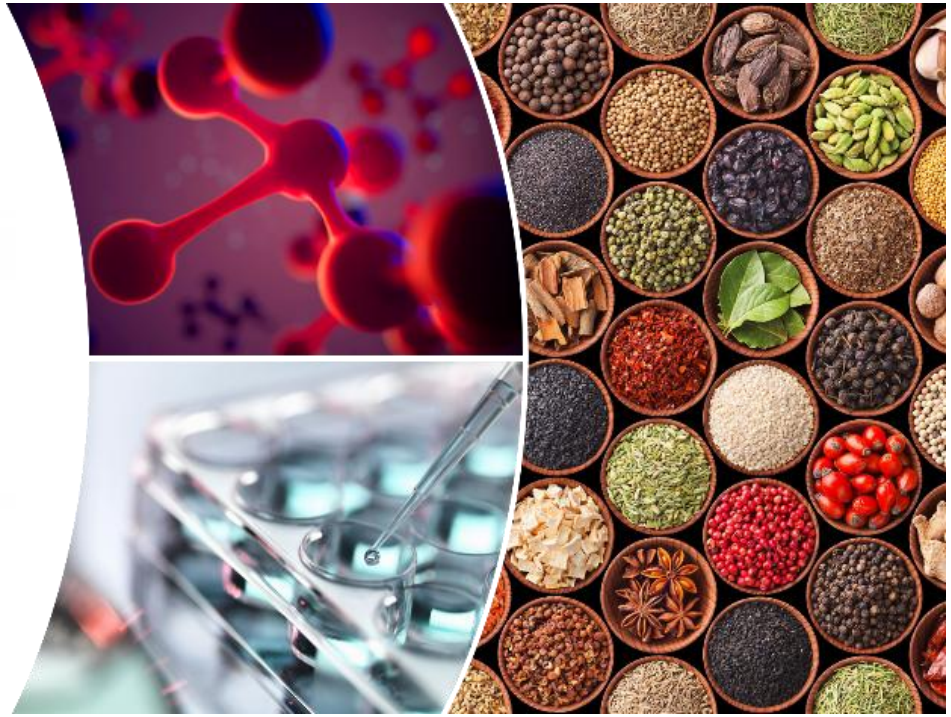
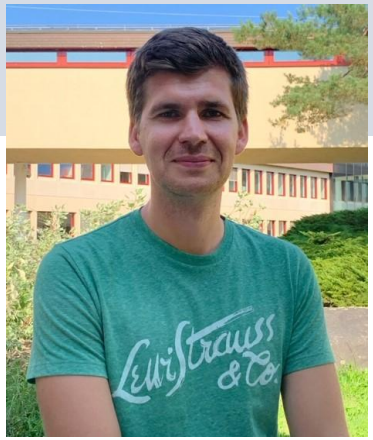


Entrepreneurship in Food
&
Nutrition Science

Scientific substantiation 2: Clinical trials designs

- Introduction to clinical trials
- Design considerations
- Clinical trial designs

Feel free to ask your questions anytime



Mickaël Hartweg

- Biostatistics team lead, Clinical Research Unit, Nestlé Research
- Master in Applied Statistics, University of Strasbourg, France
- Hobbies: Hiking , Dog training, Reading (sci-fi)

expertise

Biostatistics

Clinical trial methodology

Analysis and mining of clinical data

Translation of clinical data

- **Introduction to clinical trials**
- Design considerations
- Clinical trial designs

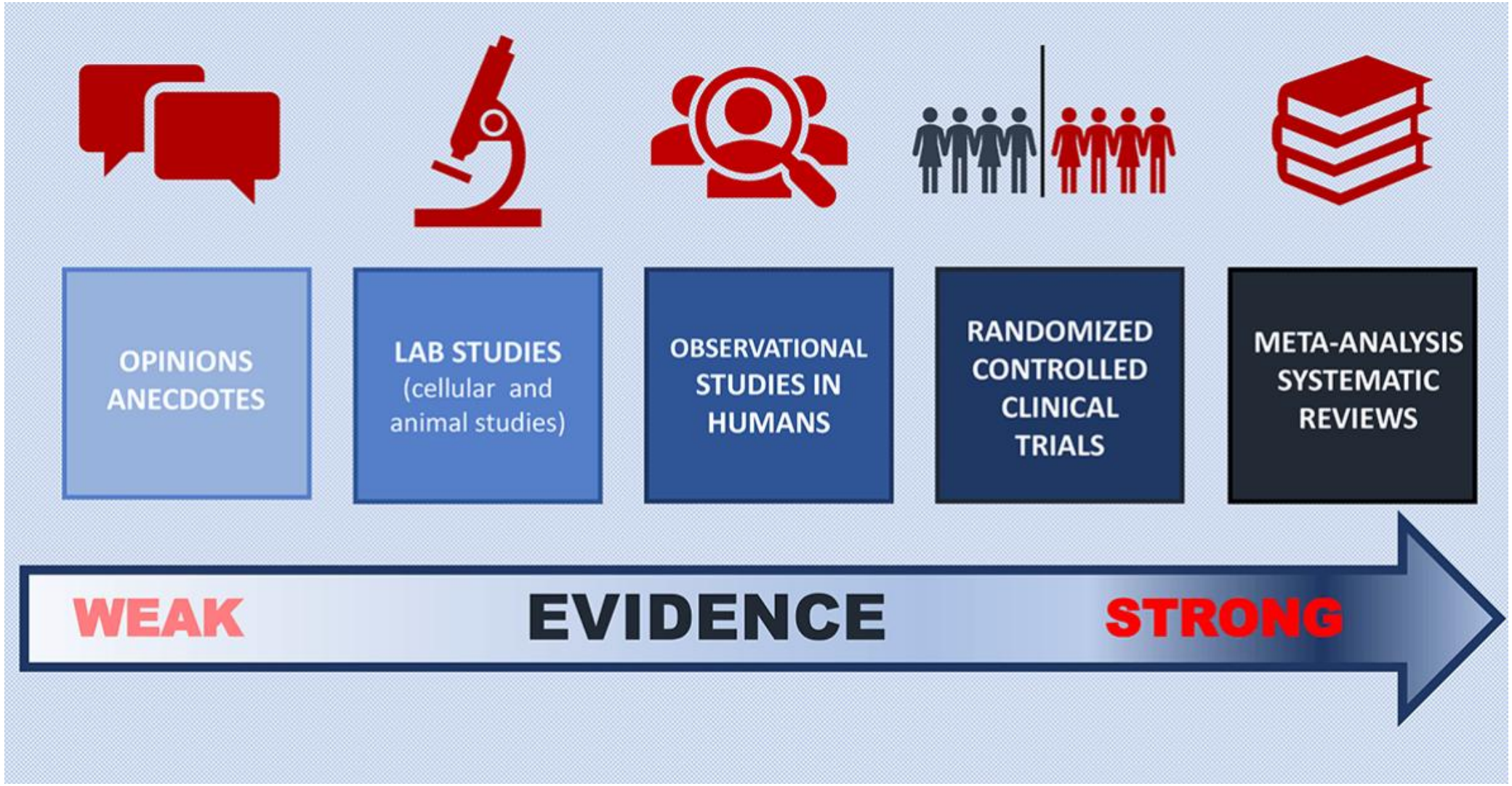
What is a clinical trial?

