# Epidemiological study designs, 3

E2040: Introduction to Epidemiology and Environmental Health

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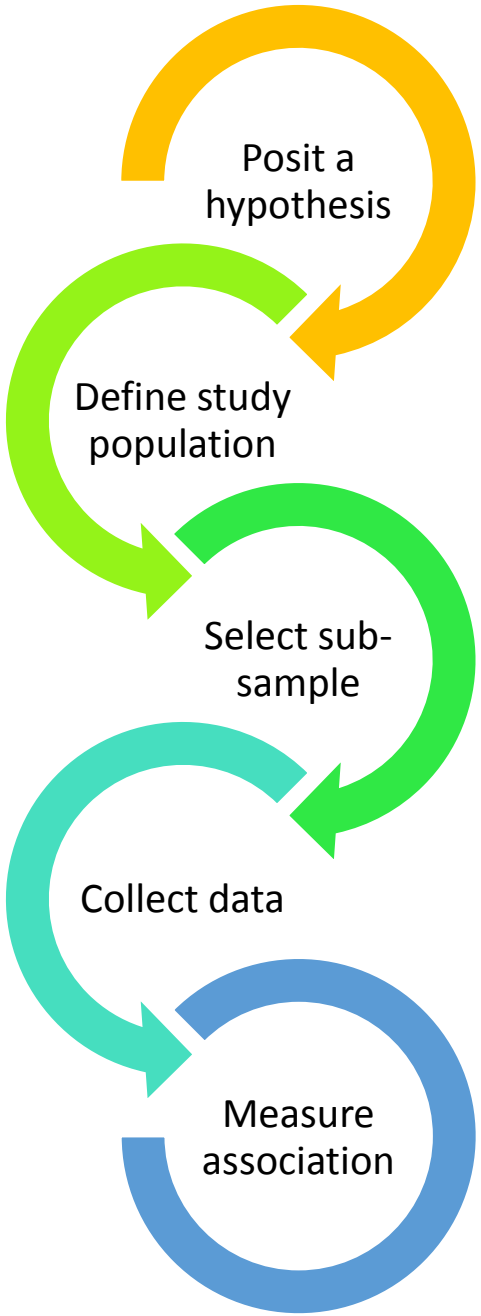
# Today's learning objectives

- Describe the features of intervention studies
- Describe the reason for and process of randomization in intervention studies
- Discuss advantages and disadvantages of intervention studies
- Explain what problems with epi studies randomization addresses

# But first, a bit of review

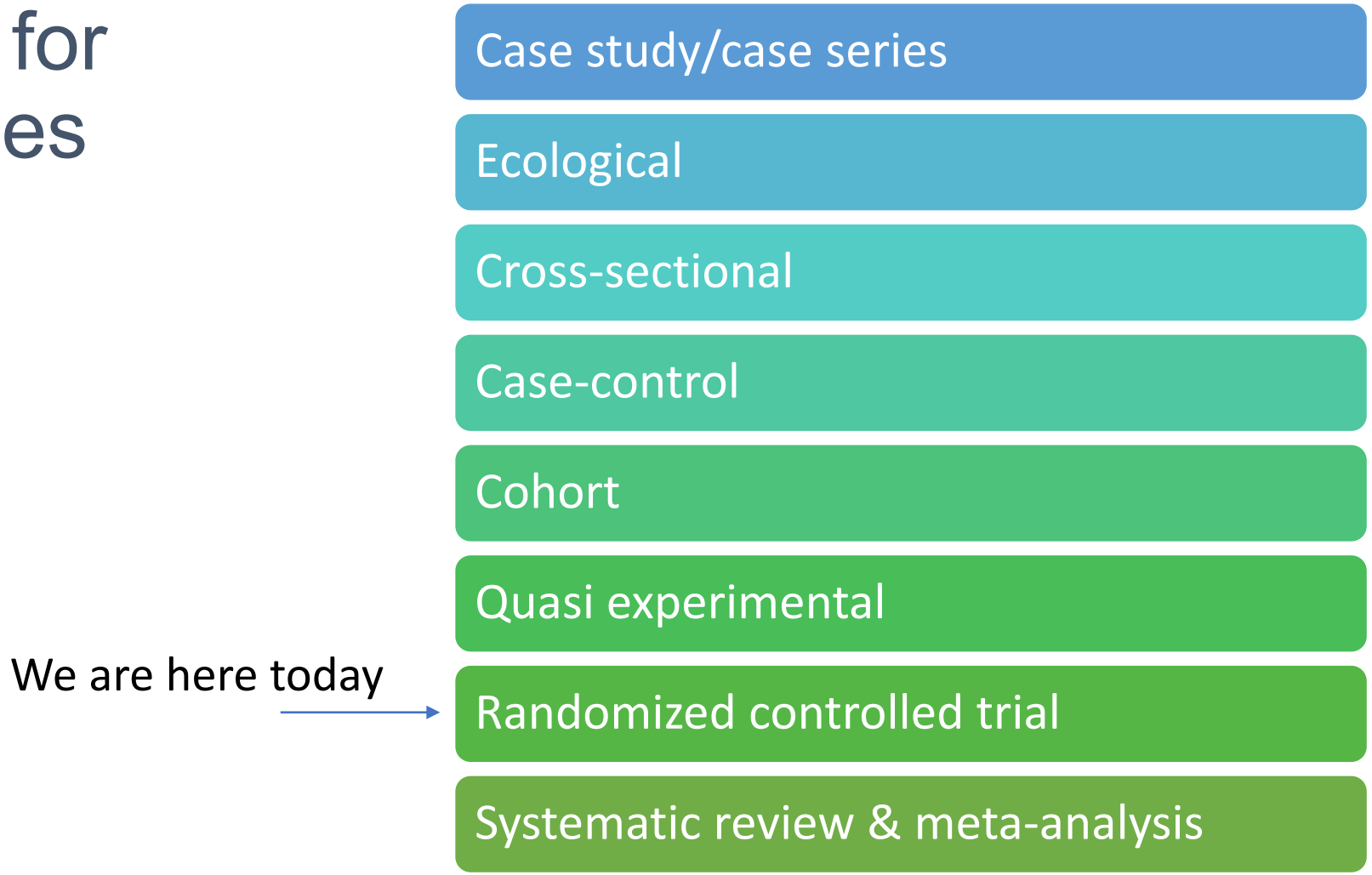
Epidemiology allows us to quantify the association between exposure/factor and outcome

