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Clinical trial

A ALWAYS

S SEEK

K KNOWLEDGE

Research domain

Description of a new health phenomenon

Evaluation of a diagnostic procedure

Evaluation of a therapeutic approach

Evaluation of a risk/ protective or prognostic factors

Learning Objectives

By the end of this lecture, students will:

- Understand what a clinical trial is
- Know the phases of clinical trials
- Identify types of study designs in dentistry
- Understand ethical considerations
- Interpret basic results of clinical trials
- Apply knowledge to dental research scenarios

Trial versus Clinical trial

- trial = the act of testing something
- A clinical trial is a prospective research study
- Conducted on human subjects
- Evaluates:
 - Treatments
 - Procedures
 - Preventive measures
- Compares outcomes between groups

Importance in Stomatology

- Evidence-based dental practice
- Validation of:
 - Restorative materials
 - Implant systems
 - Orthodontic techniques
 - Periodontal therapies
- Improves patient safety and outcomes

Clinical study

- experimental
 - or interventional
- blind – masking treatment allocation
- double blind – for both patients/medical doctors
- randomized – treatment allocation by chance
- controlled – with comparison group

Evaluation of a therapeutic or preventive approach

- definitions

- therapeutic approach – intervention made with the aim to treat a disease

- efficacy

- side effects

- preventive approach – intervention made with the aim to decrease the risk factor

- effectiveness

Clinical Research vs Laboratory Research

Clinical Research

Laboratory Research

Human subjects

In vitro / animals

Real-life conditions

Controlled conditions

High variability

Low variability

Scenario

Comparison of two treatments

- Ex. treatment of dental pain
 - Objective: dental pain relief
- Analgesic: Ibuprofen
 - findings: in 80% of patients have dental pain relief
- Local anesthesia: injection of 2% Lidocaine with 1:100,000 epinephrine
 - findings: in 95% of patients have dental pain relief

- Intervention
 - drug
 - surgical intervention
 - intervention (social, behavioral etc.)
 - medical procedure
 - etc.

Scenarios

Comparing two surgical interventions

- Ex. treatment of angina pectoris
 - Coronary angioplasty
 - Coronary artery bypass graft
 - effectiveness?

Comparing different diets

- Ex. diabetic patients
 - Atkins diet (based on protein) versus vegetarian diet
 - effectiveness in controlling the diabetes?

Trial without control group

- Ex. prevention of hypo- and hyperglycemic episodes in patients with diabetes
- establishment of a forum-type discussion group on the internet
- effectiveness of the forum?

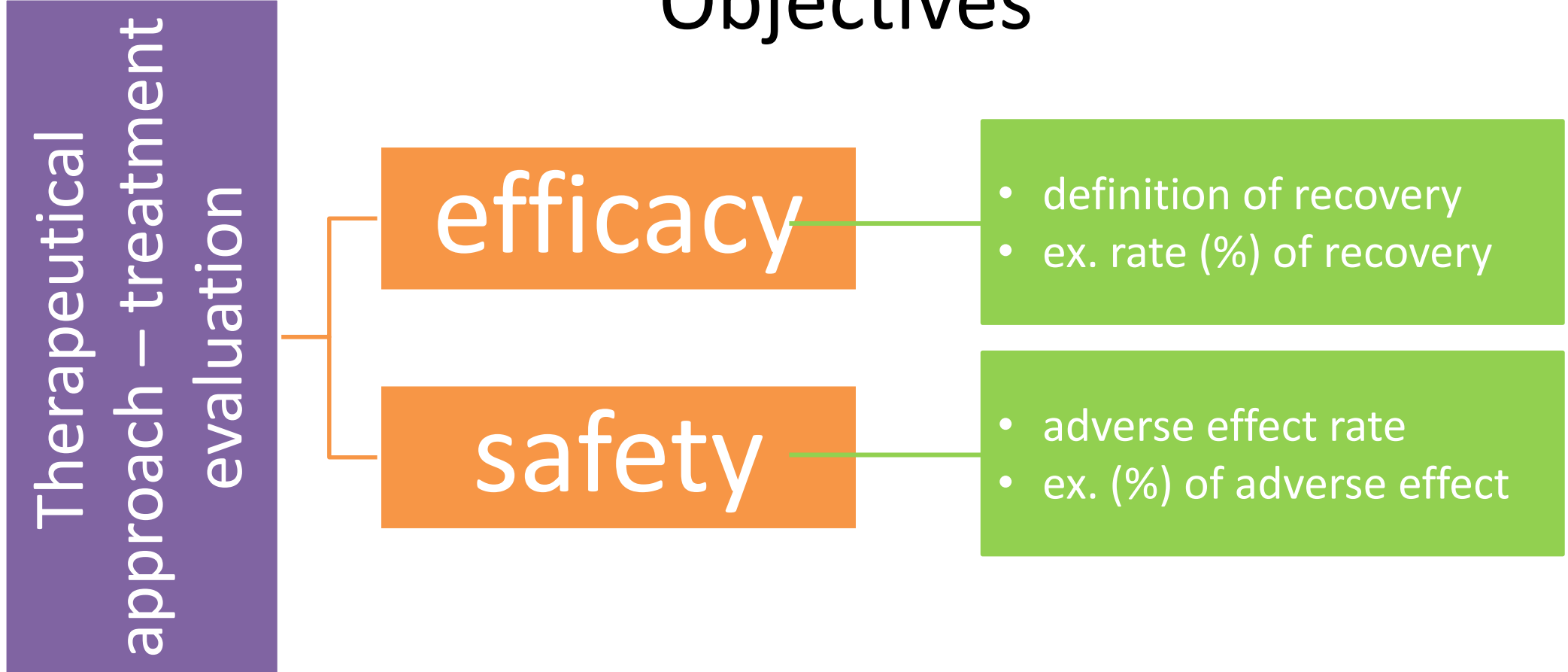
Clinical trial

Experimental studies

Treatment efficacy

- Treatment efficacy
 - produces the intended beneficial effect
- outcome:
 - improvement
 - recovery
- the potential of a treatment protocol to produce a beneficial change in a given clinical population (NHS)

Objectives



Treatment safety

- Adverse effect
 - unexpected medical problem occurring during treatment with a
 - medicine
 - therapy
 - intervention
- Side effects
 - mild
 - moderate
 - severe
- Side effects
 - common (e.g. 1 in 10 patients, 1 in 100 patients)
 - rare (1 in 100,000, 1 in 1,000,000 patients)

Scenarios

Therapeutic approach

Aim

- presurgical antibiotic treatment versus placebo in healthy subjects receiving dental implants

Preventive approach

Aim

- to evaluate **smoking** cessation medication on smoking behaviour
 - bupropion compared with placebo

Legislation

Clinical trials have been regulated by:

- The Nuremberg Code,
- The Declaration of Helsinki,
- The Belmont Report,
- The International Conference on the Harmonization of Clinical Practice Guidelines
- The Conference on the Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use
- In the European Union, trials are regulated by Regulation EU No 536/2014 on clinical trials.
- The European Medicines Agency (EMA) is responsible for the guidelines and guidelines for conducting trials (<http://www.ema.europa.eu/ema/>).

Ethical Principles

- Respect for persons
- Beneficence
- Justice

Informed Consent

- Must be:
 - Voluntary
 - Informed
 - Written
- Patient must understand:
 - Risks
 - Benefits

Legislation

- when it is in the protocol stage
 - The protocol is approved by an ethics committee (either of the respective country or of the respective research institution).
 - before the start of the study
 - Each clinical trial is registered in a database (EU Clinical Trial Portal)

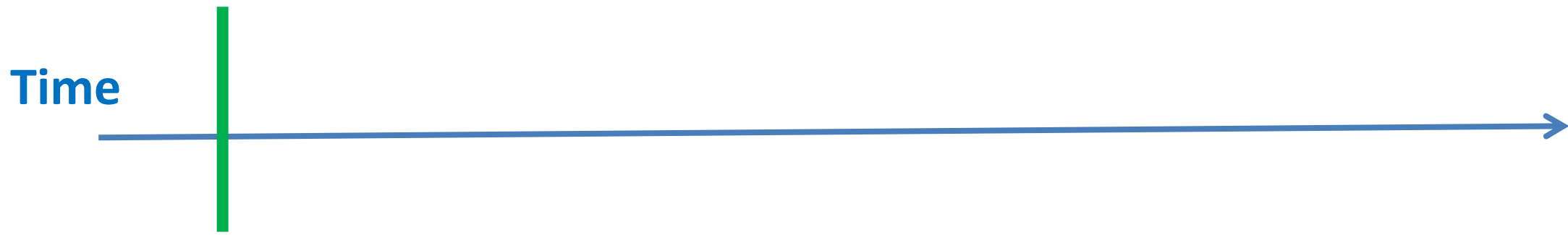
Experimental studies design

Clinical trials

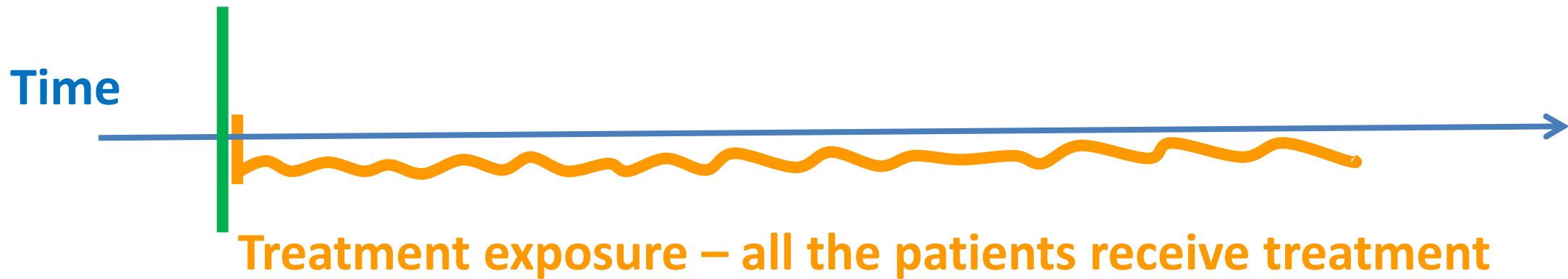
- **Parallel design trials**
 - Randomized
 - Non-randomized
- Sequential design trials
- Self-controlled trials
- Crossover design trials
- External control group trials (including historical)
- Open trials
- Factorial design trials
- Superiority, equivalence or non-inferiority trial
- Uncontrolled trials
- Adaptive design trials