Clinical Research is the study of health and illness in humans

Clinical trials

- Research studies performed in **humans**
- Aim at evaluating the effect of an **intervention**
- Form the foundation for **evidence-based medicine**

Strength of evidence



Why doing a clinical trial in nutrition

Substantiation of health benefits for product communications

Safety assessment for product registrations (e.g. new ingredients)

Knowledge building for future innovations

Nutrition versus Pharmaceutical Clinical Trials

Pharmaceutical

- Document the safety and efficacy of a specific drug for **treating**, **mitigating** or **curing** a disease
- Target population: **patients** with a specific disease type
- Drugs are **highly purified** and designed to have a **targeted effect** on a disease

- Phase I,II,III,IV
- Strongly regulated (e.g. FDA, EMA)

Nutrition

- Document the safety and efficacy of a specific food intended for **prevention** of diseases
- Typical target population: **healthy individuals**

- Nutritional interventions are **complex matrixes** of ingredients, have a **general health effect**

- Mainly phase III & IV (shorter clin.dev)
- Mix of mandatory (e.g. EFSA) and voluntary regulation

Conducted using **Good Clinical Practices**, all products used in human testing produced under **Good Manufacturing Practices**

ICH
harmonisation for better health

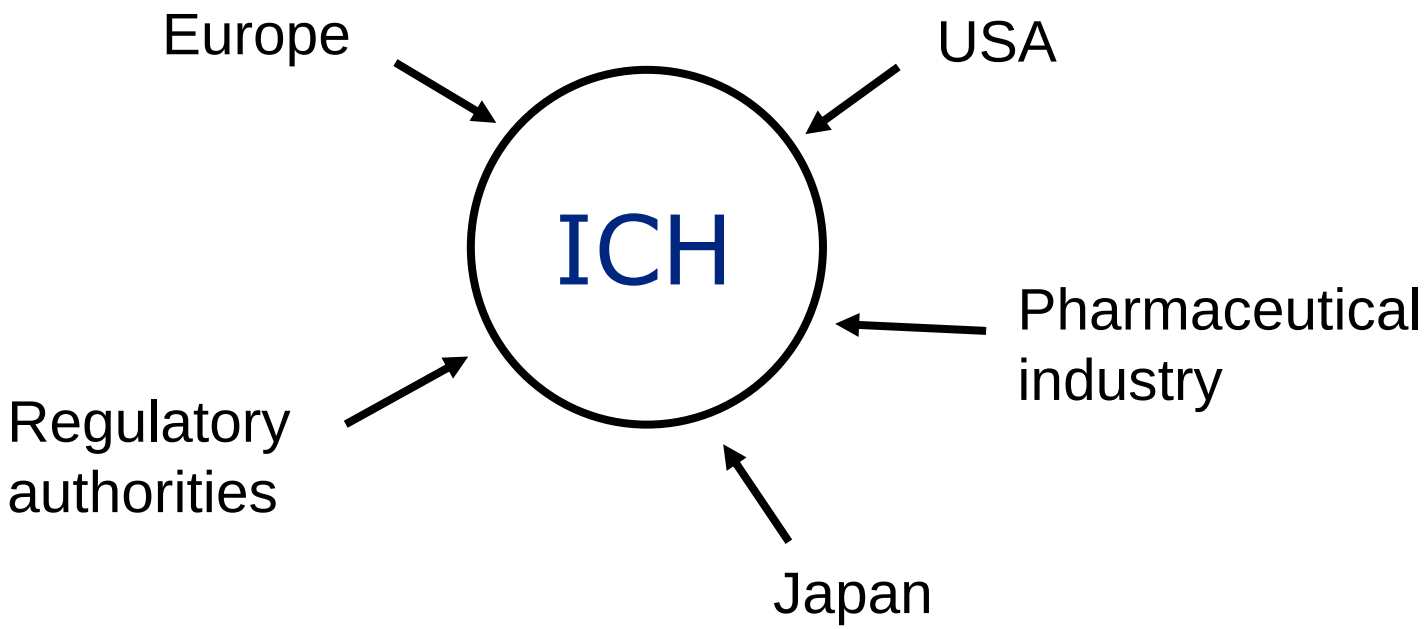
EPFL

Phases of a clinical trial

Ensuring compliance and quality

Guidelines for running clinical trials

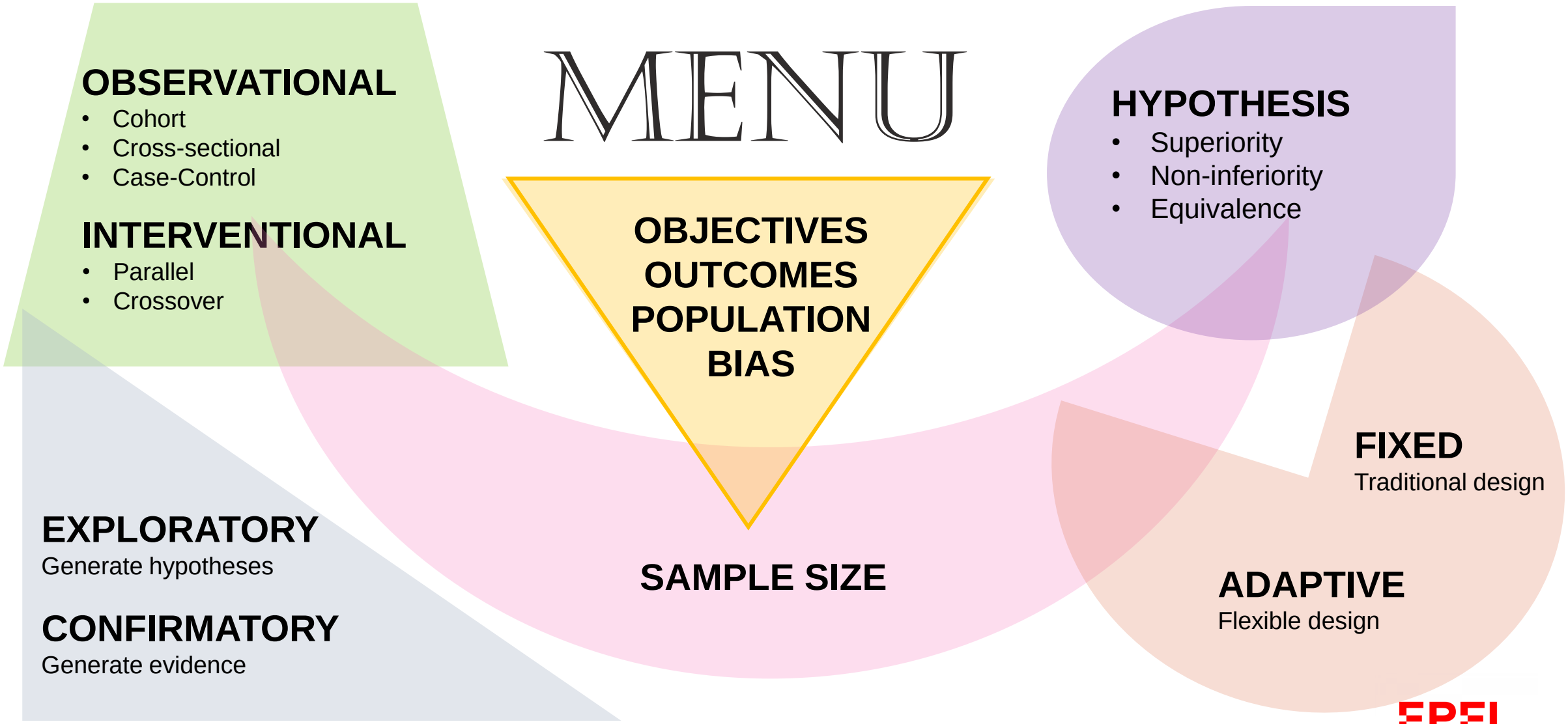
Good Clinical Practice (GCP)