Data for this comes from epidemiological studies

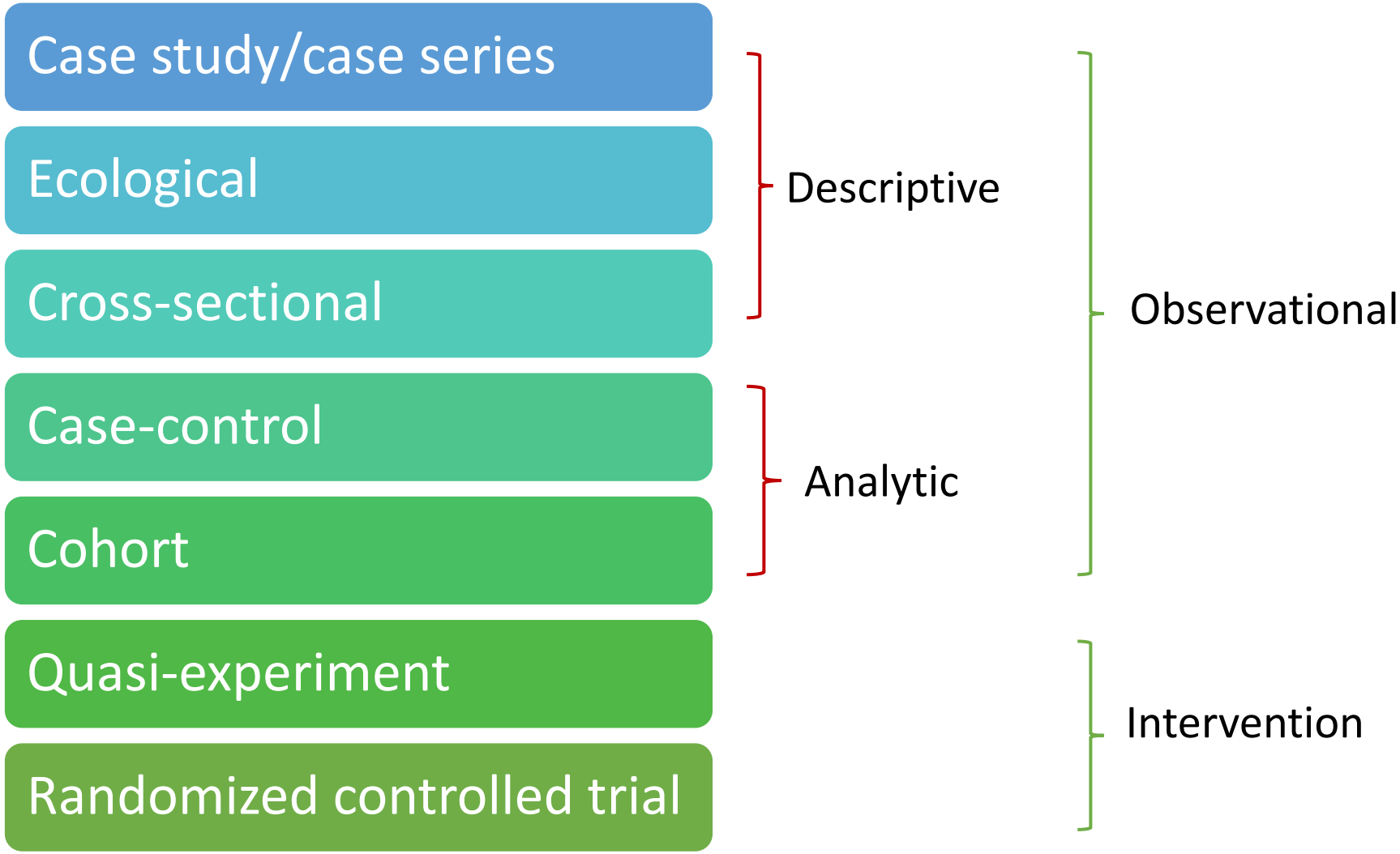



Epidemiological study

# Different epi designs are appropriate for different purposes and types of questions



# Study designs can be grouped by type



# And a few words about bias

# What is bias in epi?

**Bias:** systematic, rather than random, error

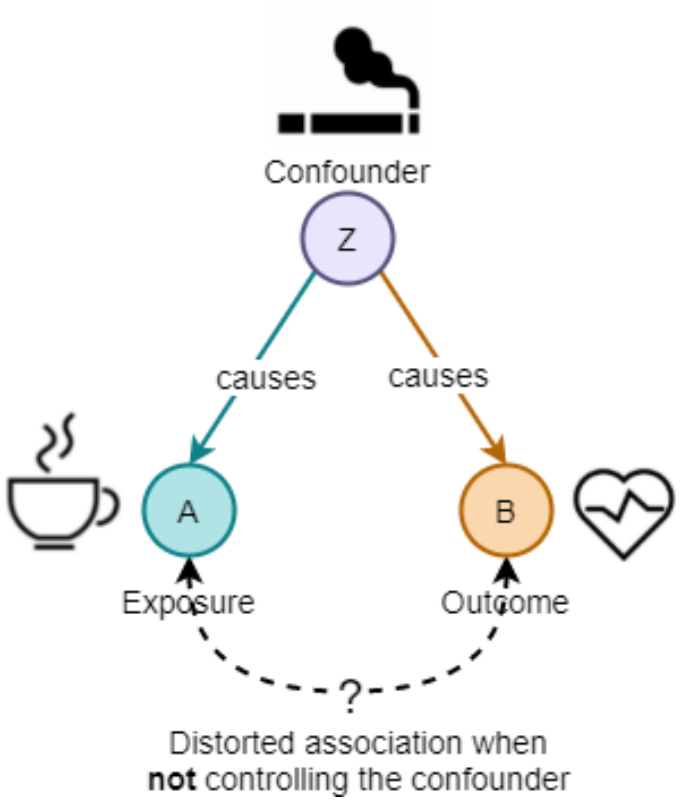
It's *caused* by something, like a design feature, mistake, or ignoring confounding factors

Epidemiologic bias is error that *systematically* affects one group in our study more than another

If an error **systematically affects** my epidemiologic study, I'll make an error in calculating my measure of association: I'll come to the wrong conclusion about the *X/Y* relationship

We spend a lot of time in epi studies trying to prevent or reduce bias and trying to predict how bias influences our study results.

# Three categories of bias




**Information bias:** when *how we measure something* in a study is related to both *X* and *Y*

**Selection bias**: *how people are selected* into the study is related to both *X* and *Y*

**Confounding:** when a *third variable Z* is related to both *X* and *Y*

# Finally, to intervention studies…

# Goal of public health

| | |
|---|---|
| Modify | In clinical practice and public health, the objective is to **modify the natural history of a disease** (prevent or delay death or disability) and to **improve the health** of the patient or the population. |
| Select | The challenge is to select the **best available preventive or therapeutic measures** to achieve this goal. |
| Benefit/risk | Trials can help us **determine the value** of a measure we have selected (benefit/risk). |

# What is an intervention study?

- Intervention studies are research designs where **researchers actively assign participants to receive specific interventions** to assess their effects on health outcomes.
- These studies are distinct from observational studies, where researchers simply observe and record outcomes without manipulating any variables.
- **Investigator intervenes**; controls what the exposure is; chooses which participants are exposed and not exposed
- Intervention studies evaluate both, the benefits and the risks of new forms of intervention (medications, exercise, vaccination… etc.)
- Also known as **randomized controlled trials (RCT).**



There are different types of RCT…

# There are different types of RCT…

## Clinical trials

- Test new medical, surgical, or diagnostic interventions in human patients.
- They are primarily designed to determine the safety and efficacy of these interventions.
- Successful clinical trials can lead to the development of new therapies for various diseases

**Treatment Trials:** Focus on testing new treatments or drugs.

•**Prevention Trials**: Aim to find ways to prevent diseases (e.g. Vaccination).

•**Diagnostic Trials**: Evaluate new tests for diagnosing diseases.

## Non-clinical trials

Oriented on public health and behavioral changes.
Examples:

- Water fluoridation,
- grain fortification with folate,
- workplace exercise program, diet,
- wearing a step counter,
- school-based health clinic...

# What happens in a **randomized** trial?

1. **Define the population to study**
2. **Sample people from that population**
3. **Randomly assign the exposure/intervention (X) or the control**
   - Inactive treatment (placebo)
   - Active treatment (standard of care)
   - It is “randomized” because exposure is assigned randomly
4. **Follow up for the outcome (Y)**
   - How many in each group have developed disease? How many have improved?
5. **Compare outcome between exposed and unexposed. We can calculate:**
   - **Risk (rate) ratio of outcome in exposed compared to unexposed**
   - **Risk difference**


We’re measuring <u>incident</u> (new) outcomes here, so we can measure risk!

# How are subjects selected?

- Based on **eligibility criteria** (also called inclusion and exclusion criteria)
- Characteristics that define the individuals you want to participate in the study
- **Inclusion criteria**:
  - Participants with the potential to benefit from the intervention and a high probability of developing the outcomes of interest
- **Exclusion criteria**:
  - Higher risk of unwanted events (allergic reactions, pregnant women, children)
  - Risk of not complying with the study protocol

- Must be explicitly specified in a study protocol, before the study begins. Why?
  - Allows clear selection of the sample
  - Allows homogeneity of the sample
  - Allows others to reproduce the study, assess if the sample was appropriate for the research question
  - Identifies the individuals to whom findings apply