Uncontrolled clinical trial (single group)

start of the study – random recruitment of patients

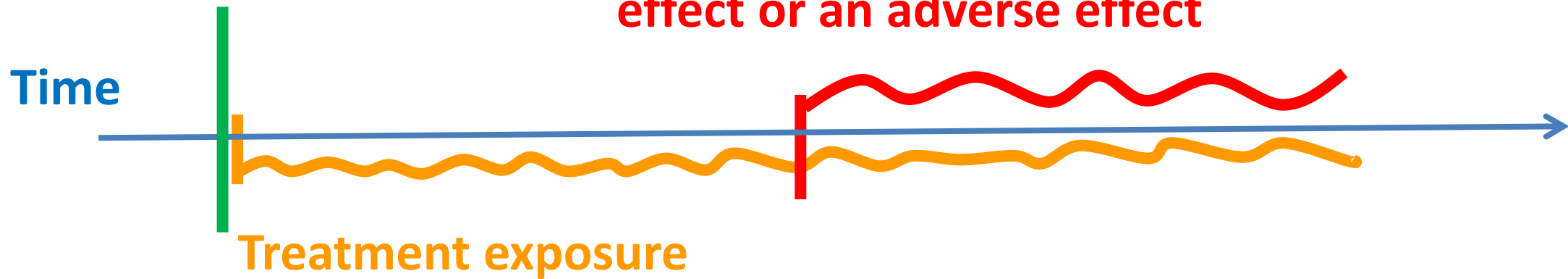


start of the study – random recruitment of patients



start of the study –
random recruitment of
patients

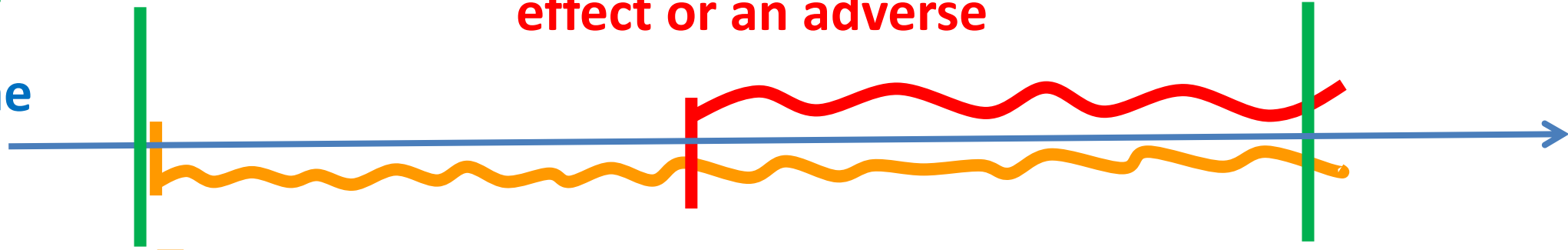
The occurrence of a beneficial
effect or an adverse effect



start of the study –
random recruitment
of patients

The occurrence of a beneficial
effect or an adverse

Time



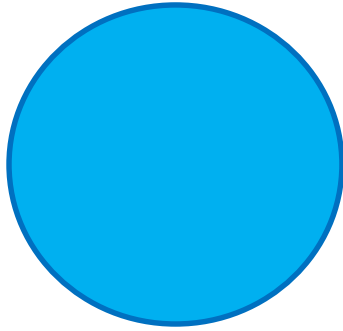
Treatment exposure

Follow-up – Evaluation

Parallel design trials (classical)

Controlled clinical trial

**Random
inclusion of
patients**

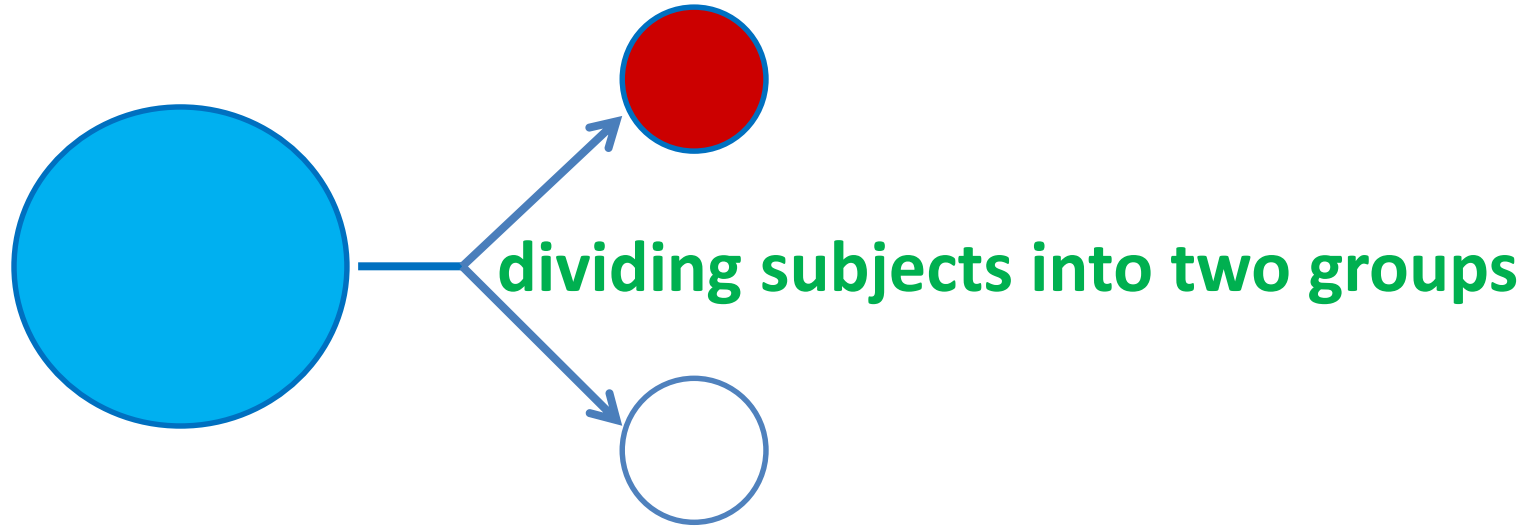


Time

Start of the study



**Random
inclusion of
patients**



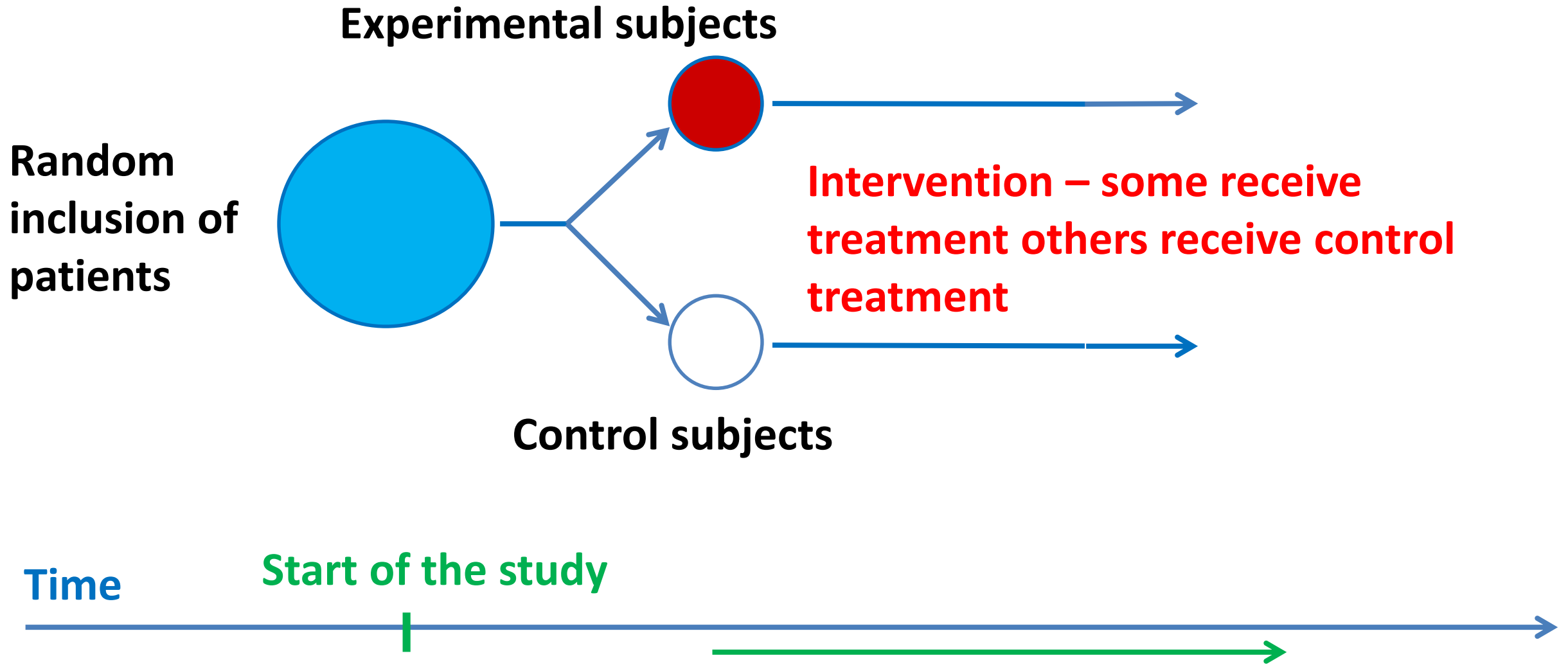
Experimental subjects - exposed to treatment