International Conference on Harmonisation

ICH Official web site : ICH

Clinical trial designs – different dimensions



- Introduction to clinical trials
- **Design considerations**
- Clinical trial designs

Study Objectives – SMART

OBJECTIVES

Evaluate the efficacy of oleuropein-based dietary supplement versus placebo on muscle energy after 36 days of supplementation in healthy male aging population

- **Specific**: Identifies the **action** (*evaluate the efficacy*), the **intervention** (*oleuropein-based supplement and placebo*), **population** (*aging males*) and **indication** (*healthy*)
- **Measurable**: Ensure it is **quantifiable** (muscle energy metabolism measured through *pyruvate dehydrogenase* (*PDH) activation in skeletal muscle biopsy*)
- **Achievable**: **Feasible** and **easily obtainable** for ALL study participants (to be confirmed by the trial expert)
- **Realistic (Relevant/Reliable)**: **Clinically-relevant** and **established** methods (to be confirmed by the trial expert)
- **Timed**: Important **timepoints** to be well-defined (*after 36 days of supplementation*)

EPFL

ENDPOINTS and ESTIMATES

Indicator measured in a trial participant or biological sample to assess a trial objective

- Should be measurable
- Captured in the schedule of assessments
- Consistency between objectives, endpoints, estimates and analyses

Objective

- Evaluate the efficacy of oleuropein-based dietary supplement versus placebo on muscle energy after 36 days of supplementation in healthy male aging population

Endpoint

- Muscle energy metabolism measured through PDH activation in skeletal muscle biopsy

Estimate

- The difference between Oleuropein group and placebo group in mean PDH activation in skeletal muscle biopsy after 36 days

EPFL

Study POPULATION

General population (8 billion)

Eligibility criteria
(inclusion / exclusion)

Target population

Enrollment / recruitment
(according to sample size)

Study population (sample)

Observed in the study

Study POPULATION – Eligibility criteria

- **Consistent with the objectives**
- **Demographic characteristics** (e.g. age, sex, BMI)
- **Medical indication** under study, acceptable / prohibited comorbidities, acceptable / prohibited medications
- **Ethical requirements**
  - Subject Inform Consent Form signed/obtained
- **Generalizability**
  - Healthy volunteers (unless diseased target under investigation)
- **Exclusion criteria** that may bias result interpretation or pose an unnecessary risk to the participant

EPFL

Study POPULATION – Oleuropein example

- **Target population**: Free-living healthy aging male
- **Inclusion criteria**:
  - Male 50-70 years of age
  - BMI between 18.5 and 29.9 kg/m^2 (normal and overweight)
  - Healthy as per medical history and investigator's/ physician's judgement
  - Having signed an informed consent
- **Exclusion criteria:**
  - Allergy / intolerance to the study product
  - >5% body mass change in the previous 3 months 3
  - HbA1c ≥ 6.5%
  - Blood pressure: systolic/diastolic >140/ and >90 mmHg
  - Participating in a structured (progressive) exercise program
  - Smoking
  - … Related to medication and other associated diseases

EPFL

Sources of bias

Definition (ICH E9)

➢The systematic tendency of any factors associated with the design, conduct, analysis and evaluation of the results of a clinical trial to make the estimate of a treatment effect deviate from its true value

→ **Bias compromises the ability to draw valid conclusions**

Types

More than 50 bias identified at different stages of a trial at which it can occur.

- In reading the literature – *One-sided reference bias*
- In analyzing the data – *Data dredging bias*
  (presenting the results of unplanned statistical tests as if they were a fully prespecified course of analyses)
- In interpreting the analysis result – *Hot stuff bias*
  (topic is fashionable ('hot') - be less critical in approach to research)
- In publishing the results – *Positive results bias*
- *…*

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Sources of bias – cont.

- **Observer bias** – Subjective judgement in reporting, evaluation, data processing and statistical analysis due to the knowledge of the identity of the treatments *(Systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest)*

  → *Blinding*

- **Selection bias** – Selection of subjects and the corresponding treatment assignments *(Systematic differences between baseline characteristics of the groups that are compared)*

  → *Randomization*

BLINDING

Procedure in which one ore more parties in a trial are kept unaware of which products have been assigned to the trial participants

Open-label

- No blinding is employed. Both investigator and subjects are aware of the product received

Single blind

- Either the subject or the investigator is blind to the assignment of the subject. The sponsor of the trial is blinded

Double blind

- Neither the subject nor the investigator are aware of the product assignment. The sponsor of the trial is blinded