# Exampl
# e

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 4, 2021 VOL. 384 NO. 5

## Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine

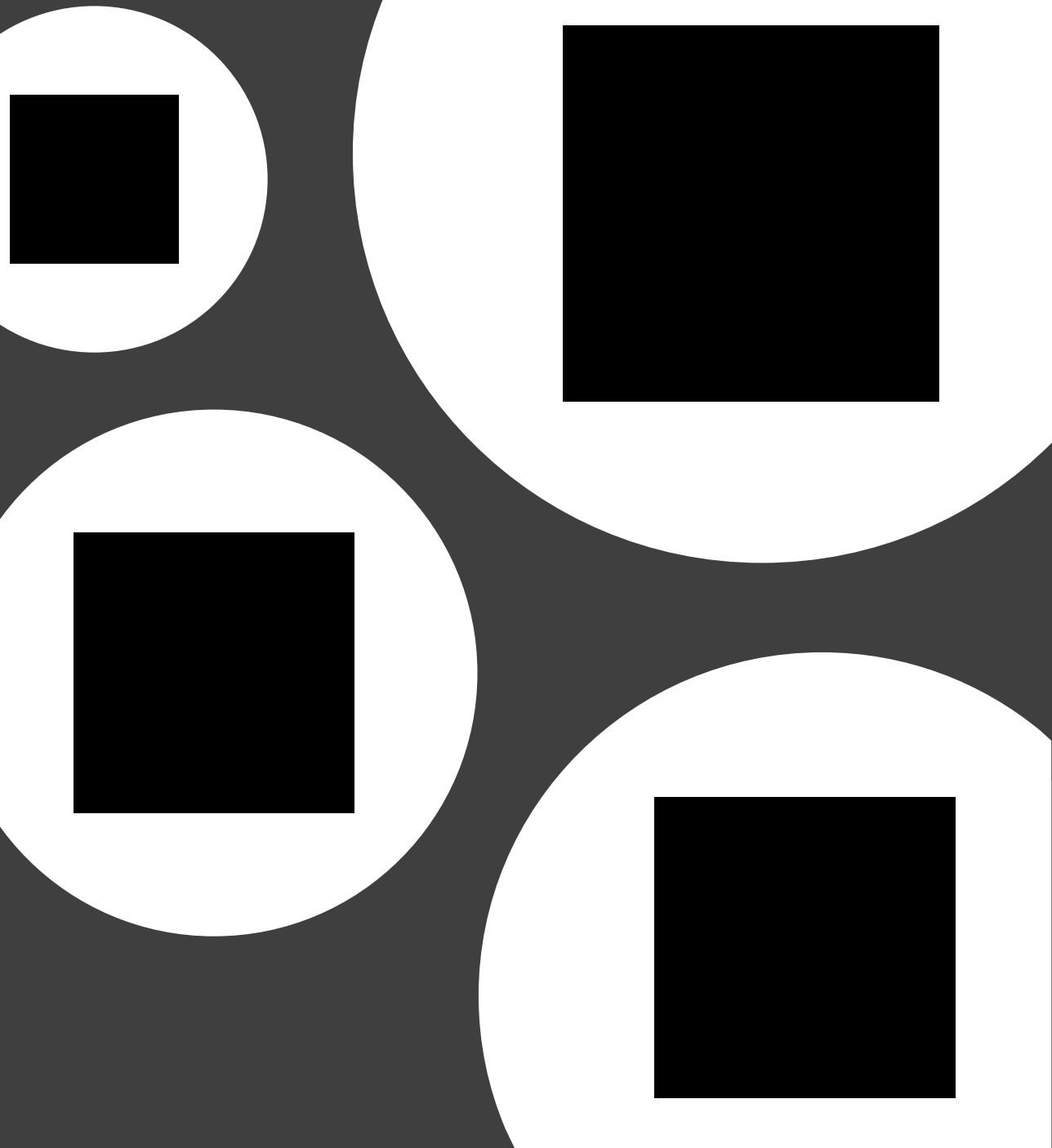
L.R. Baden, H.M. El Sahly, B. Essink, K. Kotloff, S. Frey, R. Novak, D. Diemert, S.A. Spector, N. Rouphael, C.B. Creech, J. McGettigan, S. Khetan, N. Segall, J. Solis, A. Brosz, C. Fierro, H. Schwartz, K. Neuzil, L. Corey, P. Gilbert, H. Janes, D. Follmann, M. Marovich, J. Mascola, L. Polakowski, J. Ledgerwood, B.S. Graham, H. Bennett, R. Pajon, C. Knightly, B. Leav, W. Deng, H. Zhou, S. Han, M. Ivarsson, J. Miller, and T. Zaks, for the COVE Study Group*

### PARTICIPANTS, RANDOMIZATION, AND DATA BLINDING

versity of the trial population in accordance with Food and Drug Administration Draft Guidance, site-selection and enrollment processes were adjusted to increase the number of persons from racial and ethnic minorities in the trial, in addition to the persons at risk for SARS-CoV-2 infection in the local population. The upper limit for

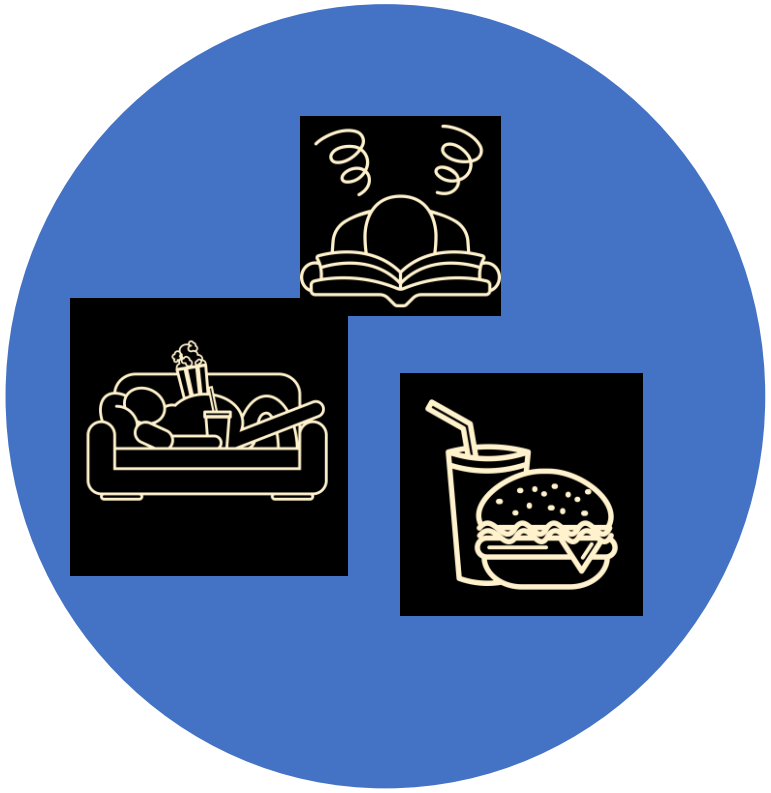
# Why randomize?

- Different people participate in randomized trials
  - Older vs. younger
  - Men vs. women
  - Sicker vs. healthier
  - Better vs. poorer: SES, physical activity, mental health, sleep, diet
- Different people respond differently to experimental condition/treatment
  - Possibly due to genetic traits
  - Possibly due to above characteristics



# Purpose of randomization

Condition A



Condition B

Who will tend to do better?