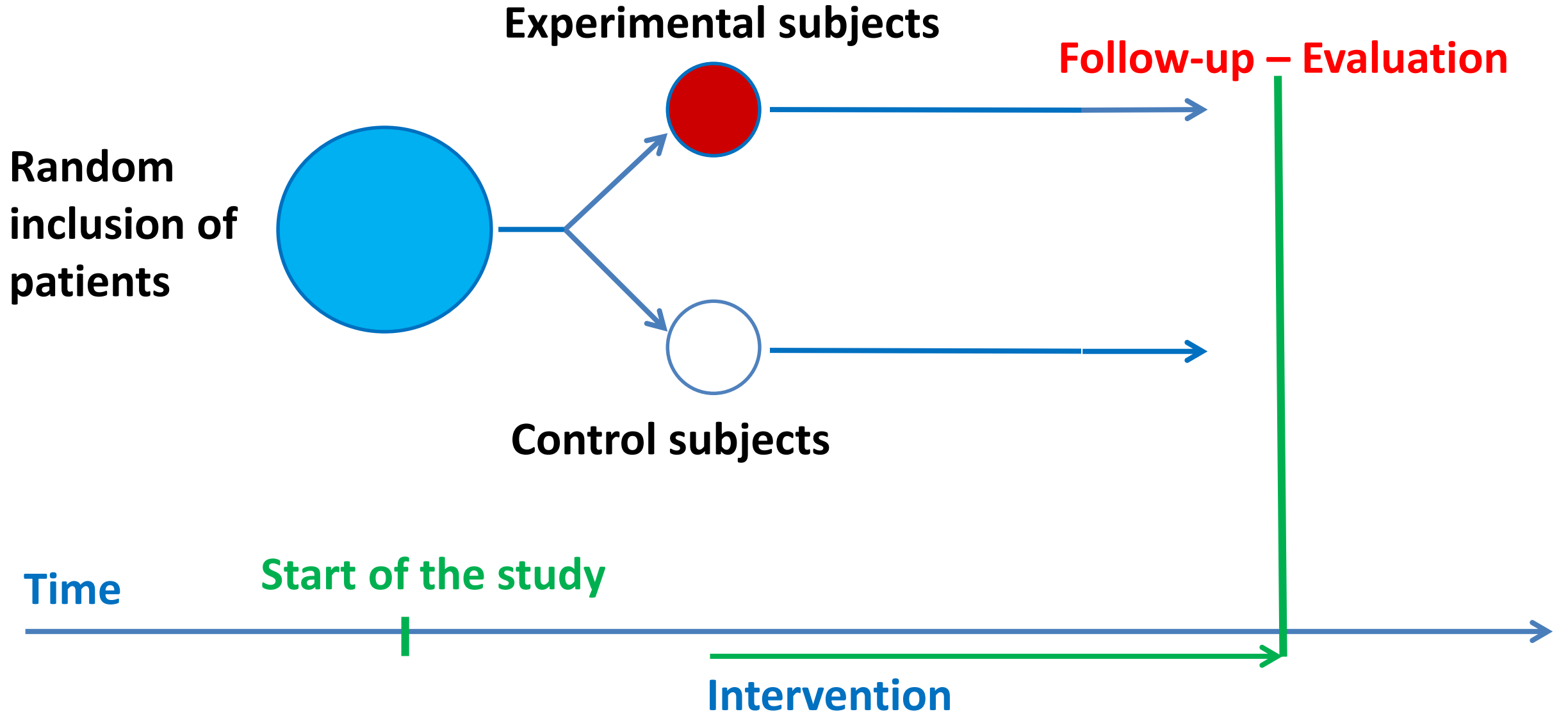
**Control subjects – not exposed to treatment
(placebo or another known treatment)**

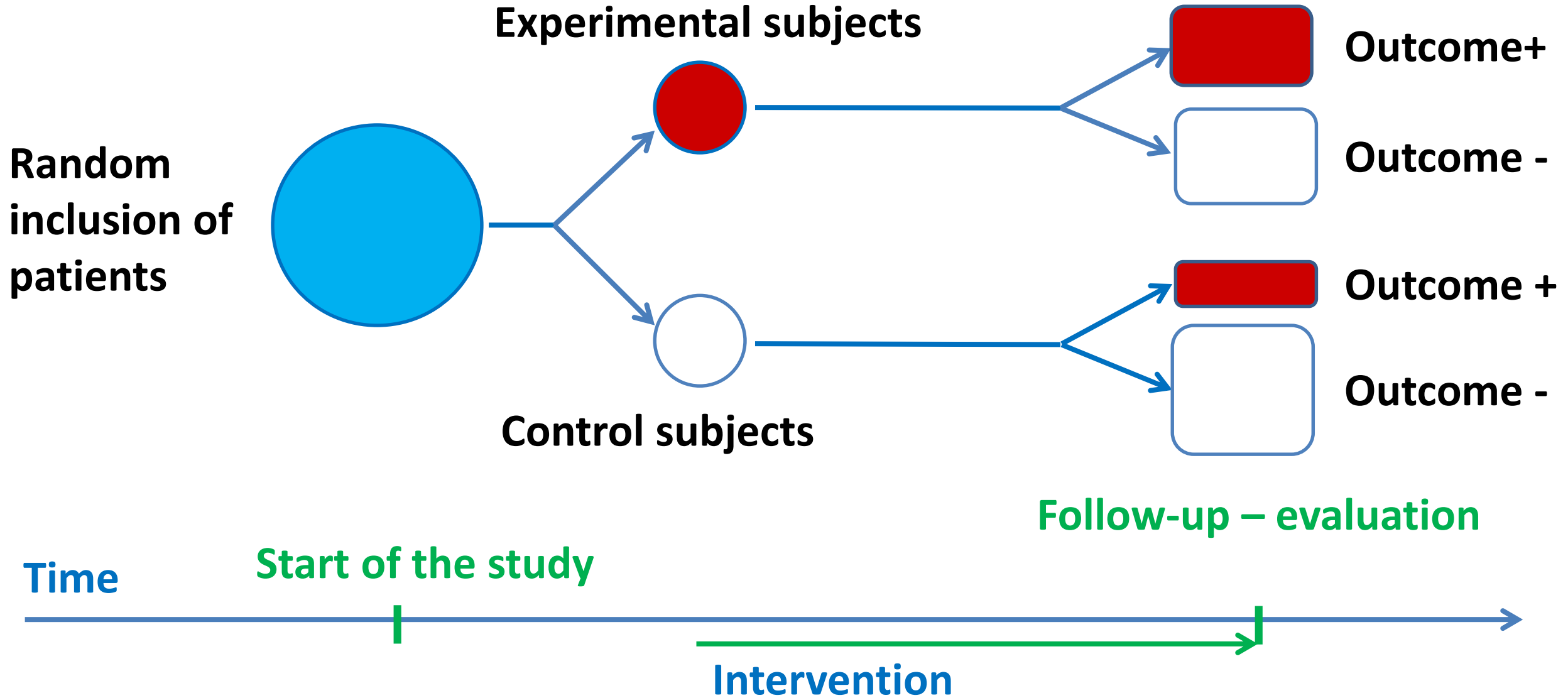
Time

Start of the study







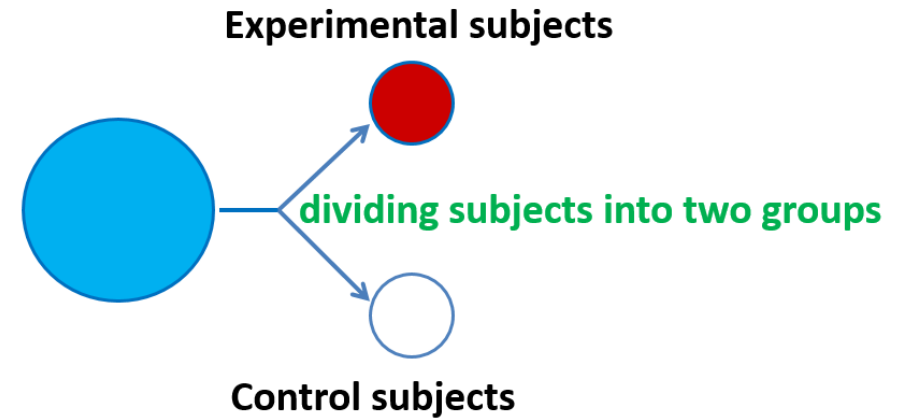


Controlled trial

- with control group
 - placebo control
 - sugar pill
 - look exactly the same as treatment
 - syringe with serum
 - active control - another known treatment
 - Is it ethical to treat with placebo?
 - only if there is no other treatment for the condition
 - no-treatment control

