bias
- response bias

We must be careful about this bias especially when the study is multicentric, about how the measures were made in different groups, in different hospitals.

For examples:

- faulty equipment?
- co-founder?
- absence of blinding?
- poorly trained observers?

⇒ **Systematic error in data collection**

C) Performance bias or selection bias or achievement bias

It’s a type of conductive bias that can distort conclusions because of the way data were collected or interpreted. This bias can lead to erroneous conclusions as it does not take into account the whole patients or external factors that may influence the results.

Performance bias occurs when there are systematic differences in the care or treatment provided to participants in different groups of a study, aside from the interventions being compared. This type of bias affects the validity of study results because it can influence outcomes in ways unrelated to the intervention itself, leading to distorted conclusions.

It occurs mostly in study where blinding is impossible.

Consequences:

- Placebo effect : patient who know they receive the actual drug may have higher expectation of his effectiveness leading to a subjective reduction in pain even if the drugs itself has only limited effects
- Modified behavior: participants taking the actual drugs may alter their behavior or lifestyle believing that there are better off as the results of the treatment , they may adopt additional strategies to reduce pain (for example avoiding headache triggers), these behaviors changes could distort the result by showing a greater reduction in pain when in reality it could be due to the lifestyle changes rather than the effectiveness of the medication
- Doctors or researchers could be influence by their knowledge of how is receiving the actual drug or not and this could lead to assess patients' symptoms differently, or interpret results subjectively or to provide different care depending on the treatment received

Strategies to avoid performance bias:

- Use of double or triple blinding ⇒ reduce possibility of consciously or unconsciously influencing the results
- Standardization of procedures: establishment of standardized protocols and procedures for treatment, data collection and assessment of results ⇒ minimize variation in the way treatments are administered and evaluated
- Randomization: randomly assigned participant to different treatments groups ⇒ uniform distribution of characteristics that can influence outcomes and reduction of potentials bias
- Objectives measures and endpoints

Intent to treat analysis considers all participants according to the group to which they were initially assigned regardless of treatment compliance. This helps to maintain equivalency between groups even if some participants did not complete the treatment.

Conclusion: Performance bias is an indolence in scientific studies which complicates or makes impossible any objective conclusion on the result obtained.

D) Sponsorship bias or founding bias

It happens when results of scientific study are biased in a way that supports the financial support of the research.

It was shown in 90's that industries supported studies are more likely to publish positive results than those sponsored by non-profit independent organizations.

This kind of bias usually happens when studies are financed by pharmaceutical industry companies. It influences both the reporting of the result, the access to the data or the algorithm used to analyze the data.

Solutions:

- Erect a fire wall between the money and the people doing the research and the data analysis (it' often not the case)
- Developing entirely separate founding source that is independent of the pharmaceutical industry

E) Selection bias

It's an experimental error that leads to inaccurate representation of the research sample leading to screwed or misleading results, it means that the groups of participants are not representative of the targeted population. In this situation the sample under study deviates from a fair random selection process. This influences the outcome and interpretation of the research study.

Types:

- Sampling bias: researchers' sampling methods aren't representative of the entire population (ex: selecting people because of their proximity or accessibility)
- Volunteering bias: occurs when participants volunteer to unroll in a study but are differents from the targeted population (for example patients who are sicker may be more likely to volunteer to the study than the others)
- Non-inclusion bias
- Exclusion bias: occurs when certain subgroups of the sample population are intentionally excluded, it could be due to the specific criteria defined in the study design or the involuntary exclusion of groups resulting from the recruitment strategy
- Berkson's bias
- Survival ship bias: when the study is focused on the subject who survived or succeed

How to avoid selection bias ?

- Stratified sampling: the larger population is first divided into different subgroups based on certain characteristics (age, geographic location, socio-economics groups, …)
- Randomization

To assess the probable degree of selection bias authors should include some information in the study : number of participants screened as well as randomized and how intervention groups are compared at baseline for example.

F) Attrition bias

Attrition = patient's dropout in a study.

Attrition bias is a selective drop out of some participants who systematically deferred from those who remain in the study.

Some groups of participants may leave because of bad experiences, unwanted side effects, issues to attend the study sites, personal reasons, unsatisfactory of the treatment efficacy.
The rate of loss can be higher in one group compared to the other. It can lead to unbalanced group sizes.

It almost always happens.

- HOW DOES IT AFFECT STUDIES :

Almost every longitudinal studies will have some dropout but the type and scale of the dropout can causes problems.

Attrition bias can lead to inaccurate results because it can affect internal and/or external validity. The internal validity can be affected because without complete data, the researchers may not be able to form a valid conclusion about the population. The external validity can also be affected because some groups of the population are underrepresented. So, with the biased final sample, we may not be able to generalize the findings. It changes the characteristics of the groups and therefore, trials can be no longer significant. Indeed, a rule thumb states that <5% attrition leads to little bias, and >20% attrition poses serious threats of validity.

(Internal validity is the ability of a study to establish a reliable cause and effect relationship between a treatment and an outcome.)
(External validity to generalize results from a study)

- WHICH TYPE OF STUDY IS AFFECTED:

Attrition bias affects longitudinal studies (= when there is a follow-up over time of a group) and is especially problematic in randomized controlled trials for medical research.

- WHAT ARE THE EFFECTS OF ATTRITION :

Concretely, attrition bias can lead to inaccurate results, because they are based on a biased sample, which doesn't represent the population.