BLINDING - Coding

Simple group coding

	Control	Test
Color		
Code	P	T

2 codes/group A, B = control; C, D = test

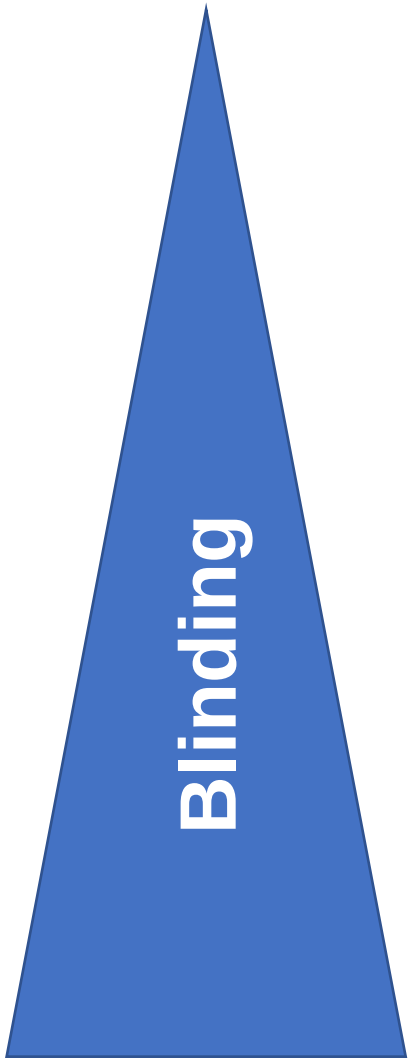
Control	A B	A C	A D	B C	B D	C D
Test	C D	B D	B C	A D	A C	A B

3 codes/group. A, B, C = control; D, E, F = test

Control	A B C	A B D	A B E	A B F	A C D	…
Test	D E F	C E F	C D F	C D E	B E F	…

. . .

Individual coding, number of codes = number of subjects



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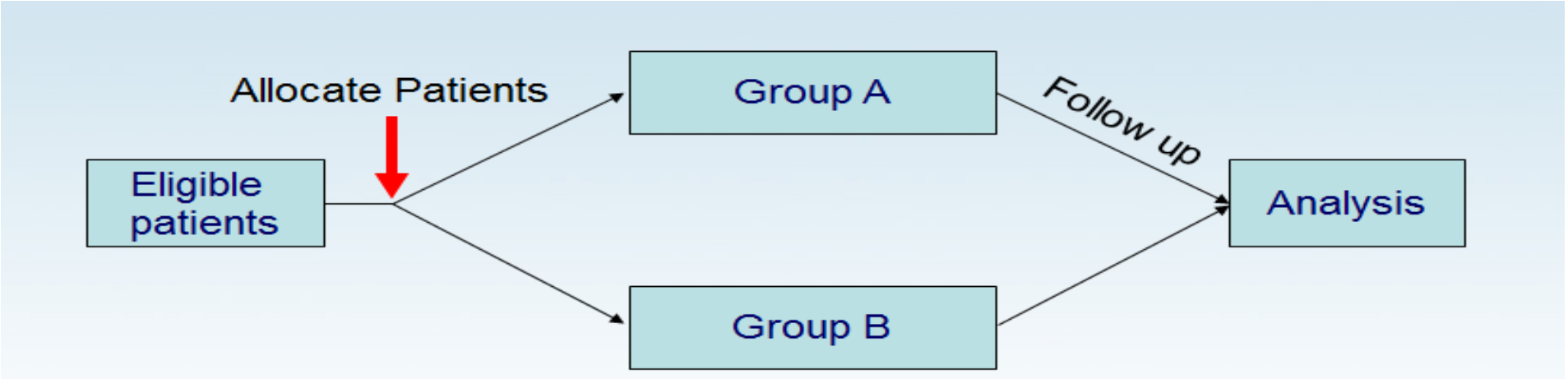
RANDOMIZATION

Process of assigning clinical trial participants to treatment groups



- Gives each participant a known (usually equal) chance of being assigned to any of the groups
- Successful randomization requires that group assignment cannot be predicted in advance (concealment)

WHY RANDOMIZE?

If, at the end of a clinical trial, a difference in outcomes is observed between two treatment groups (e.g. intervention and control) possible explanations for this difference would include:

- the intervention exhibits a real clinical effect
- the outcome difference is solely due to chance
- there is a systematic difference (or bias) between the groups due to factors other than the intervention

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If, at the end of a clinical trial, a difference in outcomes is observed between two treatment groups (e.g. intervention and control) possible explanations for this difference would include:

- the intervention exhibits a real clinical effect
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- there is a systematic difference (or bias) between the groups due to factors other than the intervention

Randomization aims to prevent the third possibility

EPFL

RANDOMIZATION designs

- **Simple randomization** (or unrestricted randomisation)
- Block randomization
- **Stratified Block randomization**
- Dynamic random allocation (or minimisation)

Simple RANDOMIZATION

- Each product assignment is ”memory less” - made without considering the previous assignments
  - Coin Tossing
  - Roll an unbiased dice
  - Computer generated sequence

Three Groups:

(criteria:{1,2,3}=A, {4,5,6}=B, {7,8,9}=C; ignore 0’s)

A computer generated random sequence:

4,8,3,2,7,2,6,6,3,4,2,1,6,2,0,.....

4	8	3	2	7	2	6	6	3	4	2	1	6	2	0
B	C	A	A	C	A	B	B	A	B	A	A	B	A	-

+	-
• Simplistic implementation • Allocation is random and unpredictable	• Can produce unbalanced allocation (ex: toss a coin 10 times)

Stratified RANDOMIZATION

➢ Balancing groups with respect to prognostic factors which may be related with subject response, in order to prospectively achieve product group comparability

STRATA: Age

AGE <50	BABA	AABB	ABBA	BBAA	BAAB	...
AGE ≥50	BAAB	ABBA	BBAA	ABAB	BABA	...

	GROUP A	GROUP B
AGE <50	50%	50%
AGE ≥50	50%	50%

If AGE has an impact then it should be considered as a stratification factor

+	-
• Balances important factors between arms • Improves power by reducing variance	• Too many strata can lead to “sparse” data

EPFL

«The foundation of design are observation and theory»

- S. Piantadosi

MD/Statistician

«Math is easy; Design is hard.»

- J. Veen

Web Designer

«Good design is obvious. Great design is transparent. »

- J. Sparano

Graphic Designer

- Introduction to clinical trials
- Design considerations
- **Clinical trial designs**

MENU

OBSERVATIONAL
- Cohort
- Cross-sectional
- Case-Control

INTERVENTIONAL
- Parallel
- Crossover

OBJECTIVES
OUTCOMES
POPULATION
BIAS

HYPOTHESIS
- Superiority
- Non-inferiority
- Equivalence

FIXED
Traditional design

ADAPTIVE
Flexible design

SAMPLE SIZE

EXPLORATORY
Generate hypotheses

CONFIRMATORY
Generate evidence

EPFL

Observational vs Interventional

Observational

Identify subjects → **Observe and record characteristics** → **Look for associations**

- No product
- Exposure to risk factors

Interventional

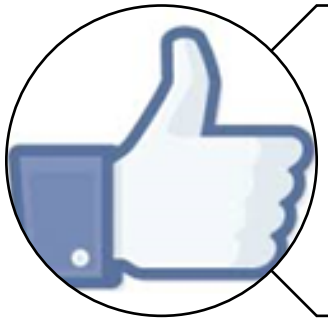
Identify subjects → **Place in common setting** → **Intervene** → **Evaluate effects of intervention**