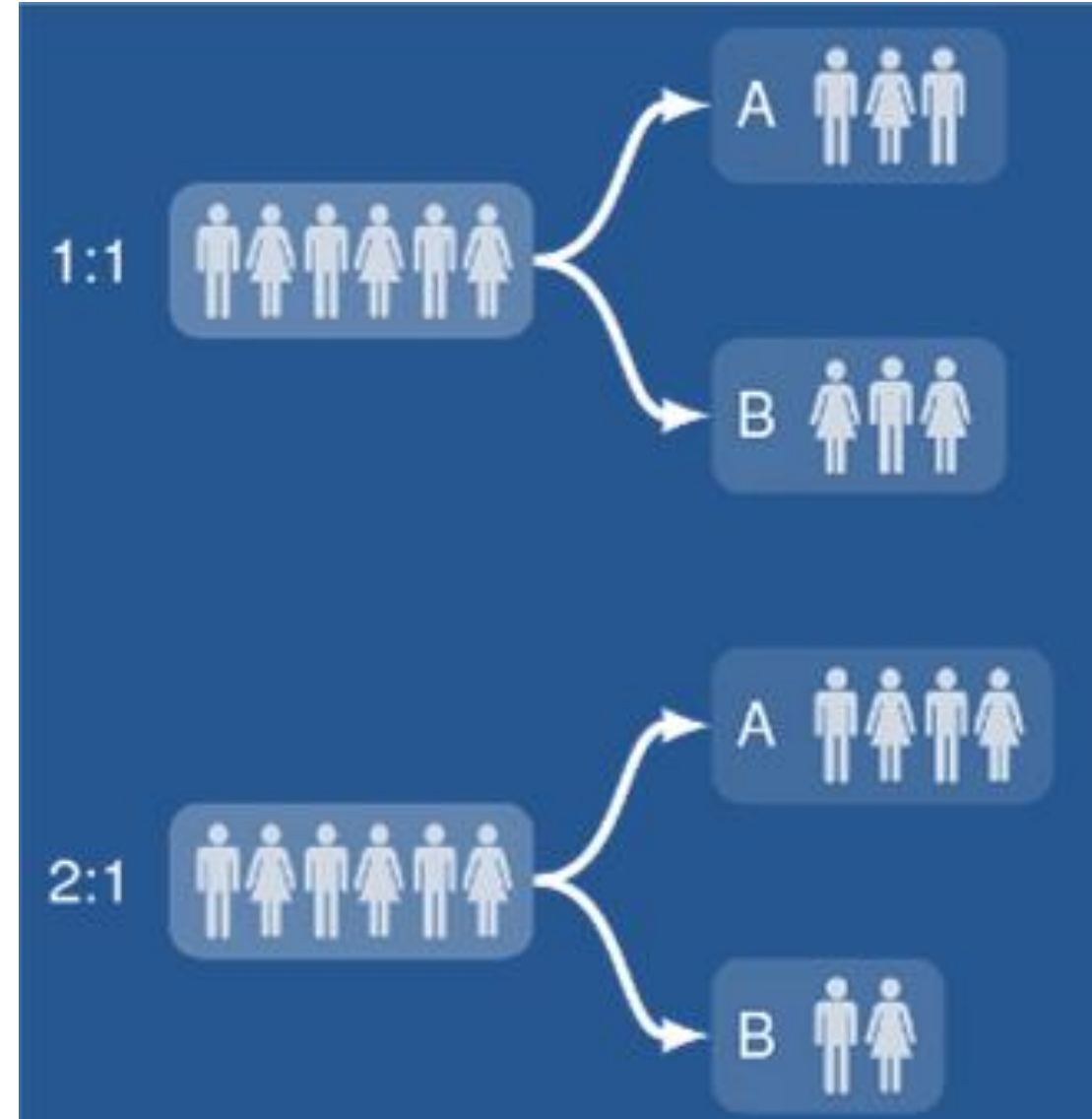
Treatment randomization

- Randomization = random division into therapy groups
- How?
 - using a computer application
 - by drawing lots
 - etc.
- 1:1 ratio division (equal groups)
- 2:1 (one group has twice as many subjects as the other),
- etc.



Randomization

- 1:1 ratio
- 2:1 ratio



Study Design: Randomization

- Reduces bias
- Types:
 - Simple randomization
 - Block randomization
 - Stratified randomization

Similar condition

- we say “it was carried out under similar conditions”:
 - if the difference between the groups is only the treatment
 - The influence of other factors was eliminated

Comparability

“comparability” of groups

– at baseline (before administration, after randomization)

= the groups do not have different characteristics

– The influence of other factors eliminated

If there is no comparability:

- the differences found at the end of the study
 - are due to the treatment or to the initial differences?
 - they may be due to the initial differences
 - we failed to demonstrate what we set out to do

Comparability of groups at the time of selection

- Differences between groups at baseline may influence the outcome:
 - mean age – if the age influence the disease/recovery we are interested in
 - percentage of women - if the sex influence the disease/recovery we are interested in
 - percentage of comorbidities (diseases present at the same time as the disease of interest) - if the these comorbidities influence the disease/recovery we are interested in
 - percentage of known risk factors (e.g. smoking, salt intake, etc.) - if these risk factors influence the disease/recovery we are interested in

Observational / not randomized clinical trial

- not preferably
- Errors: comparing groups which are not randomized to the treatment
 - high probability of differences between groups at the beginning of the study
 - Ex.
 - if the patient is severe
 - » medical doctors prescribe a better treatment, but expensive
 - if the patients condition is mild
 - » medical doctors prescribe a less effective treatment, but cheap
 - observational study results: no difference between the recovery rate
 - No difference is because there is no difference between the treatments or is because of the difference between the condition of the patients when we start the medication?

Blind - Allocation concealment

Concealed (blind) treatment/placebo allocation

subjects do not know whether they are receiving the treatment or the control treatment

Human behaviour is influenced by what we know or believe

source of errors

Single or double blind

Patients know if they receive treatment or placebo

The doctor who give the treatment know if they receive treatment or placebo

The doctor who evaluate the treatment know if they receive treatment or placebo

} open trial

Patients **don't** know if they receive treatment or placebo

The doctor who give the treatment know if they receive treatment or placebo

The doctor who evaluate the treatment know if they receive treatment or placebo

} allocation concealed

Patients **don't** know if they receive treatment or placebo

The doctor who give the treatment **don't** know if they receive treatment or placebo

The doctor who evaluate the treatment know if they receive treatment or placebo

} blind

Patients **don't** know if they receive treatment or placebo

The doctor who give the treatment **don't** know if they receive treatment or placebo

The doctor who evaluate the treatment **don't** know if they receive treatment or placebo

} double blind

Study characteristics

- By objective:
 - analytical study
- By population included in the study:
 - sampling
- By duration:
 - Longitudinal
 - Prospective
- By research field
 - Research on therapeutic factors
- By collection method:
 - exposed-unexposed after randomization

Treatment effectiveness

- A treatment is considered to have an effect
 - if its effect is statistically significantly greater than the effect observed in the control group
- The effect = the study objective (endpoint)

Data analysis type

```
graph TD; A[Data analysis type] --> B[Intention to treat]; A --> C[per protocol]; A --> D[Side effect analysis];
```

Intention to treat

all patients are analyzed in the groups they were randomized to

per protocol

only analyze patients who were treated according to the study protocol

Side effect analysis

analyze all subjects who received at least one dose

Intention to treat

= The patient enters the analysis in the group to which he was initially allocated, regardless of whether they completed it

- not completed
 - the patient is lost from the study
 - sudden worsening of health condition
 - the experiment is interrupted
 - in the case of treatments administered by the patient at home
 - treatment compliance cannot be verified
 - = not all patients take (apply) the prescribed treatments
 - » forgetfulness
 - » ignorance
 - » etc.

Per protocol

- studies with a protocol that approaches ideal conditions
- The doctor administers the patient's treatment
- The patient is under continuous monitoring
- if patients are lost from the study, the exact reason is known

Follow-up

- Follow-up = monitoring patients over time
- Subject monitoring
 - Continuous
 - Discontinuous
- Treatment may be interrupted for various reasons:
 - patient safety,
 - a faster appearance of the desired effect than expected in the protocol
- Subject monitoring
 - two repeated measurements
 - multiple repeated measurements.