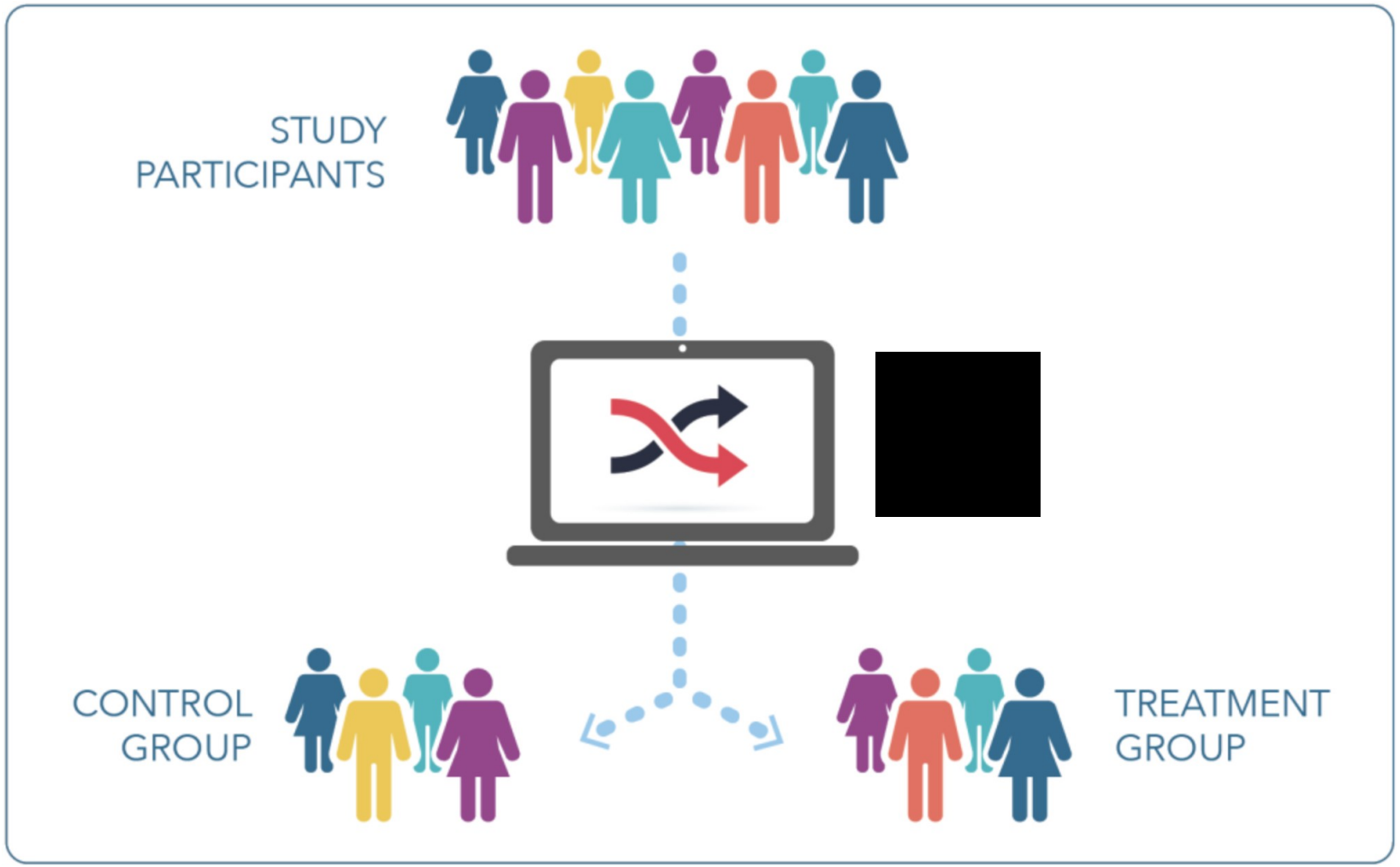
# Purpose of randomization

Condition A

Condition B

- If there are enough participants, we hope that randomization will **increase the likelihood that the groups will be comparable** on characteristics about which we may be concerned (such as sex, age, race, and severity of disease).
- Randomization **does not guarantee** comparability – by chance, groups could differ. If groups that are being randomized are large enough and the randomization procedure is free of bias, they will **tend to be similar**.

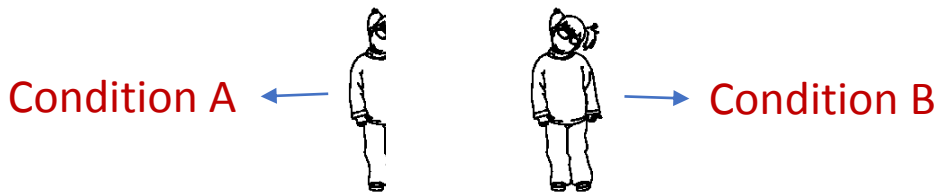
# The critical element of randomization is the unpredictability of the next assignment



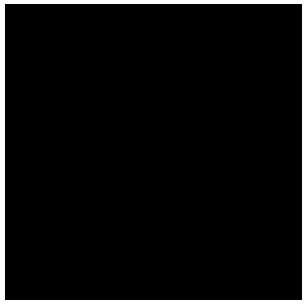

https://mrctcenter.org/clinical-research-glossary/glossary-words/randomization/

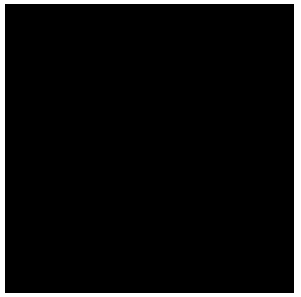
# There are different types/levels of randomization

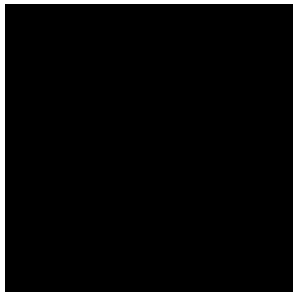
- Individual – each person is randomized to an experimental/treatment group and the individual is the unit of analysis

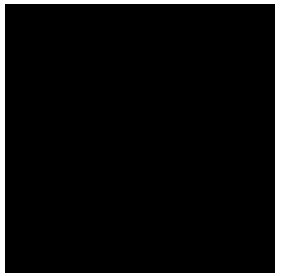



- Cluster – a group of people is randomized and the cluster is the unit of analysis