- Product intake
- Randomization

EPFL

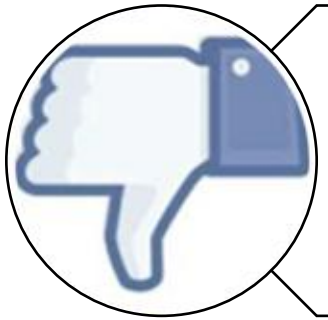
Observational - COHORT

- Data obtained from groups who have already been exposed (or not) to factor of interest
- Best for studying effects of risk factors on an outcome



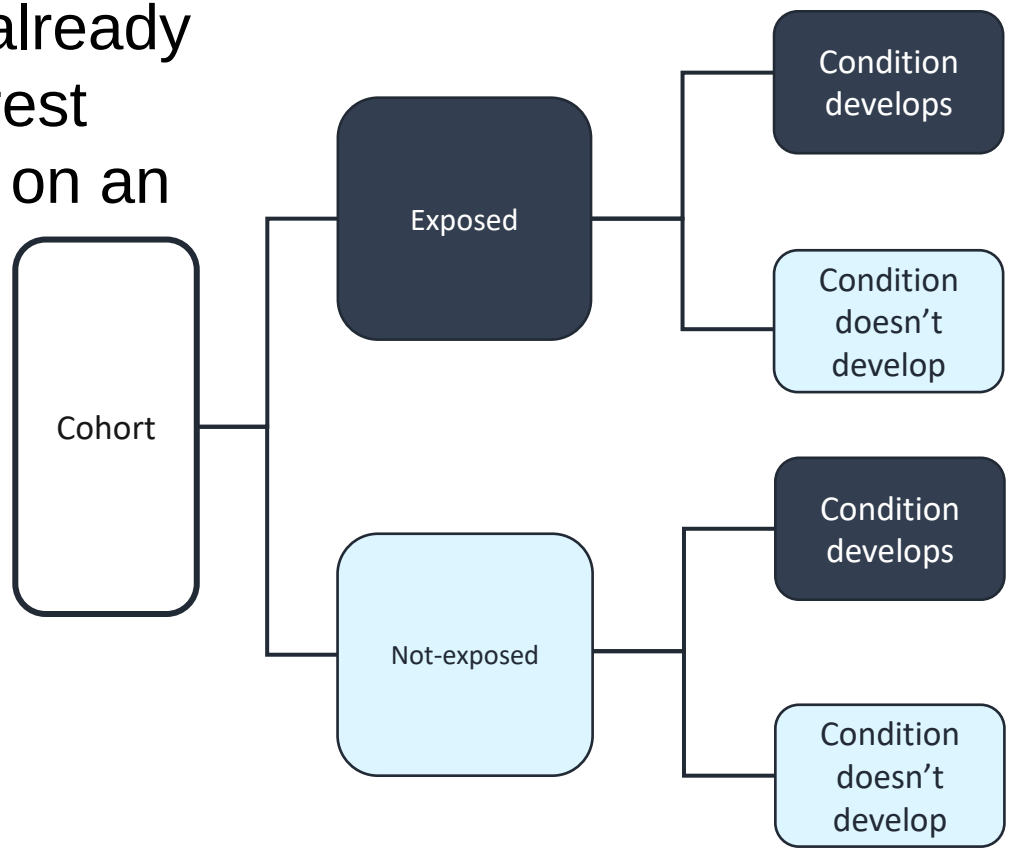
PROS

- Ethically safe
- Can establish timing and direction of events
- Eligibility criteria and outcome assessment can be standardized



CONS

- Controls maybe difficult to identify
- Exposure linked to a confounder
- Rare outcomes would require large sample size or long follow-up

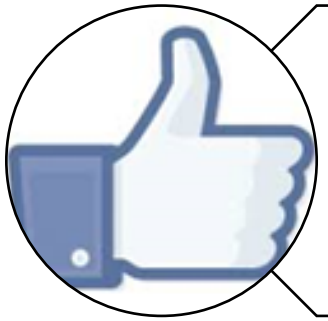


Ex. Development of Type 2 diabetes on adults exposed to a diet low in dietary fibre

EPFL

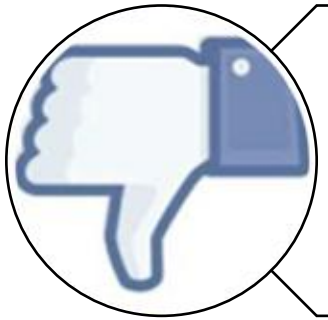
Observational – CROSS SECTIONAL

- One timepoint when all data are collected
- Exposure and outcomes both measured at the same time



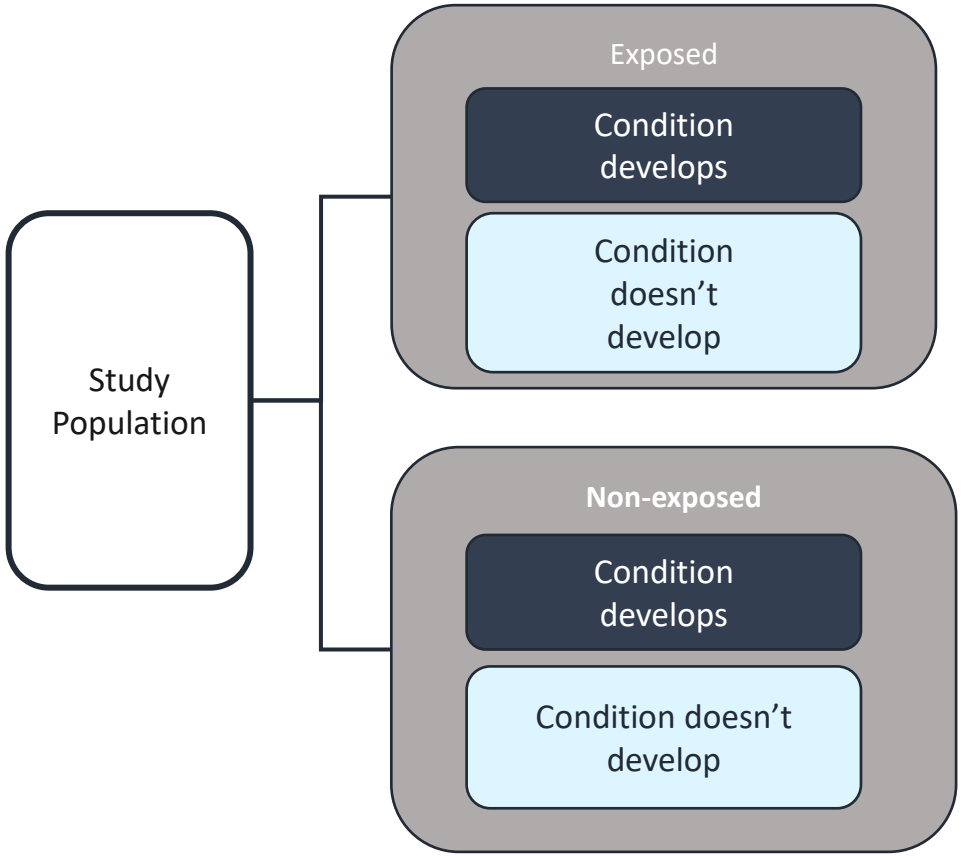
PROS

- Ethically safe
- Fast and simple



CONS

- Association at best, never causality
- Exposure and outcome are determined simultaneously: CONFOUNDING