Causality

- “causality” - a cause-effect relationship
- experimental method - randomized controlled clinical trial
- the only one capable of demonstrating “causality”

End-point a quantitative variable

evaluated parameter - the end-point

Statistical analysis

the treatment is effective if the quantitative variable change (decreases/increases) more than in those treated with placebo

Treatment effect = δ (delta, Δ)

- the difference between the initial and final moment for each patient
- calculate the averages of the differences
 - mean delta 1 - those treated with the drug
 - mean delta 2 - those treated with placebo
- compare the mean delta 1 with 2
 - T-test for independent samples (or an analogous non-parametric test)
 - if $p < 0.05$ - there is a statistically significant difference between the two compared means, in the sense of improvement, then the treatment is considered efficient/effective.

Scenario

Aim: A cardiologist wants to test the effectiveness of a new treatment in lowering blood pressure, compared to a reference treatment.

expected effect: lowering systolic blood pressure

randomized double-blind clinical trial

200 hypertensive patients

100 receive the new treatment Valsartan

100 receive Indapamid

Treatment efficacy – quantitative variable

TAS – Systolic blood pressure; Delta TAS=TAS initial – Final TAS

| | A | B | C | D | E | F |
|----|------------|-----------|------------|-----------|-----------|---|
| 1 | Id_pacient | Tratament | TAS intial | TAS final | Delta TAS | |
| 2 | 1 | Valsartan | 169 | 133 | 36 | |
| 3 | 2 | Valsartan | 169 | 158 | 11 | |
| 4 | 3 | Valsartan | 173 | 130 | 43 | |
| 5 | 4 | Valsartan | 173 | 150 | 23 | |
| 6 | 5 | Valsartan | 155 | 145 | 10 | |
| 7 | 6 | Valsartan | 177 | 133 | 44 | |
| 8 | 7 | Valsartan | 181 | 122 | 59 | |
| 9 | 8 | Valsartan | 184 | 110 | 74 | |
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| 15 | 14 | Indapamid | 215 | 133 | 82 | |
| 16 | 15 | Indapamid | 170 | 133 | 37 | |
| 17 | 16 | Indapamid | 155 | 115 | 40 | |
| 18 | 17 | Indapamid | 219 | 133 | 86 | |
| 19 | 18 | Indapamid | 145 | 137 | 8 | |
| 20 | 19 | Indapamid | 151 | 137 | 14 | |
| 21 | 20 | Indapamid | 221 | 140 | 81 | |

- Mean Delta Valsartan = 45 mmHg
- Mean Delta Indapamid = 30 mmHg
- apply the **t-test for independent samples**
- **null hypothesis:** there is no statistically significant difference between the mean delta of **those treated with Indapamid and those treated with Valsartan**
- **alternative hypothesis:** there is a statistically significant difference between the mean delta of those treated with Indapamid and those treated with Valsartan
- $p = 0.04 \leq 0.05$
 - we reject the null hypothesis we accept the alternative hypothesis:
there is a statistically significant difference between the mean delta of those treated with Indapamide and those treated with Valsartan

Treatment efficacy – quantitative variable

mean Delta Valsartan - mean Delta Indapamide = 15 mmHg,
95% CI 10; 20

Interpretation - If the entire population will be treated with Valsartan instead of Indapamid, the mean SBP would decrease with 10 to 20 mmHg more with an error of 5%

Clinical interpretation

- The difference between the mean Delta Valsartan and the mean Delta Indapamid = 15 mmHg
 - indicates a clinically insignificant difference between Valsartan and Indapamid
- 95% CI 10; 20
- The confidence interval is narrow – precise study
- Given that one end of the interval indicates a possible decrease of 10 mmHg
 - if we treated the entire population with Valsartan compared to Indapamid, this is not of clinical importance.
 - So we cannot say that Valsartan produces clinically significant effects

End point a qualitative variable

Data analysis – qualitative variables as end-point

treatment is effective in one patient if patient marker (end-point) touch the threshold for normality

more patients have effective treatment if they are treated with the drug compare with placebo

Treatment effect = frequency % of patients with effective treatment

calculate

frequency 1 of patients with effective treatment - those treated with the drug

frequency 2 of patients with effective treatment - those treated with placebo

compare frequencies 1 with 2

Chi-square test (or Fisher exact for small samples)

If $p < 0.05$ - there is a statistically significant difference between the two compared frequencies, in the sense of improvement, then the treatment is considered effective

Data analysis – qualitative variables as end-point

| | | | |
|------------------------|---------------------------|---------------------------|------------------------------|
| | Effect ⁺ | Effect ⁻ | |
| Treatment ⁺ | a | b | Total treatment ⁺ |
| Treatment ⁻ | c | d | Total treatment ⁻ |
| | Total effect ⁺ | Total effect ⁻ | n |

Calculations

- Experimental Event Rate (EER)

- the relative frequency of subjects in the experimental group for whom the treatment was effective:

$$EER = \frac{a}{a + b}$$

- Control Event Rate (CER)

- the relative frequency of subjects in the control group for whom the treatment was effective:

$$CER = \frac{c}{c + d}$$

- Relative risk (RR)

- the ratio of the experimental event rate to the control event rate:

$$RR = \frac{EER}{CER}$$

- Absolute Risk Reduction (ARR)
 - the absolute difference between the experimental event rate and the control event rate:

$$ARR = |EER - CER|$$

- Number Needed to Treat (NNT)
 - the number of patients who need to be treated with the study treatment in order to have an effect in 1 patient:

$$NNT = \frac{1}{ARR}$$

Scenario

Aim: A cardiologist wants to test the effectiveness of a new treatment in lowering blood pressure, compared to a reference treatment.

expected effect: lowering systolic blood pressure

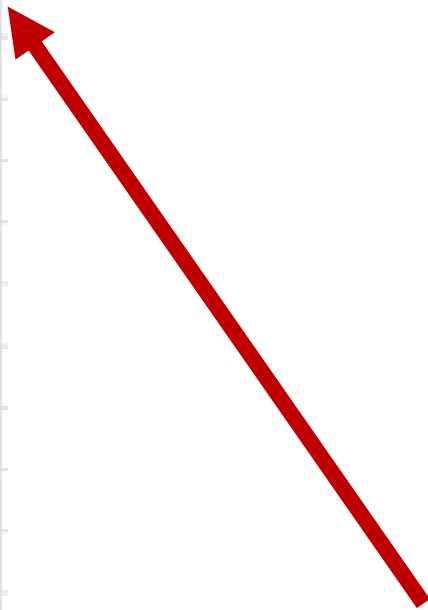
randomized double-blind clinical trial

200 hypertensive patients

100 receive the new treatment Valsartan

100 receive Indapamid

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|----|------------|-----------|------------|-----------|
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| 4 | 3 | Valsartan | 173 | 130 |
| 5 | 4 | Valsartan | 173 | 150 |
| 6 | 5 | Valsartan | 155 | 145 |
| 7 | 6 | Valsartan | 177 | 133 |
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| 9 | 8 | Valsartan | 184 | 110 |
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| 11 | 10 | Valsartan | 196 | 145 |
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| 16 | 15 | Indapamid | 170 | 133 |
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| 18 | 17 | Indapamid | 219 | 133 |
| 19 | 18 | Indapamid | 145 | 137 |
| 20 | 19 | Indapamid | 151 | 137 |
| 21 | 20 | Indapamid | 221 | 140 |



TAS = SBP – Systolic blood pressure;
Efficient – if the patient have
normal SBP (<145) at the follow-up

Results:

Of the 200 subjects,

100 used Valsartan

Of these 80 had normal blood pressure at follow-up

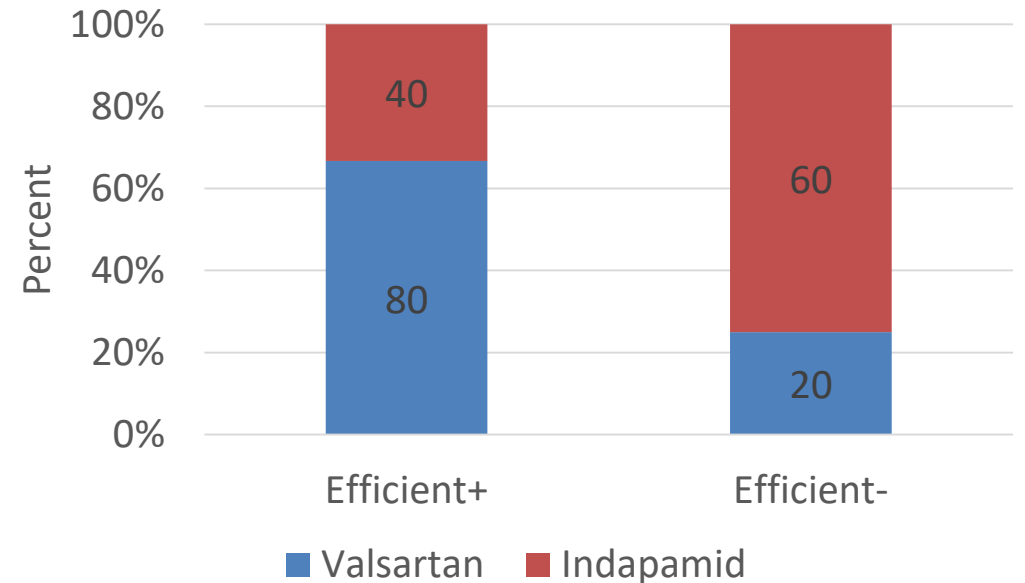
100 used Indapamid

Of these 40 had normal blood pressure at follow-up

Observed contingency table

| | Normal SBP Efficient+ | Hipertension Efficient- | |
|-----------|--------------------------|----------------------------|-----|
| Valsartan | 80 | 20 | 100 |
| Indapamid | 40 | 60 | 100 |
| | 120 | 80 | 200 |