- HOW CAN IT BE AVOIDED :

preventing steps can be taken during and after the follow up of patients

During the follow-up to minimize withdrawing:

- Grant compensation for attending every session
- Ensuring that the study is relevant for the participants
- Set a number of follow-ups as low as possible and making them brief, flexible, and convenient for participants
- Send routine reminders to schedule follow-ups
- Recruit more participants than you need for your sample (oversample)
- A good communication between patients and study staff

After the follow-up:

- Replacement of missing data by analysis treatment

Teacher's explanation:

Example: we give a treatment to a certain population and because this treatment have certain side effects that negatively affect women they will refuse to follow the treatment so in the end we will get a real majority of men who have completed the study.
So they prooved that the treatment is effective but only on men and a minority of women.

Attrition happens all the time, people leave the study, but it's important to find out who left and why. To evaluate the risk of attrition when we read an article, we have to look at the loss of follow-up section and at the **flowchart.**

→ Toujours se demander si on n'a pas perdu trop de participants quand on analyse une étude.

If we want to analyze this information, we have two option, either we only take the population at the end of the study so we only have the perfect patients, it's called per protocol, it only prove the efficacy of the treatment but in real life we are not going to have the perfect patient every time, so to know if the treatment is going to work or not in real life we have to do our analysis after patient had received at least one dose and that's call intention to treat, this analysis is going to give us some results which we can apply to perfect patients and the other patients too.

G) Publication bias

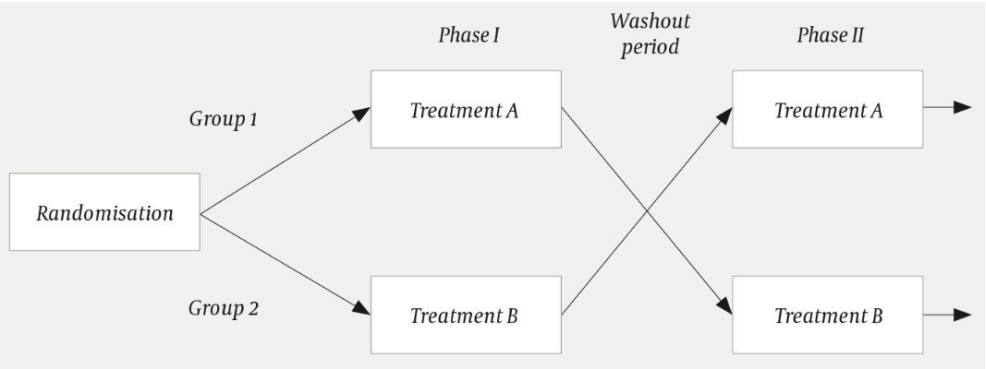
It's defined as a padder to publish the results of the study under basis of the direction or strength of the studies results. This may mean that only studies which have statistically significant positive results get published and the statistical insignificant or negative studies do not get published.

Among the many reasons for this bias there are: rejection by editors or reviewers and competing interest. Many researchers do not publish their research with negative results because they consider it as failure research, which is not true.

Publication bias is quite an illusion of positivity in research.

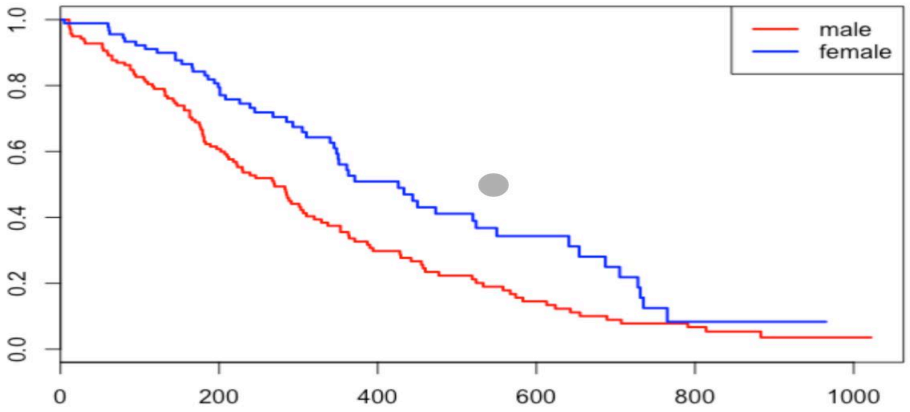
2) KAHOOT

1. **What does this represent ?**



⇒Crossover RCT

2. **What is this ?**



⇒ Kaplan meier curve

3. **True or false : In the solaris cancer study the difference in PFS between the two groups was significant**

⇒ False

4. **The solaris study studied the effect of what ?**

⇒ Vitamin D

5. **How many patients were included in the study about vaping seen in class 4 ?**

⇒ 60

6. **True or false : Cohort studies provide higher quality evidence than RCTs.**

⇒ FALSE

7. **What are features of phase 2 clinical trials ?**

⇒ Assess adverse effect + don't use a small sample size

8. **<u>What primary endpoint is typically measured in RCT's about cancer ?</u>**

⇒ Overall survival

9. **<u>What are ADCs ?</u>**

⇒ Antibody drug conjugates

10. **<u>True or false : Baseline characteristics are measured at the same time as outcomes</u>**

⇒ False

POINT VOC

Difference between efficacy, efficiency and effectiveness :

efficacy (to be effective) : refers to the ability to produce the desired result under ideal or controlled conditions "*does it work in the best possible scenario ?"* Example: we talk about efficacy in clinical trials

efficient (to be efficient) : refers to how economically or quickly a process is carried out *"How well are the resources being utilized to achieve the result ?"*

effectiveness (does it work in real life ?): refers to the ability to produce the desired results in real world conditions "*Does it work in practice ?*"

Example in healthcare:

- <u>Efficacy</u>: A drug shows a 90% cure rate in clinical trials.
- <u>Efficiency</u>: The drug is considered efficient if it achieves this cure rate with minimal cost, time, or side effects compared to alternatives.
- <u>Effectiveness</u>: The same drug shows a 70% cure rate when prescribed in regular healthcare settings, where patients may have other health conditions or not follow instructions precisely.