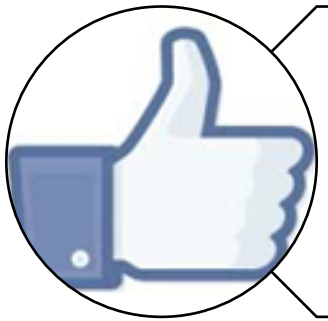


Ex. Number of adults who have Type 2 Diabetes that are exposed to a diet low in dietary fibre

EPFL

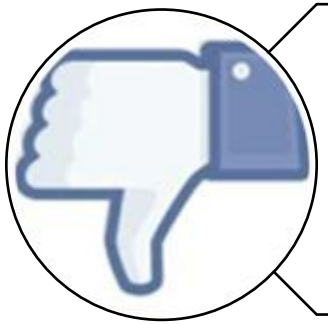
Observational – CASE-CONTROL

- Subjects with certain outcome (cases) and a control are selected.
- Information is obtained whether the subjects have been exposed to the factor under investigation



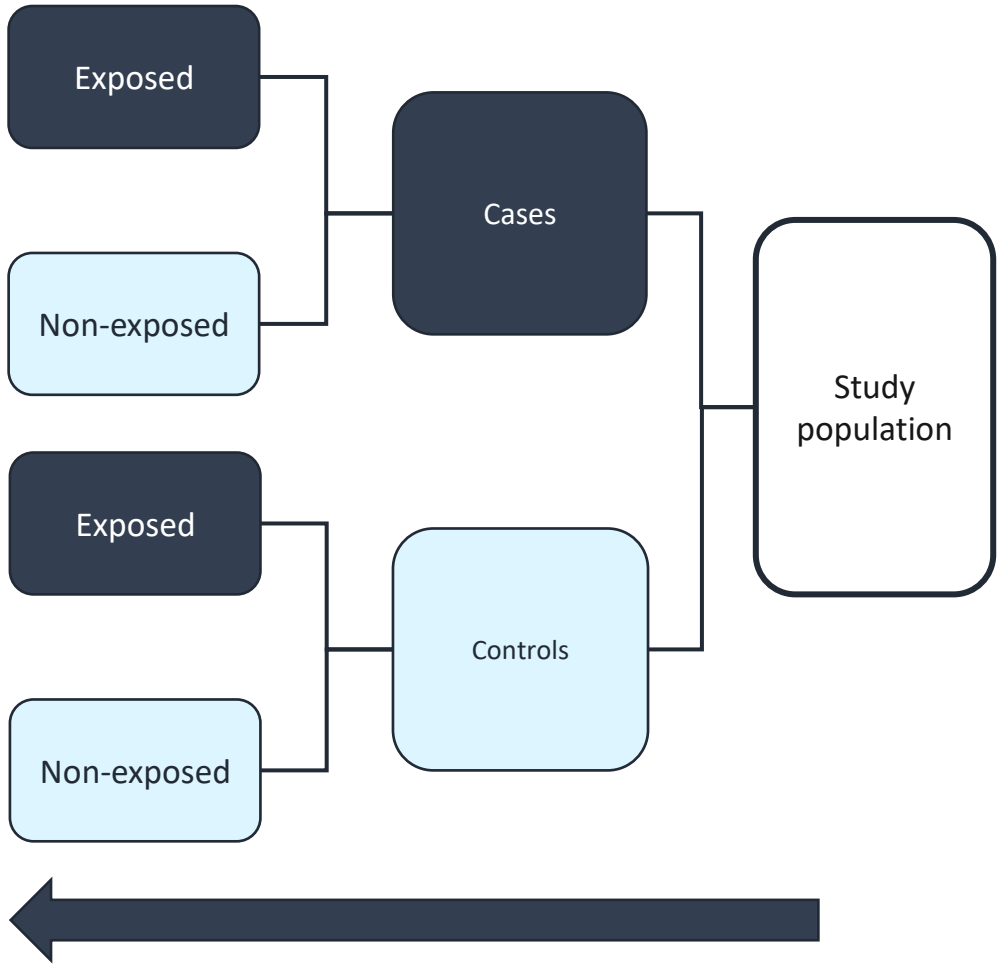
PROS

- Fewer subjects needed
- The only feasible method for very rare conditions or long lag between exposure and outcome



CONS

- Dependent on recall and/or records to determine level of exposure
- Confounders
- Selection of control group is difficult
- Recall and selection bias



Ex. Association between diet and people who developped Type 2 Diabetes and people who didn't develop Type 2 Diabetes

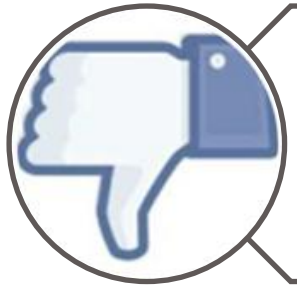
EPFL

Interventional - PARALLEL

- Randomization to groups (test or control)
- Groups need to be comparable at baseline

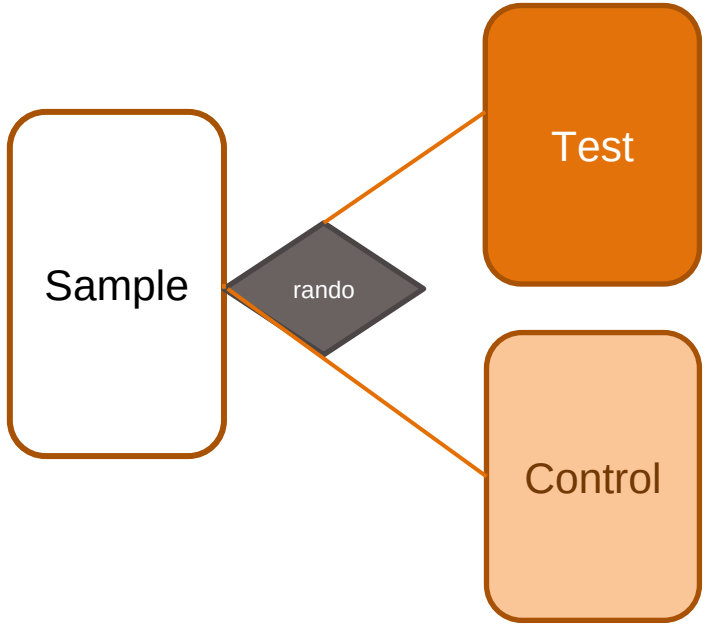
PROS

- Design and interpretation are straightforward
- Always applicable



CONS

- Relatively high number of subjects needed
- Hidden factors not taken into account