- Experimental event rate (EER) = $80/100 = 0.80$
- Control event rate (REC) = $40/100 = 0.40$
- 80% of patients treated with Valsartan had normal SBP at follow-up
- 40% of patients treated with Indapamid had normal SBP at follow-up



Chi-square test

- **Null hypothesis (H0):** Treatment and SBP are independent
- **Alternative hypothesis (Ha):** Treatment and SBP are dependent

$p=0.00000001$

- $p < 0.05$ we reject H0, we accept Ha: Valsartan and Indapamide differ significantly in terms of lowering HTA

RR – relativ risk

- $RR = \frac{EER}{CER} = \frac{\frac{a}{a+b}}{\frac{c}{c+d}} = \frac{0.80}{0.40} = 2$
- $RR > 1$ indicates a risk factor (here protection, because the “disease” is a positive event: the absence of high SBP).
- Interpretation:
- Twice as many subjects who were treated with Valsartan did not have high SBP compared to those treated with Indapamide

95% confidence interval (CI) for RR

- RR=2, 95% CI 1.30-2.80
- The 95% confidence interval indicates the presence of a prognostic factor (the value 1 is not in the interval, the RR in the population cannot take the value 1)
- interpretation: The RR of the population is in the range 1.30-2.80 with an error of 5%

Absolute risk reduction (ARR)

- $ARR = |ERR - CER| = \frac{a}{a+b} - \frac{c}{c+d} = 0.80 - 0.40 = 0.40$

→ ARR = 40%

- Interpretation:

- 40% more patients did not have high SBP as a result of treatment with Valsartan compared to Indapamid
- Valsartan treatment is 40% more effective than Indapamid

Number needed to treat (NNT)

- $NNT = 1/ARR = 1/0.40 = 2.5$
- 2.5 patients need to be treated with Valsartan for 1 to have an additional blood pressure reduction compared to Indapamide

Clinical interpretation

- NNT=2.5 and RR =2 – indicates a significant difference between Valsartan and Indapamid
- 95% CI 1.30-2.80
- Confidence interval is narrow – precise study
- Not both ends of the confidence interval indicate a significant factor (1.30-not very far from 1), so the difference between the two treatments is unclear

Trial to evaluate adverse effects

Scenario

Treatment of hyperglycemia with insulin can produce hypoglycemia as an adverse effect

Hypoglycemia

glycemia below 50mg/dl (threshold for normality)

qualitative parameter

calculate frequencies

Is there a significant difference between the frequency of hypoglycemia in those treated with insulin compared to those treated with placebo?

Statistical analysis

Frequency of hypoglycemia

- frequency 1 of hypoglycemia in those treated with medication
- frequency 2 of hypoglycemia in those treated with placebo

compare the frequencies

- Chi-square test (or Fisher exact for small samples)
- $p < 0.05$ - between the two compared frequencies there is a statistically significant difference, in the sense of the occurrence of hypoglycemia, then it is considered that the treatment has an adverse effect

Adverse effects

| | Adverse effects ⁺ | Adverse effects ⁻ | |
|------------------------|------------------------------------|------------------------------------|------------------------------|
| Treatment ⁺ | a | b | Total treatment ⁺ |
| Treatment ⁻ | c | d | Total treatment ⁻ |
| | Total adverse effects ⁺ | Total adverse effects ⁻ | n |

Trial – Adverse effects

It is possible to calculate

- Individual Risk of Exposed (RIE)
- Individual Risk of Unexposed (RIN)
- Relative Risk (RR)
- Absolute Risk Reduction (ARR)
- Number Needed to Harm (NNH)

Calculation

- Individual Risk of Exposed (IRE)
 - the relative frequency of subjects in the experimental group for whom there were adverse effects:

$$IRE = \frac{a}{a + b}$$

- Individual Risk of Non-exposed (IRN)
 - the relative frequency of subjects in the control group for whom there were adverse effects:

$$IRN = \frac{c}{c + d}$$

- Relative Risk (RR)
 - the ratio of RIE and RIN:

$$RR = \frac{IRE}{IRN}$$

- Absolute Risk Reduction (ARR)
 - Absolute difference between IRE and IRN:
- Number needed to harm (NNH) –
 - the number of patients who must be treated with the study treatment for 1 patient to experience adverse effects:

$$ARR = |IRE - IRN|$$

$$NNH = \frac{1}{ARR}$$

Scenario

Aim: A cardiologist wants to test the effectiveness of a new treatment in lowering blood pressure, compared to a reference treatment.

adverse effect: treatment allergy

randomized double-blind clinical trial

200 hypertensive patients

100 receive the new treatment Valsartan

100 receive Indapamid

| | A | B | C | D | E | F | G |
|----|------------|-----------|------------|-----------|-----------|----------|---------|
| 1 | Id_pacient | Tratament | TAS intial | TAS final | Delta TAS | Eficient | Alergie |
| 2 | 1 | Valsartan | 169 | 133 | 36 | Da | Nu |
| 3 | 2 | Valsartan | 169 | 158 | 11 | Nu | Nu |
| 4 | 3 | Valsartan | 173 | 130 | 43 | Da | Nu |
| 5 | 4 | Valsartan | 173 | 150 | 23 | Nu | Da |
| 6 | 5 | Valsartan | 155 | 145 | 10 | Da | Nu |
| 7 | 6 | Valsartan | 177 | 133 | 44 | Da | Nu |
| 8 | 7 | Valsartan | 181 | 122 | 59 | Da | Nu |
| 9 | 8 | Valsartan | 184 | 110 | 74 | Da | Nu |
| 10 | 9 | Valsartan | 188 | 155 | 33 | Nu | Nu |
| 11 | 10 | Valsartan | 196 | 145 | 51 | Da | Nu |
| 12 | 11 | Indapamid | 199 | 170 | 29 | Nu | Nu |
| 13 | 12 | Indapamid | 207 | 162 | 45 | Nu | Nu |
| 14 | 13 | Indapamid | 207 | 162 | 45 | Nu | Da |
| 15 | 14 | Indapamid | 215 | 133 | 82 | Da | Nu |
| 16 | 15 | Indapamid | 170 | 133 | 37 | Da | Nu |
| 17 | 16 | Indapamid | 155 | 115 | 40 | Da | Nu |
| 18 | 17 | Indapamid | 219 | 133 | 86 | Da | Nu |
| 19 | 18 | Indapamid | 145 | 137 | 8 | Da | Nu |
| 20 | 19 | Indapamid | 151 | 137 | 14 | Da | Nu |
| 21 | 20 | Indapamid | 221 | 140 | 81 | Da | Nu |



Results:

Of the 200 subjects,

100 used Valsartan

Of these 5 had allergies due to treatment

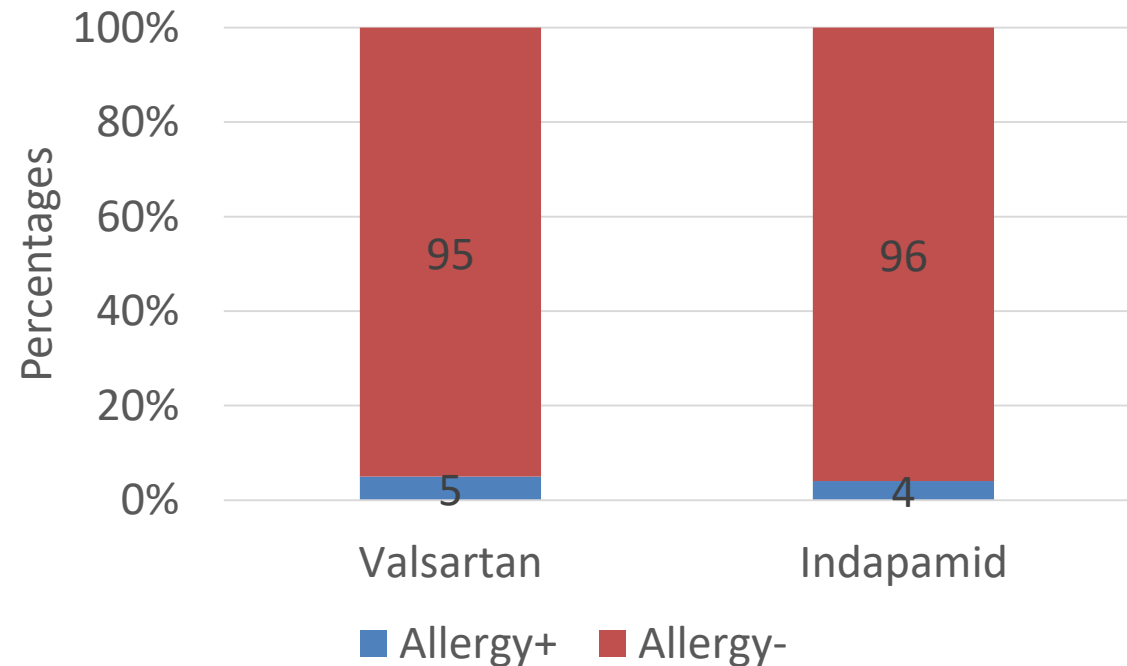
100 used Indapamide

Of these 4 had allergies due to treatment

Observed contingency table

| | Allergy ⁺ | Allergy ⁻ | |
|-----------|----------------------|----------------------|-----|
| Valsartan | 5 | 95 | 100 |
| Indapamid | 4 | 96 | 100 |
| | 9 | 191 | 200 |