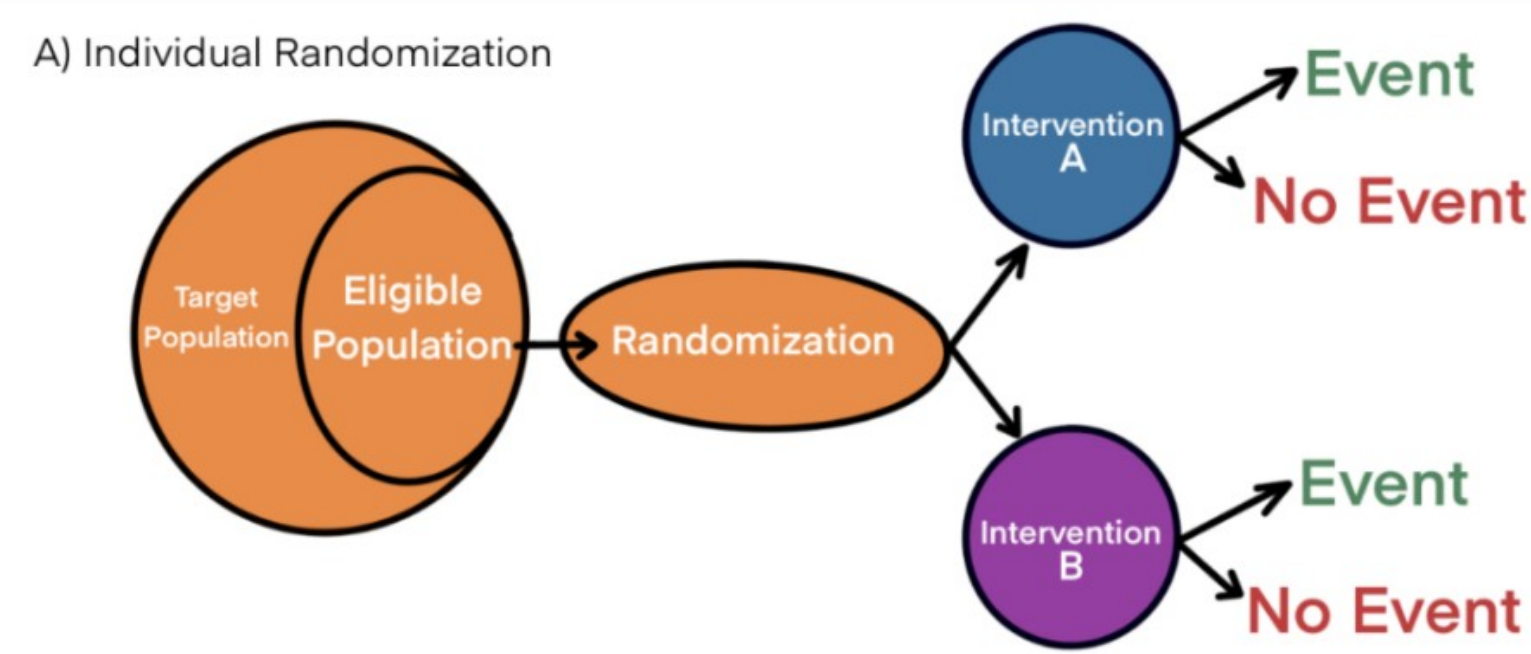




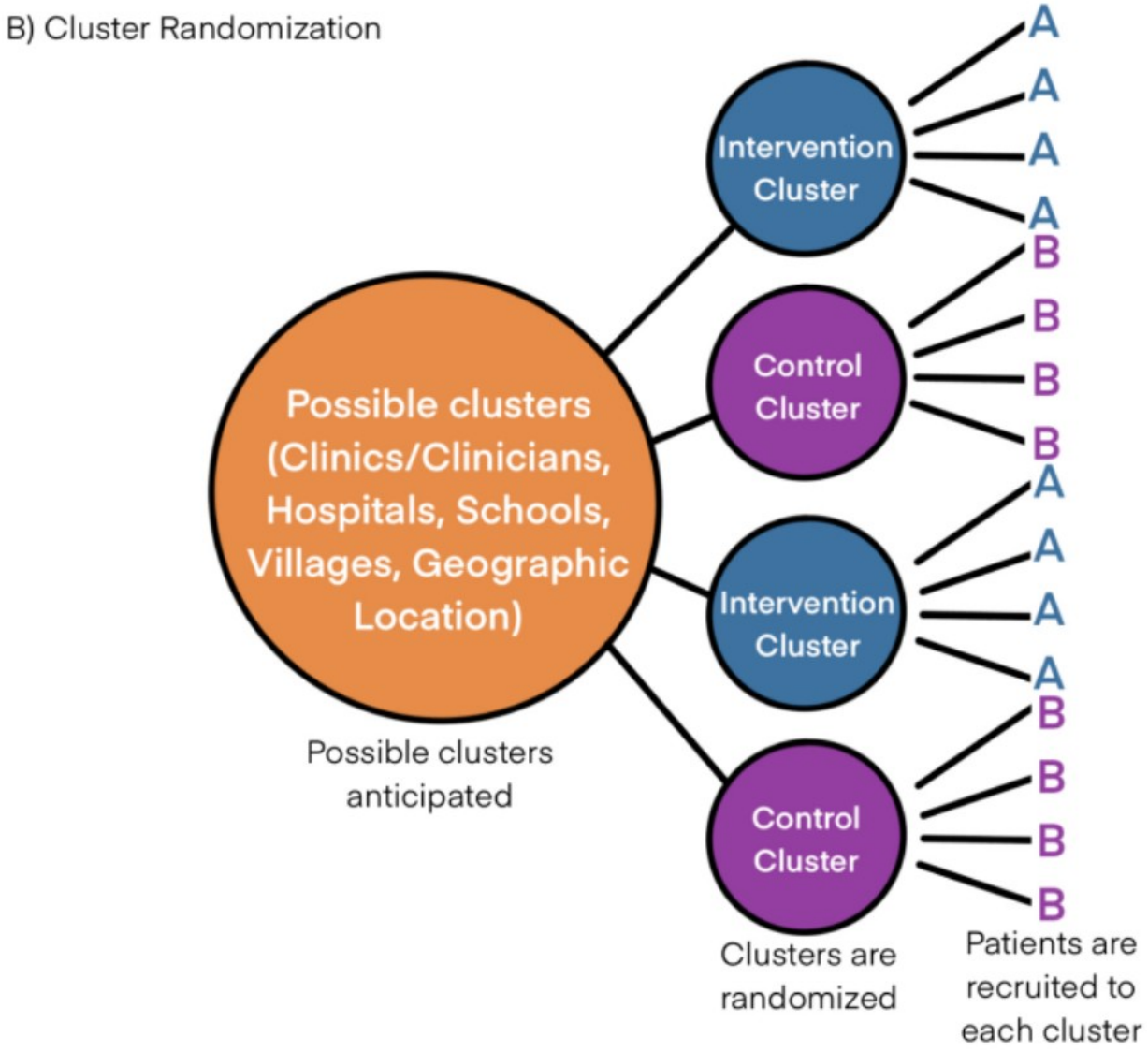


Example clusters for randomization

# Individual vs cluster RCT



# Individual vs cluster RCT




## Why would you wish to cluster-randomize?

- Unethical to assign individuals (ex., breastfeeding promotion in baby-friendly hospital)
- Difficult to implement experiment on individuals (ex., children in daycare)
- Difficult to mask assignments.

# Example cluster-randomized trial

## Effect of Salt Substitution on Cardiovascular Events and Death

Neal B et al. DOI: 10.1056/NEJMoa2105675

**Intervention:** 600 villages in rural China were assigned to use a salt substitute (75% sodium chloride, 25% potassium chloride) for all household cooking and food preservation or to continue using regular salt (100% sodium chloride). A total of 20,995 adults with a history of stroke or age ≥60 years with poorly controlled blood pressure were included. The primary outcome was stroke.


| Outcomes | Salt Substitute | Regular Salt | Rate Ratio (95% CI) | P Value |
|---|---|---|---|---|
| | *no. of events per 1000 person-yr* | | | |
| Stroke | 29.14 | 33.65 | 0.86 (0.77–0.96) | P=0.006 |
| Major Adverse CV Events | 49.09 | 56.29 | 0.87 (0.80–0.94) | P<0.001 |
| Death from Any Cause | 39.28 | 44.61 | 0.88 (0.82–0.95) | P<0.001 |
| Hyperkalemia | 3.35 | 3.30 | 1.04 (0.80–1.37) | P=0.76 |

# Example cluster-randomized trial

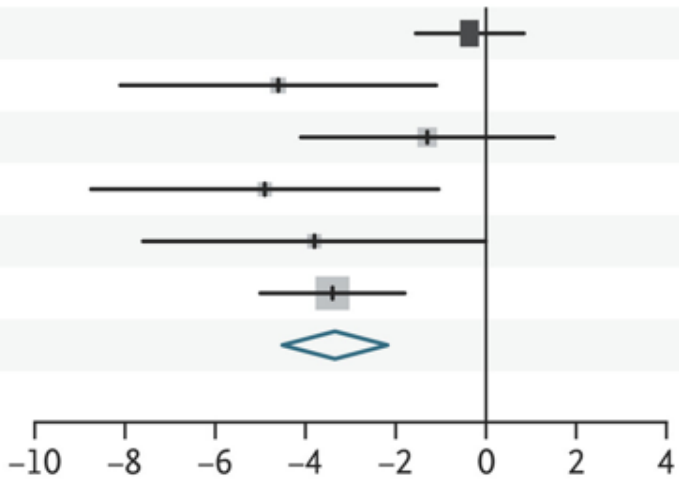
## Effect of Salt Substitution on Cardiovascular Events and Death

Neal B et al. DOI: 10.1056/NEJMoa2105675

**A Systolic Blood Pressure (mm Hg)**

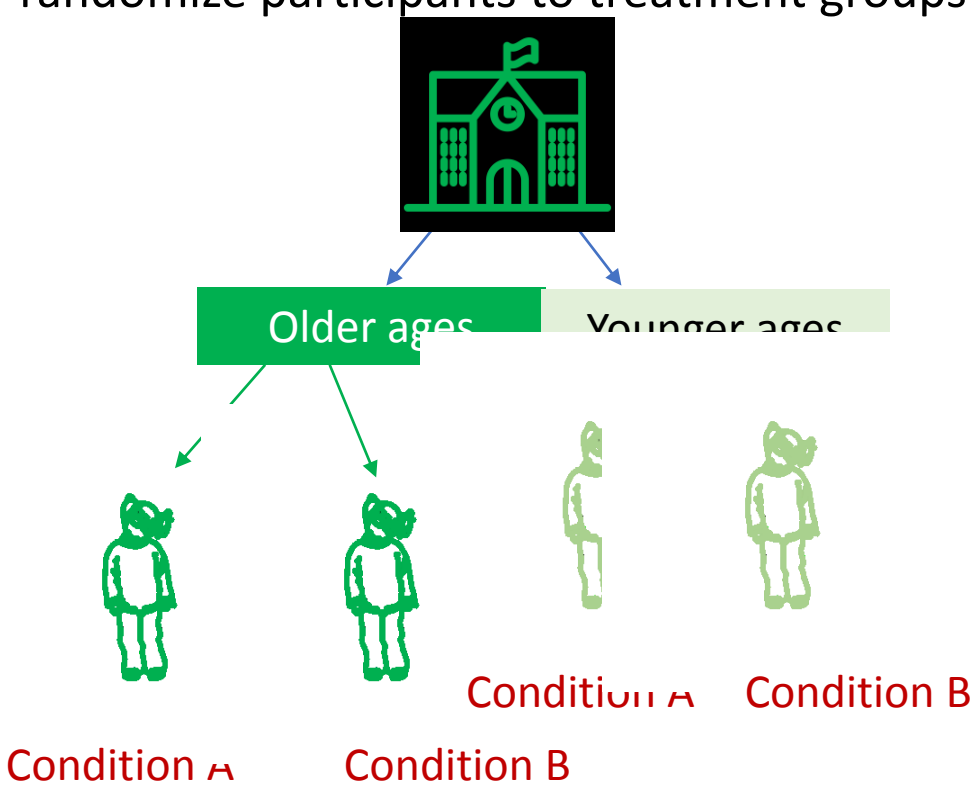
| Time Point | Salt Substitute | Regular Salt | Mean Difference (95% CI) |
|---|---|---|---|
| | *no. of participants* | | |
| Baseline | 10,504 | 10,491 | −0.40 (−2.50 to 1.70) |
| 12 Mo | 768 | 658 | −4.60 (−8.10 to −1.10) |
| 24 Mo | 1,412 | 1,374 | −1.30 (−4.10 to 1.50) |
| 36 Mo | 584 | 584 | −4.90 (−8.75 to −1.05) |
| 48 Mo | 587 | 559 | −3.80 (−7.60 to 0.00) |
| 60 Mo | 7,436 | 7,081 | −3.40 (−5.00 to −1.80) |
| **Fixed-Effects Model** | | | **−3.34 (−4.51 to −2.18)** |