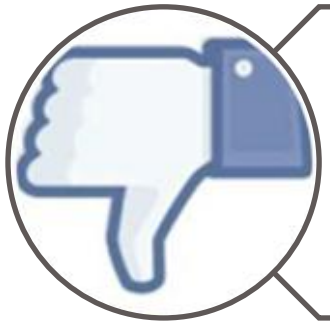


Interventional – CROSS-OVER

- Randomization to sequences
- All subjects receive both products
- Washout period

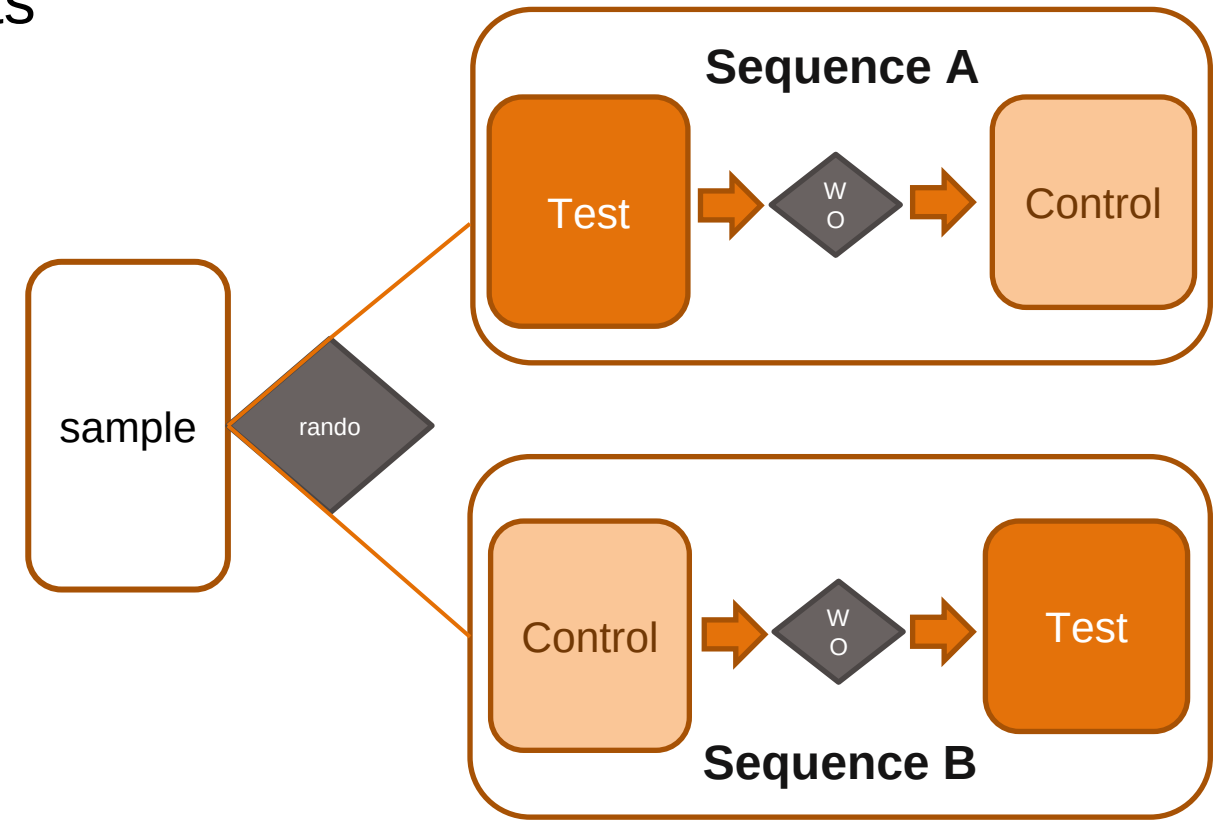
PROS

- No confounding effect
- Fewer subjects needed



CONS

- Dependent on washout period
  - Carry-over effect
  - Time effect
- Not always applicable



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EPFL

EXPLORATORY vs. CONFIRMATORY

Exploratory

- Generates hypotheses rather than evidence
- Methodological or theoretical uncertainties
- More relaxed with statistical constraints (p-values, multiplicity)

Confirmatory

- Provides evidence that scientific hypothesis is false or true
- Based on established methods and interventions
- Sample size is set to adequately test the hypothesis
- Statistical analysis decisions are made before data collection