- Individual Risk of Exposed (RIE) = $5/100 = 0.05$
- Individual Risk of Unexposed (RIN) = $4/100 = 0.04$
- 5% of patients treated with Valsartan had allergies
- 4% of patients treated with Indapamide had allergies



Chi-square test

- Null hypothesis (H_0): Treatment and allergy is independent
- Alternative hypothesis (H_a): Treatment and allergy is dependent
- $p=0.733$
- $p>0.05$ we failed to reject H_0 : Frequency of allergy side effect did not differ significantly statistically between Valsartan and Indapamid

RR – relativ risk

- $RR = \frac{IRE}{IRN} = \frac{\frac{a}{a+b}}{\frac{c}{c+d}} = \frac{0,05}{0,04} = 1.25$
- $RR > 1$ indicates a risk factor, but...

95% confidence interval for RR

- RR=1.25, 95%IC 0.95-1.95
- The 95% confidence interval does not indicate the presence of a prognostic factor (the value 1 is in the interval, the RR in the population can take the value 1)

Interpretation:

- The RR is found in the population in the range 0.95-1.95 with an error of 5%

Conclusion: when $p > 0.05$ it does not make sense to calculate the RR

ARR – Absolute risk reduction

- $ARR = |IRE - IRN| = \frac{a}{a+b} - \frac{c}{c+d} = 0,05 - 0,04 = 0,01$
- $ARR = 1\%$
- 1% more patients treated with Valsartan develop allergies than those treated with Indapamide, but
- since $p > 0.05$ the chances of having an equal or lower result at the population level are high

Number needed to harm

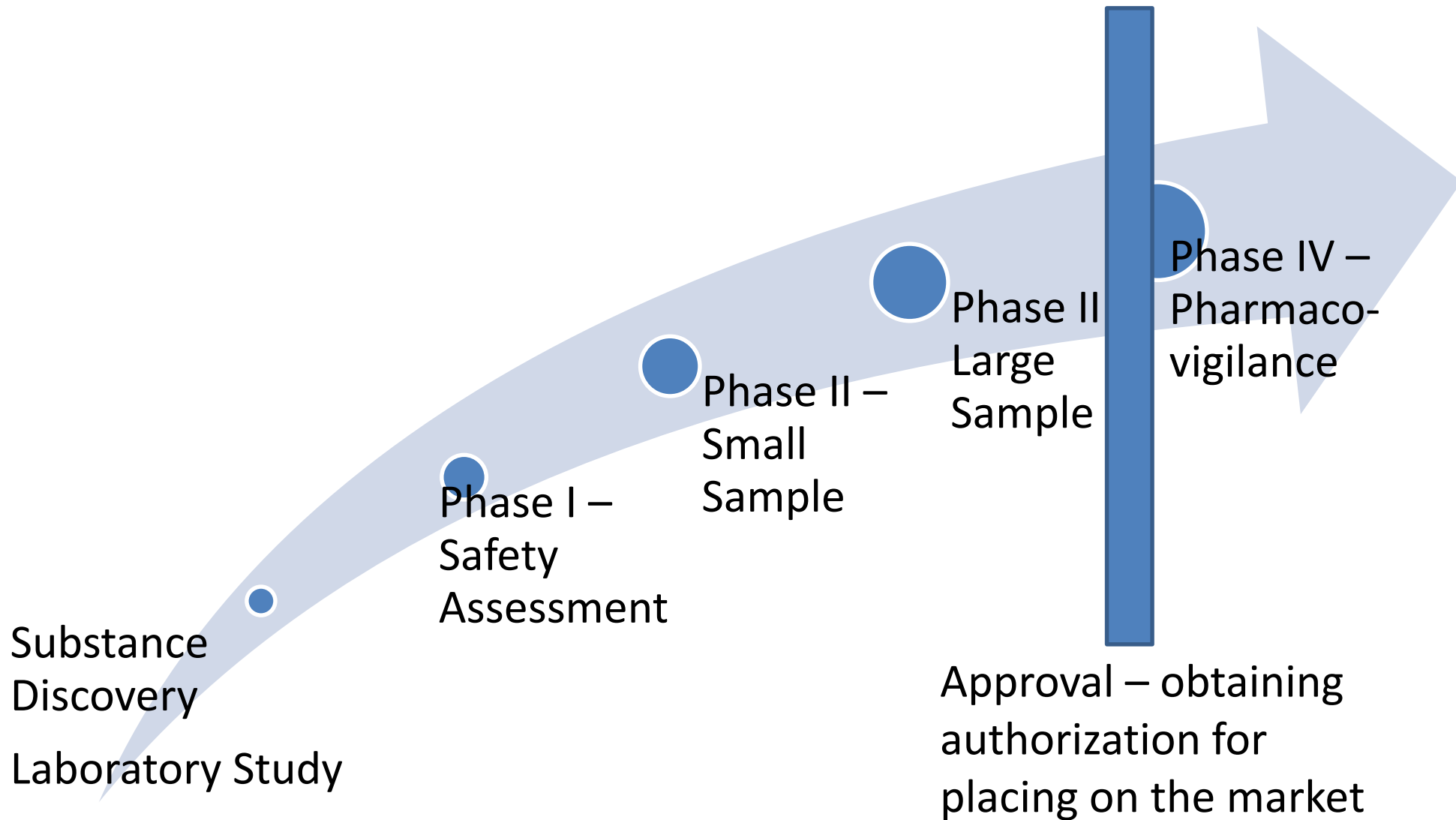
- $NNH = 1/ARR = 1/0.01 = 100$
- 100 patients must be treated with Valsartan for 1 to develop an allergy due to the difference in treatment with Valsartan instead of Indapamide, but
- since $p > 0.05$ the chances of having an equal or lower result at the population level are high

Clinical interpretations

- ARR – indicates a 1% difference between Valsartan and Indapamide
- To be able to test such a small difference we need a much larger sample
- We cannot say anything about what happens if we treat the entire population regarding the difference between the treatments in causing allergy, this difference could even be the opposite, in favor of Indapamide

Drug approval

Approval – obtaining authorization for placing on the market



Approval – obtaining authorization for placing on the market

- Completing the formalities for obtaining approval



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Phase IV – Pharmacovigilance

- Evaluation of long-term adverse effects
- Evaluation of additional therapeutic applications
- Treatment of other conditions
- Report all cases of adverse effects
 - change the drug package insert accordingly



Uncontrolled trials

- No control group
- In the case of interventions
- They are open (no randomization, no masked allocation)
- Multiple errors may occur