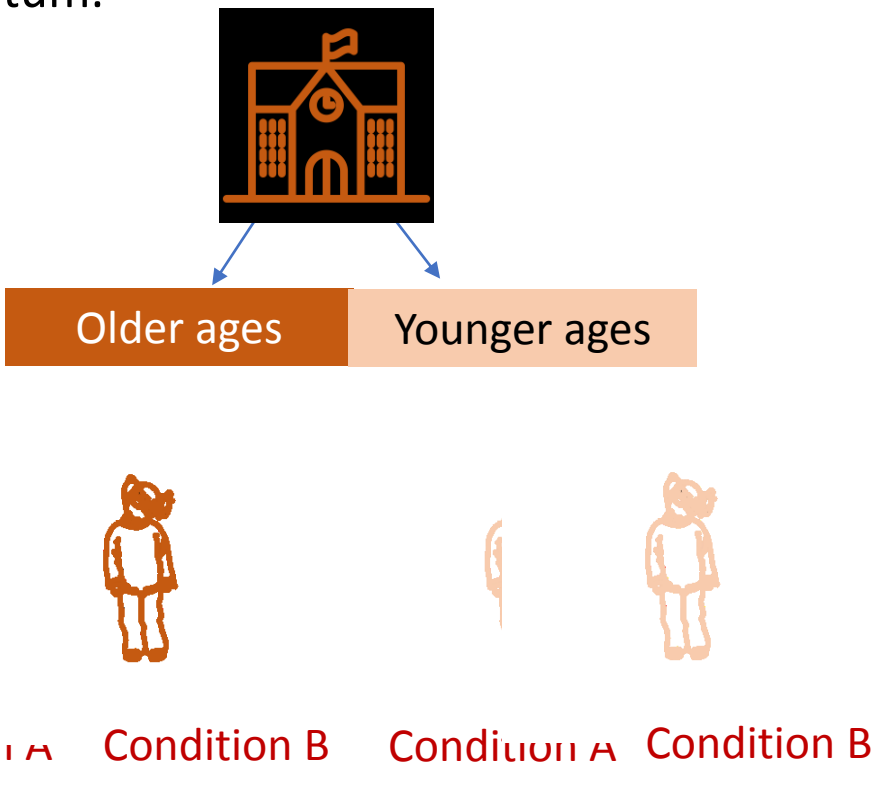
Heterogeneity: $I^2$=0%; P=0.52



# Stratified randomization

- Concern about comparability of the groups in terms of one or a few important characteristics that may influence response to intervention/experiment (Sex, classroom, city, etc.)
- Randomization does not 100% ensure comparability
  - **Randomization within strata can help increase the likelihood of comparability of the study groups.**
- We first stratify our study population by each variable that we consider important and then randomize participants to treatment groups within each stratum.



# Let’s review randomized trials

# Blinding

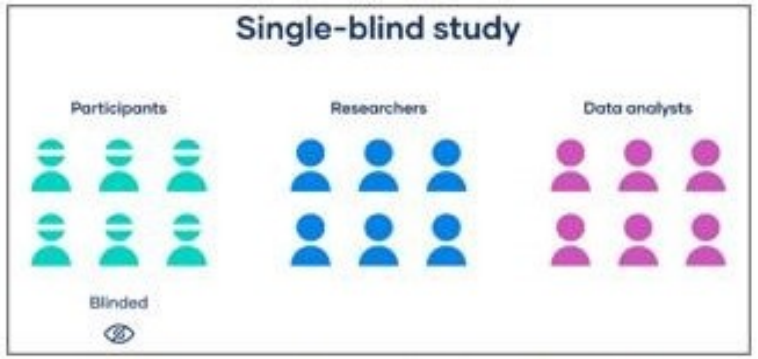

- Blinding refers to the concealment (masking) of group allocation from one or more individuals involved in a RCT.
- Blinding is particularly important when:
  - The outcome is a subjective measure, such as pain
  - The intervention may affect the participant‘s behaviour (measured as exposure)

- How can subjects be masked?
  - Using a placebo (an inert substance that looks, tastes, and smells like the active agent)

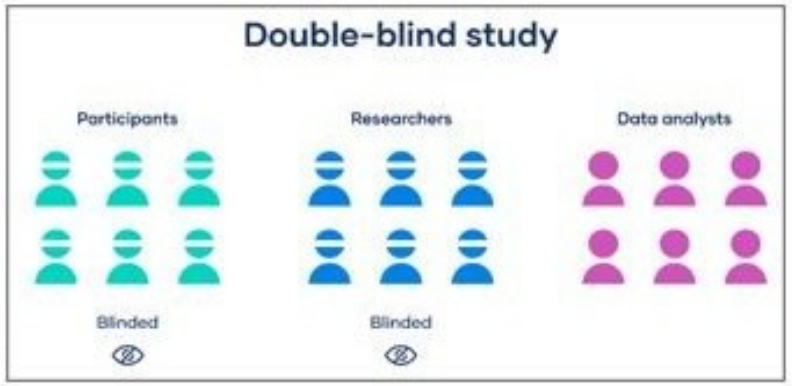
- Use of a placebo does not automatically guarantee that the patients are masked
  - Some participants may try to determine whether they are taking the placebo or active drug

https://nautil.us/sugar-pill-nation-294292/

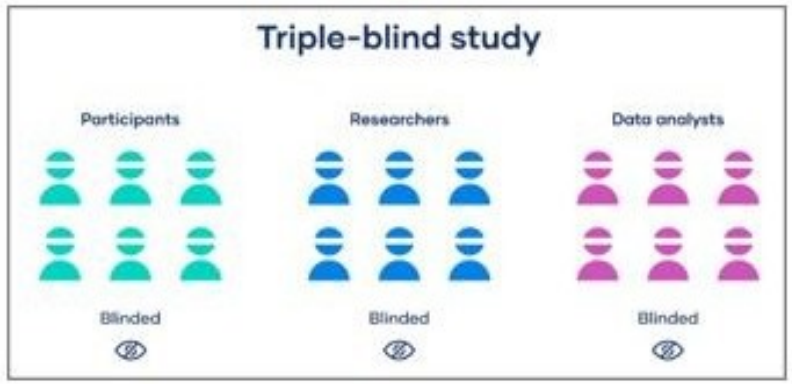
# Types of blinding




**Participants** are not aware whether receiving treatment or placebo.



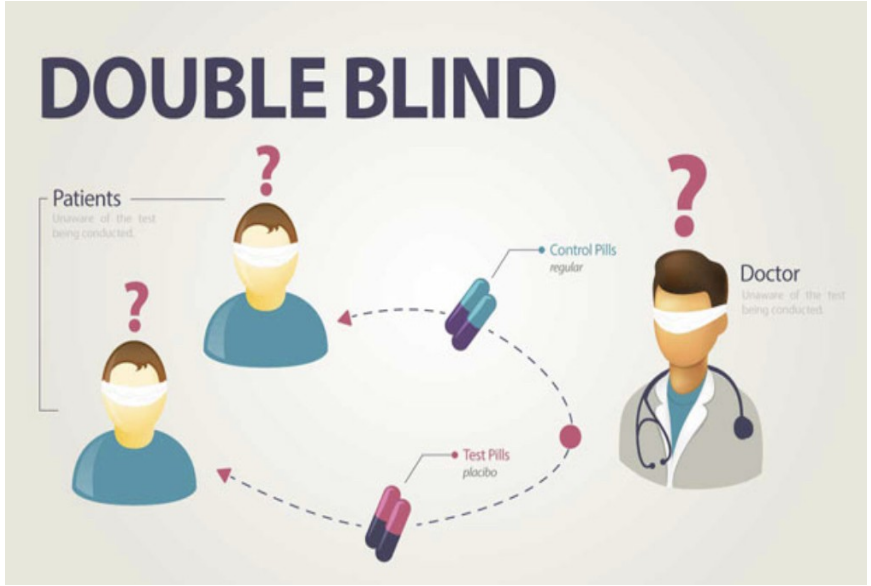

**Neither the subject nor the researcher** is aware of the participant's current treatment.




The intervention being studied is concealed from **the participants, the individuals administering the treatment, and the evaluators of the results**