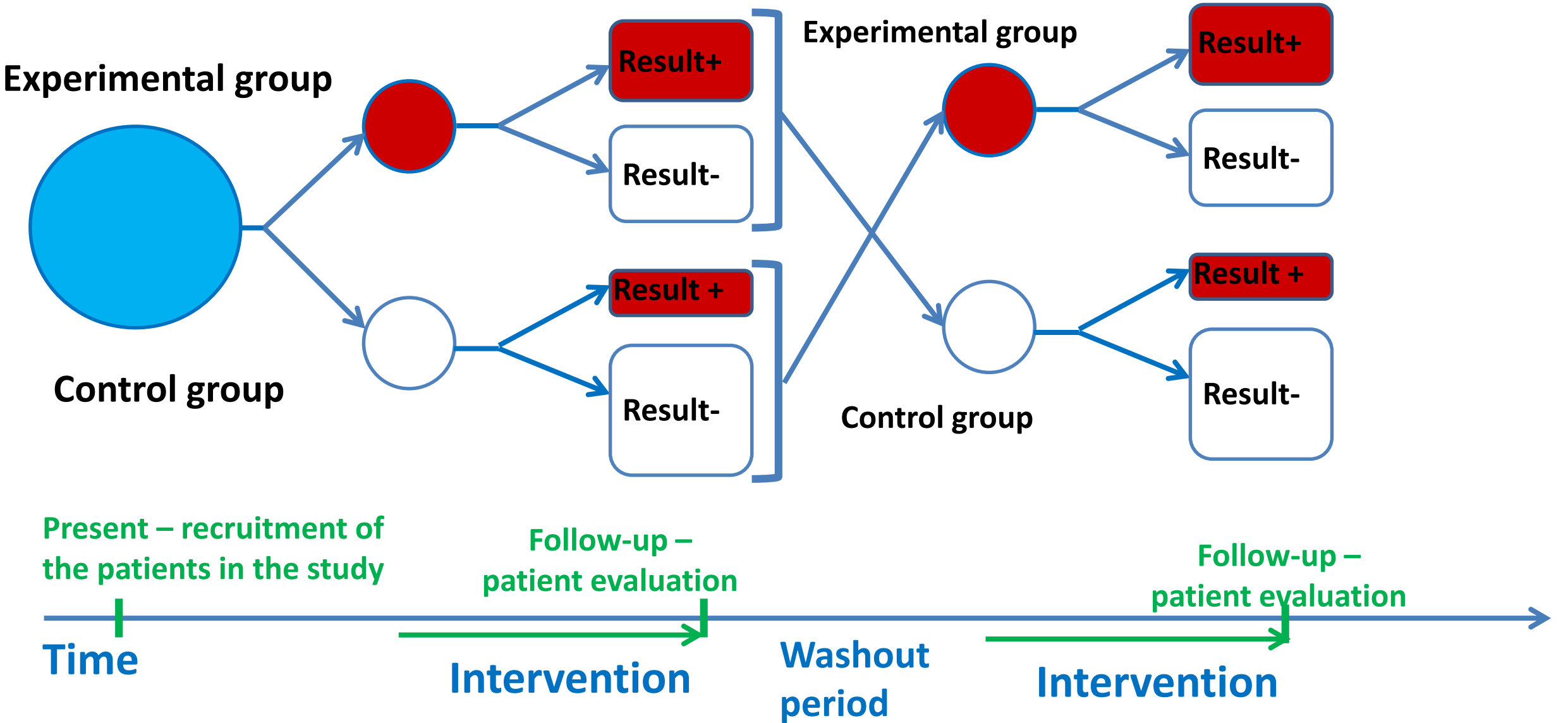
Non-randomized trial

- No randomization
- Not double-blind
- Possible errors:
- there are chances that the groups are different at baseline

trial with autocontrol

- The subject is his own control
- (e.g. intervention: vegetarian diet)
- Possible errors:
- Hawthorne effect – people in a study improve their condition only because they receive special attention

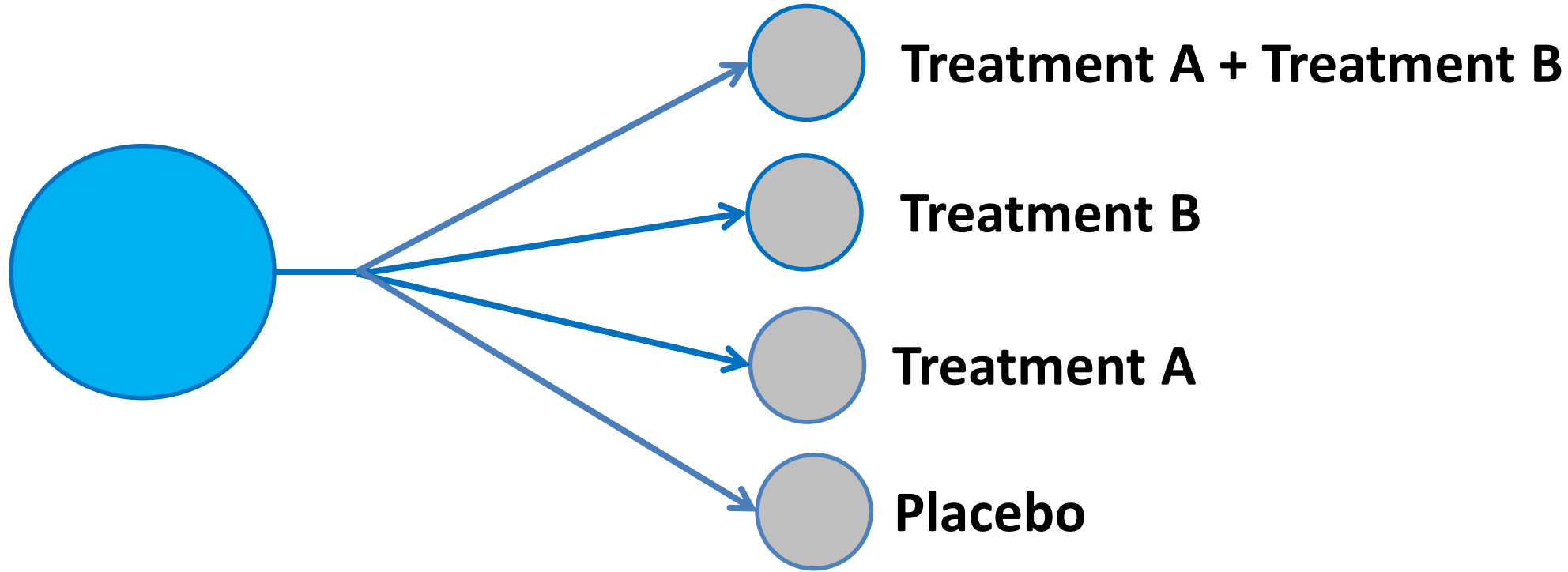
Cross-over design trials



Trials with external control group (including historical)

- Take subjects treated with placebo in another study (external control group)
- Take subjects treated with another treatment in a previous study (historical control group)
- Possible errors:
 - changes that have occurred in the meantime
 - e.g. Covid-19: another variant

Design bi-factorial



Factorial design trials

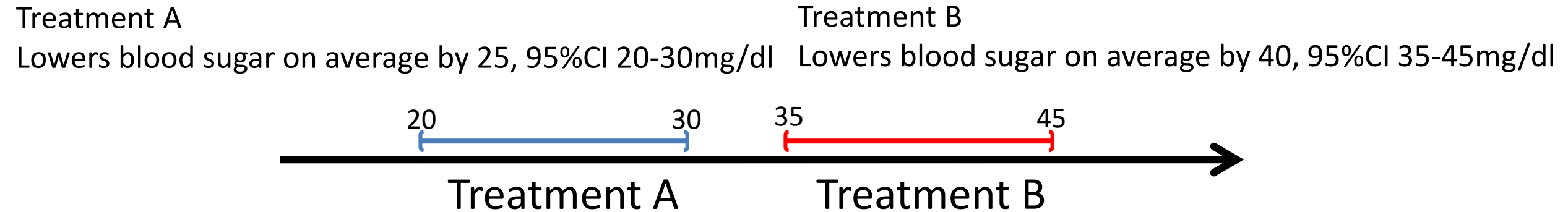
- Without interactions between treatments
- or
- with interactions
 - Treatments cancel each other out
 - They have additive action
 - They have exponential action (large interaction)

Trial with factorial design

- Bi-factorial: 4 groups
- Tri-factorial: 6 groups
- N-factorial: $n!$ groups

Superiority

 95% Confidence interval (CI)



Conclusion: Treatment A is inferior in effectiveness to treatment B

Superiority

 95% Confidence interval (CI)



Equivalence trial



Confidence interval of 95%

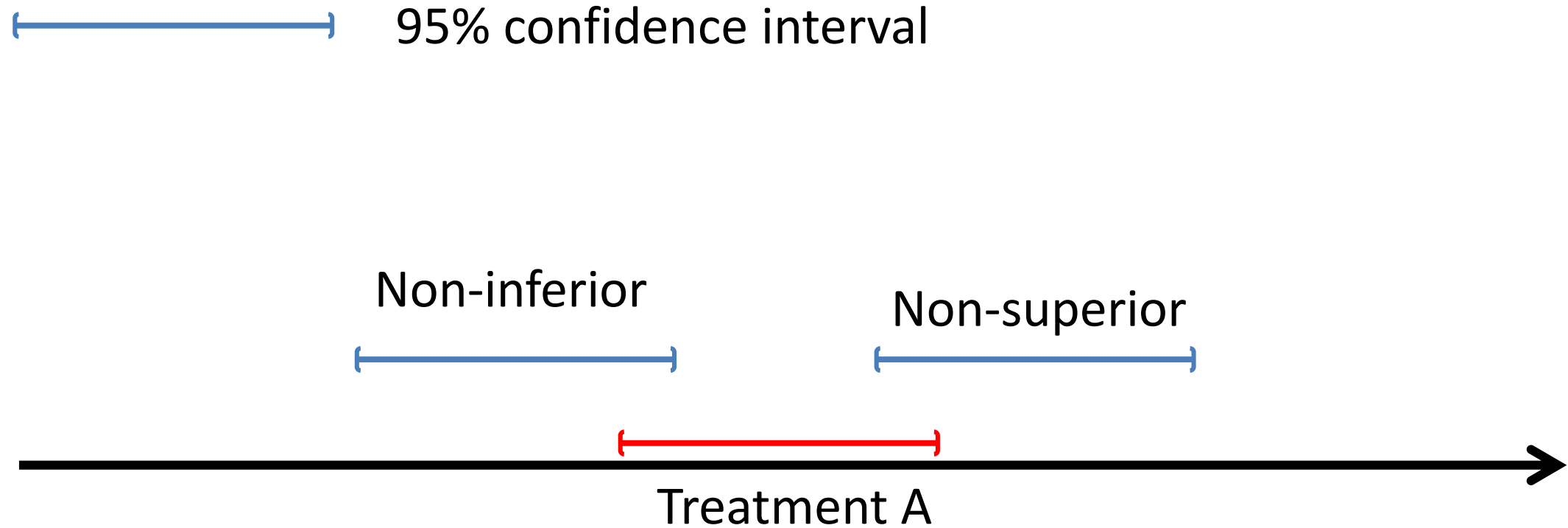
Equivalent



Treatment A



The non-inferiority, non-superiority trial



Thank you !!!