# Why do we double- or triple- blind the RCTs?

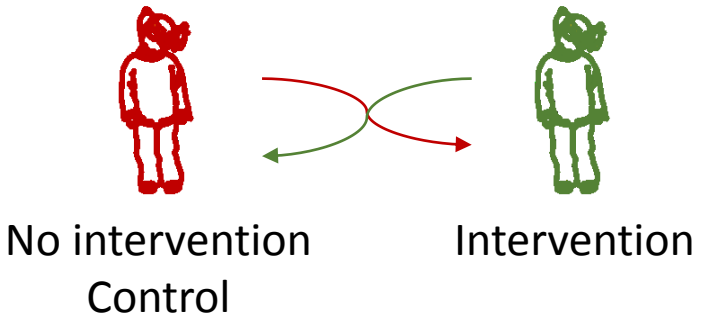
- Observers who think the intervention is effective may probe the subjects who are taking the intervention differently (Observer bias)
- Clinicians who know the subject is taking the placebo may give extra care to compensate not receiving an active treatment (Co-intervention bias)



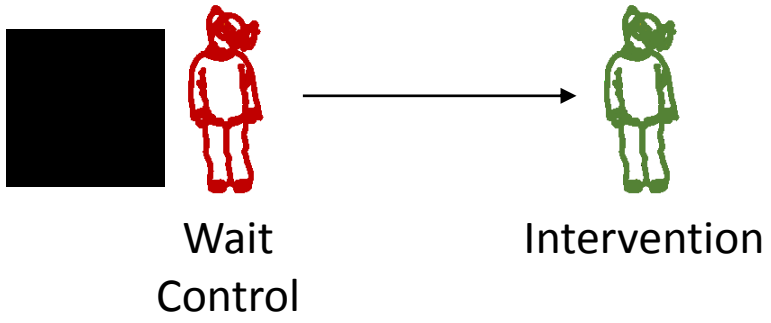

https://www.covid19recovery.net/blog/understanding-clinical-trials

# What if blinding is not possible?

- Happens in behavioral, educational, or clinical care interventions
- Cross-over trials
  - Participants serve as their own controls




- Wait-list control
  - Everyone gets the intervention, but some people randomized to wait before they get it



# Factorial design

- You can test two interventions at once! How convenient!
- Ex., Harvard Women's Health study. Randomized women to both **vitamin E** and **low-dose aspirin (LDA)**:

| | Vitamin E: yes | Vitamin E: no |
|---|---|---|
| Low dose aspirin: yes | Vit E and LDA | LDA only |
| Low dose aspirin: no | Vit E only | Neither (placebo) |

- Neither drug had strong effects on cardiovascular disease or cancer. There were some weak effects on specific outcomes like stroke.
- Factorial designs also allow testing of **effect modification**: *ex.,* is the effect of vitamin E and aspirin taken together stronger than the sum of their individual effects?

# Possible issues during the RCTs

# Data collection: Information bias

- We want comparable measurement between intervention and control groups: this reduces **information bias**
- To prevent **information bias**, you need to measure outcome equivalently for intervention and control groups

- Example, exercise frequency and intensity:
- In a study of online video intervention to increase exercise, the intervention group may report it more accurately because they're more attentive to it
- One way to solve this: **not rely on self-reports**. Maybe look at activity time or steps on a smartwatch. There are privacy and feasibility concerns, though.
- **Information bias** can affect randomized trials. Randomization doesn't solve information bias!
    - Randomization doesn't improve how we collect information

# Drop-ins

- **People in one group may unintentionally take the agent assigned to the other group.**
- **<u>For example:</u>**
  - In a trial of aspirin vs placebo, participants in the placebo group may take aspirin as an over-the-counter medication
- **Two steps were taken to address this problem:**
  - (1) controls were provided with **lists of aspirin-containing** preparations that they should avoid,
  - (2) **urine tests** for salicylates were carried out both in the aspirin group and in the controls.

# Non-compliance

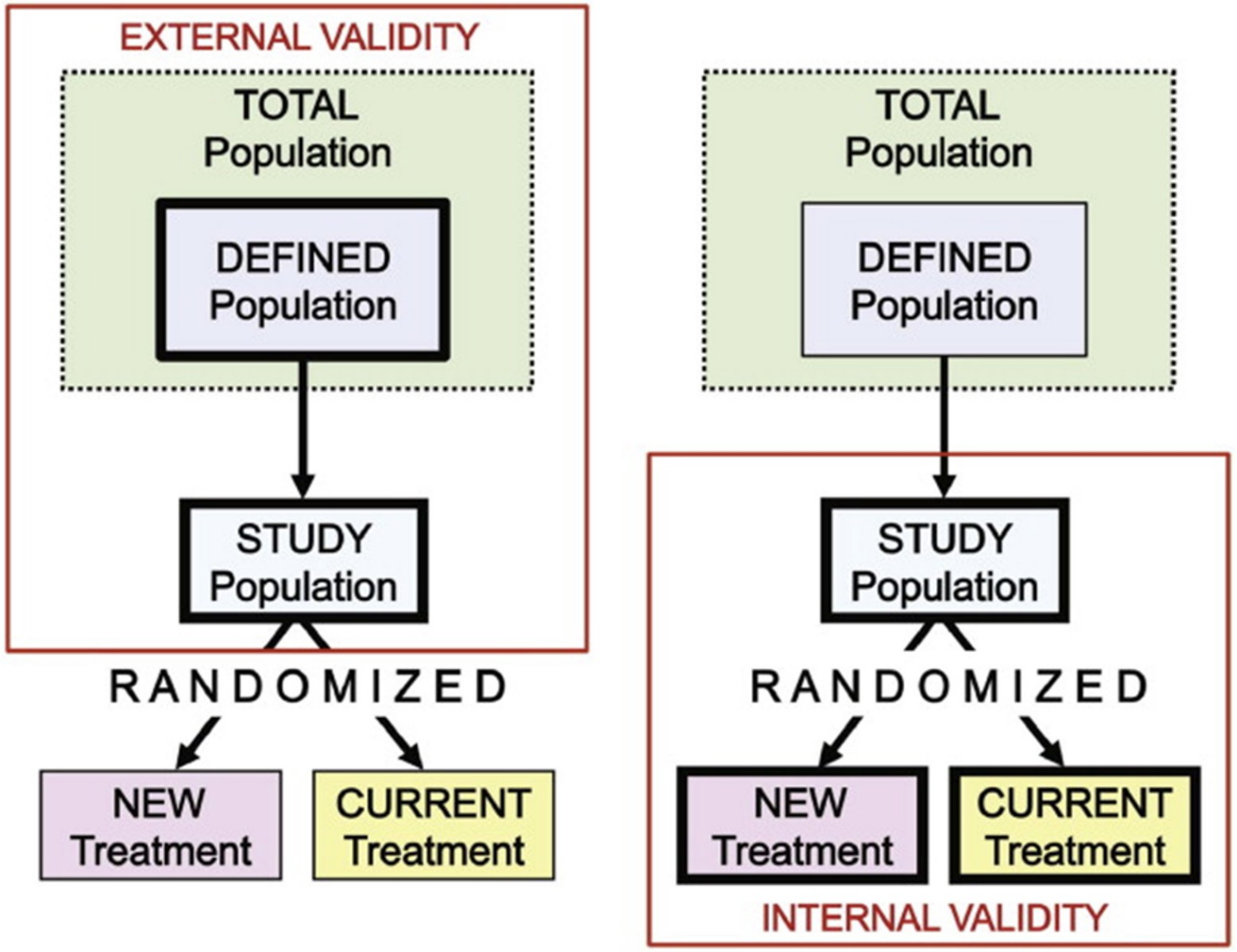
- Noncompliance arises when participants **do not receive the treatment or intervention** to which they were randomly allocated.
- For example, some participants invited to go through a screening program may not attend.

- Noncompliance may be overt or covert: people may **overtly articulate** their refusal to comply or may stop participating in the study (non-compliers are also called ***dropouts*** from the study).
- People may just stop taking the agent assigned **without admitting** this to the investigator or the study staff.
  - Whenever possible, checks on potential noncompliance are built into the study (for example, urine tests for the agent being tested or for one of its metabolites)
- Consequences:
  - The treatment group will include some who did not receive the therapy, and the no-treatment group may include some who received the treatment.
  - The experimental groups are less different.
  - Noncompliance may be differential (related to specific characteristic)→ bias.

# Recruitment and retention of participants

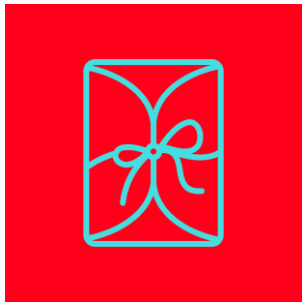
- Recruitment of sufficient numbers of eligible and willing volunteers is major challenge in randomized trials
  - Especially if treatment is long or difficult (has side effects, many tests or procedures).
- Failure to recruit enough volunteers can leave a well-designed trial without enough participants to produce statistically valid results.
- Within the limits of a randomized trial, participants must be fully informed of the risks and what arrangements have been made for their compensation if untoward effects occur.
- A related problem is **retaining volunteers for the full duration of the study**
  - Participants may lose interest in the study over time, or find participation too inconvenient, long.
- Investigators understand why participants often drop out of studies and develop appropriate measures to prevent losses to follow-up.

# External vs. internal validity




- Main objective is to generalize the results of a trial beyond the study population itself.
- Our ability to apply the results to a broader population is called the **generalizability, or external validity**, of the study.

- ***External validity*** should be distinguished from ***internal validity***.
- A randomized trial is ***internally valid*** if the randomization has been properly **done** and the study is **free of other biases** and is without any of the major methodologic problems that have been discussed.
- It should be ideally concluded that the **observed differences** in the outcomes in the two groups being compared are **attributed to the hypothesized exposure** under study, aside from sampling errors.



# Let's wrap this up

*X = Exposure*
*Y = Outcome*

- **Does randomization fix these problems?**
  - **Confounding:** yes! It ensures that nothing but random chance is related to *X*
  - **Selection bias:**
    - yes if it's due to selection *into* the study! It ensures that nothing but random chance is related to *X*
    - no if it's due to loss to follow-up! Because reasons people drop out can still be related to *X* and *Y*
  - **Generalizability:** no! People who join the trial may still be different than people who don't join
  - **Information bias:** no! There can still be measurement inaccuracies in *X* or *Y*

# How to express results from a randomized trial?

- **The number needed to treat (NTT)**

$$\frac{1}{(rate\ in\ placebo\ group\ -rate\ in\ treated\ group)}$$

- **Efficacy**

$$\frac{(rate\ in\ placebo\ group\ -rate\ in\ treated\ group)}{rate\ in\ placebo\ group}$$

A trial for a new drug shows that **30%** of patients in the treatment group and **50%** in the control group experienced an adverse event.

- The number needed to treat (NTT)

$$\frac{1}{(50\%-30\%)} = \frac{1}{20\%} = \frac{1}{0.2} = 5$$

We need to treat 5 patients to save 1 from adverse event.

- Efficacy

$$\frac{(50\%-30\%)}{50\%} = \frac{20\%}{50\%} = 0.4 * 100 = 40\%$$

The treatment is 40% efficacious

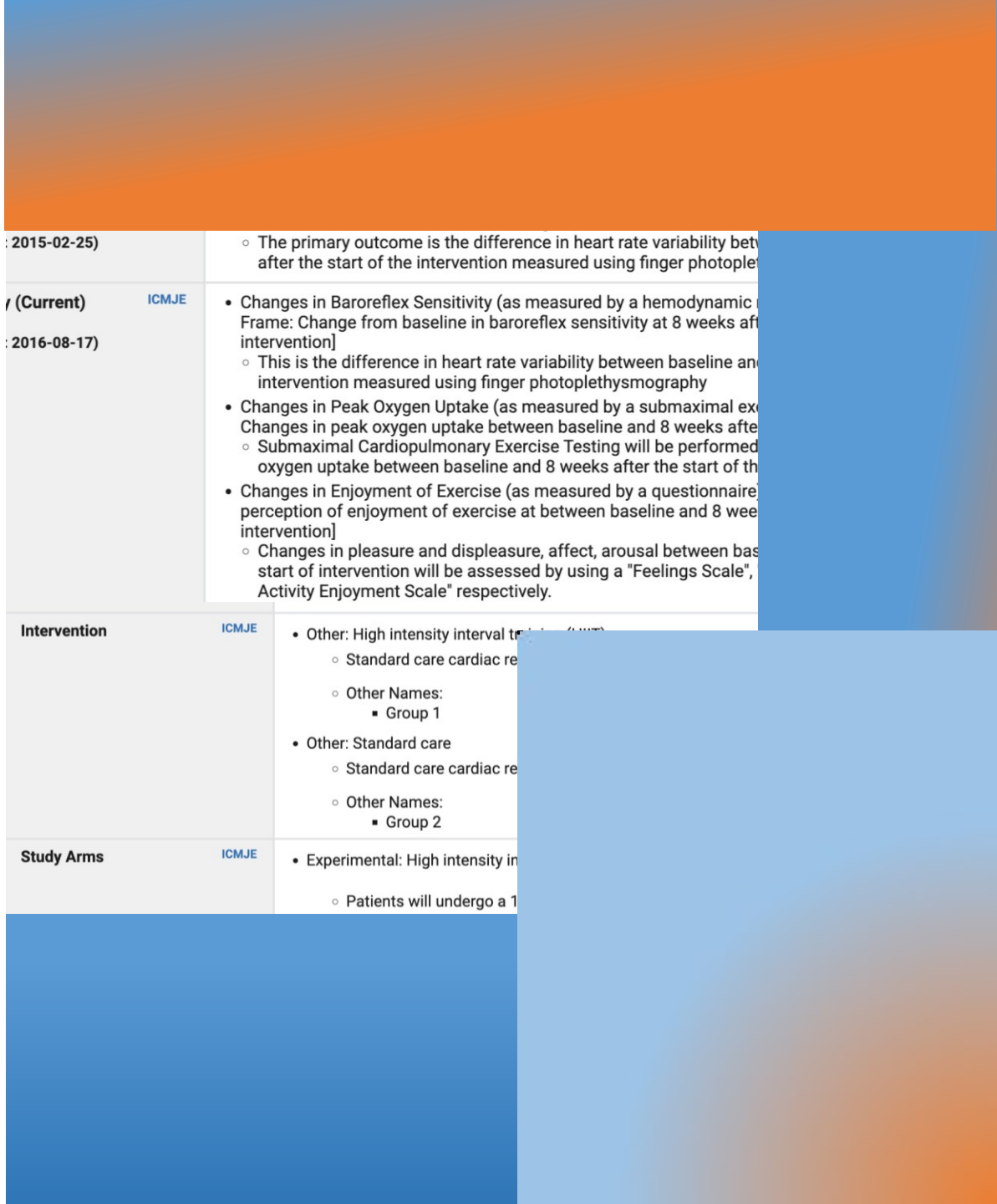
In clinical trials (like in any epi study), we also need to consider whether the result is clinically significant. What is that?

# Clinical trial registration & reporting

- To avoid selective reporting, the International Committee of Medical Journal Editors adopted a policy, which became effective in 2005, that all clinical trials must be **registered** in a public registry **before** any participants are enrolled in the study.
- [www.Clinicaltrials.gov](http://www.Clinicaltrials.gov)
- Clinical trial reporting must follow established guidelines

**CONSORT 2010 checklist of information to include when reporting a randomised trial***

| Section/Topic | Item No | Checklist item | Reported on page No |
|---|---|---|---|
| **Title and abstract** | | | |
| | 1a | Identification as a randomised trial in the title | |
| | 1b | Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts) | |
| **Introduction** | | | |
| Background and objectives | 2a | Scientific background and explanation of rationale | |
| | 2b | Specific objectives or hypotheses | |
| **Methods** | | | |
| Trial design | 3a | Description of trial design (such as parallel, factorial) including allocation ratio | |
| | 3b | Important changes to methods after trial commencement (such as eligibility criteria), with reasons | |
| Participants | 4a | Eligibility criteria for participants | |
| | 4b | Settings and locations where the data were collected | |
| Interventions | 5 | The interventions for each group with sufficient details to allow replication, including how and when they were actually administered | |
| Outcomes | 6a | Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed | |
| | 6b | Any changes to trial outcomes after the trial commenced, with reasons | |
| Sample size | 7a | How sample size was determined | |



# Is using a placebo ethical?

- Placebo-controlled trials
  - Use of an active treatment comparator in a clinical trial of a new therapy is generally the appropriate trial design when an established effective therapy exists
- Placebo can be ok in some circumstances:
    - No established therapy
    - Existing evidence raises significant doubt by medical experts regarding benefit of existing therapy
    - Patients are resistant to existing therapy due to previous history

# Questions?