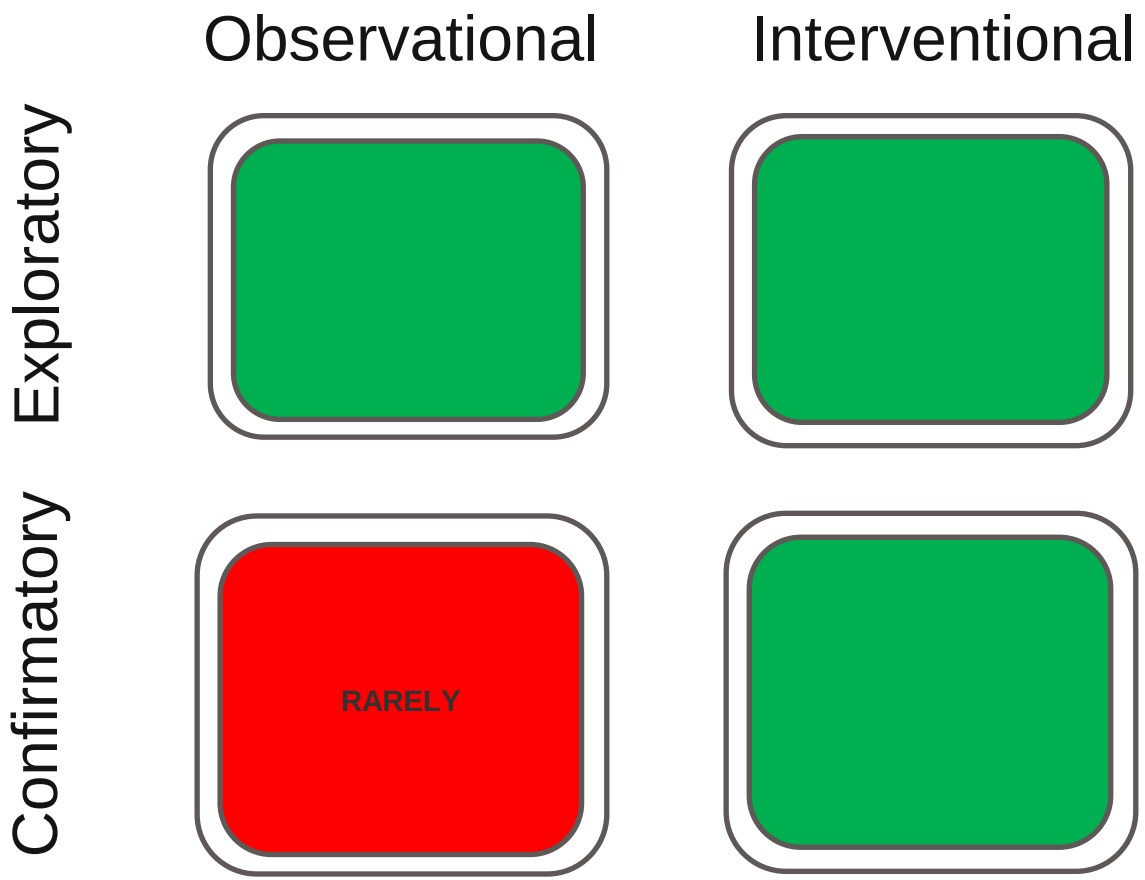
EPFL

EXPLORATORY vs. CONFIRMATORY

DATING

ENGAGEMENT

Different possibilities



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Study type – objectives / hypothesis

❖ **Superiority**

- ➢ Determine a clinically relevant difference between 2 interventions

❖ **Non-inferiority**

- ➢ Determine whether a (new) intervention is not clinically worse than another active (standard) intervention *by more than a pre-specified amount (Δ)*

❖ **Equivalence**

- ➢ Determine whether a (new) intervention is neither worse nor better (similar) than another active intervention *by more than a pre-specified margin (-Δ, + Δ)*

EPFL

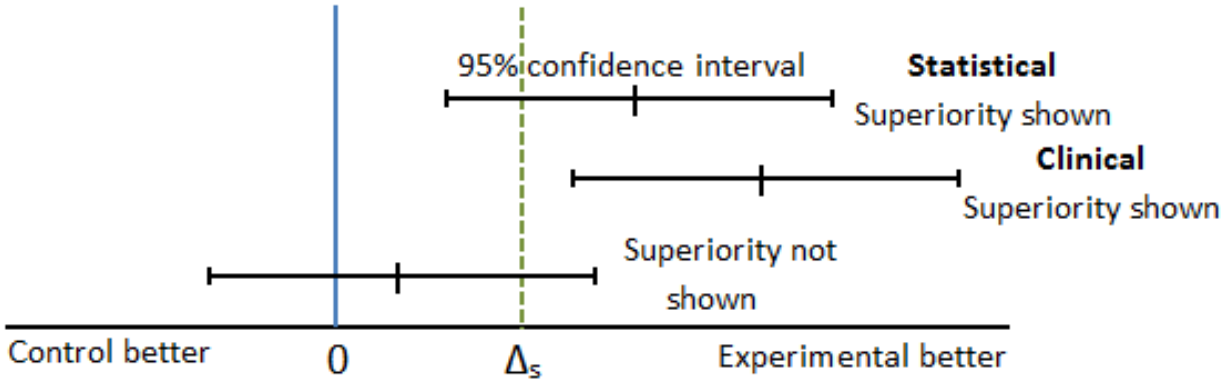
SUPERIORITY

- Goals:
  - demonstrate that the new intervention is superior to the control (active or placebo)

$$H_0 : \mu_E - \mu_C = 0$$

$$H_A : \mu_E - \mu_C \neq 0$$

H_0 is rejected (superiority proven) at 5% confidence level if and only if the (two-sided) 95% CI for $\mu_E - \mu_C$ does not contain 0



A $P > 0.05$ does not imply equivalence

Absence of evidence is not evidence of absence!

EPFL

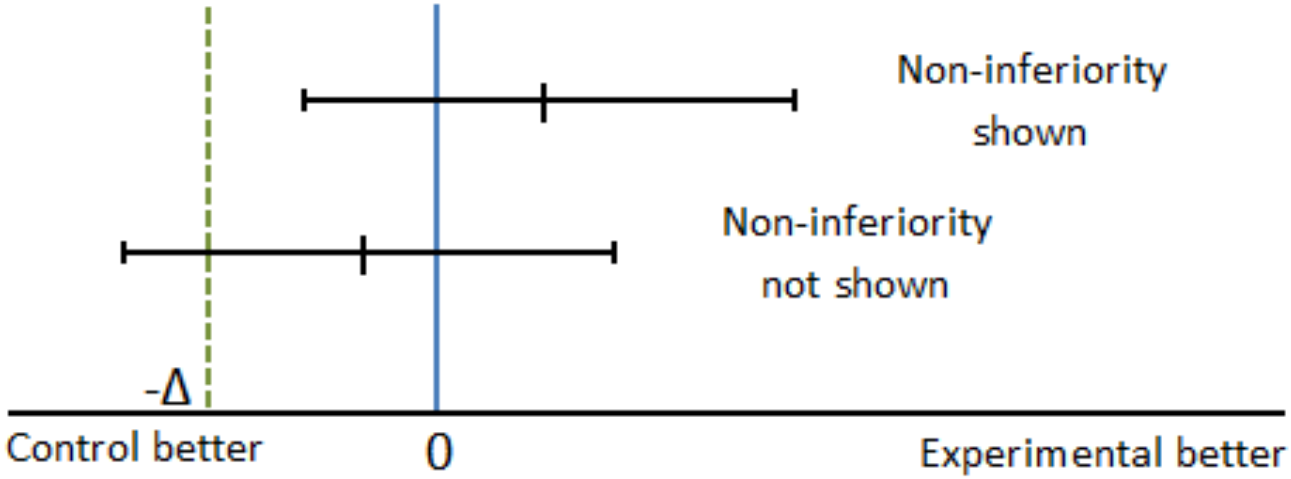
NON-INFERIORITY

A new intervention is **not less effective** than an active intervention

$$H_0 : \mu_E - \mu_C \leq -\Delta$$
$$H_A : \mu_E - \mu_C > -\Delta$$

Δ is called the NI margin and is defined prospectively

H_0 is rejected (non-inferiority proven) if and only if the (two-sided) 95% CI for $\mu_E - \mu_C$ is contained in (-Δ, +∞)



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NON-INFERIORITY

When to use non-inferioriry design:

- Superiority (compared with placebo) would be **unethical**
- The experimental intervention is **not expected to be superior** (efficacy)
- The experimental intervention might be **better in other aspects**:
  - safety (better tolerated)
  - dosing regimen (better compliance)
  - better quality of life
  - cost

Limitations:

- Can not independently show **efficacy**
- **Additional analyses** needed to show superiority

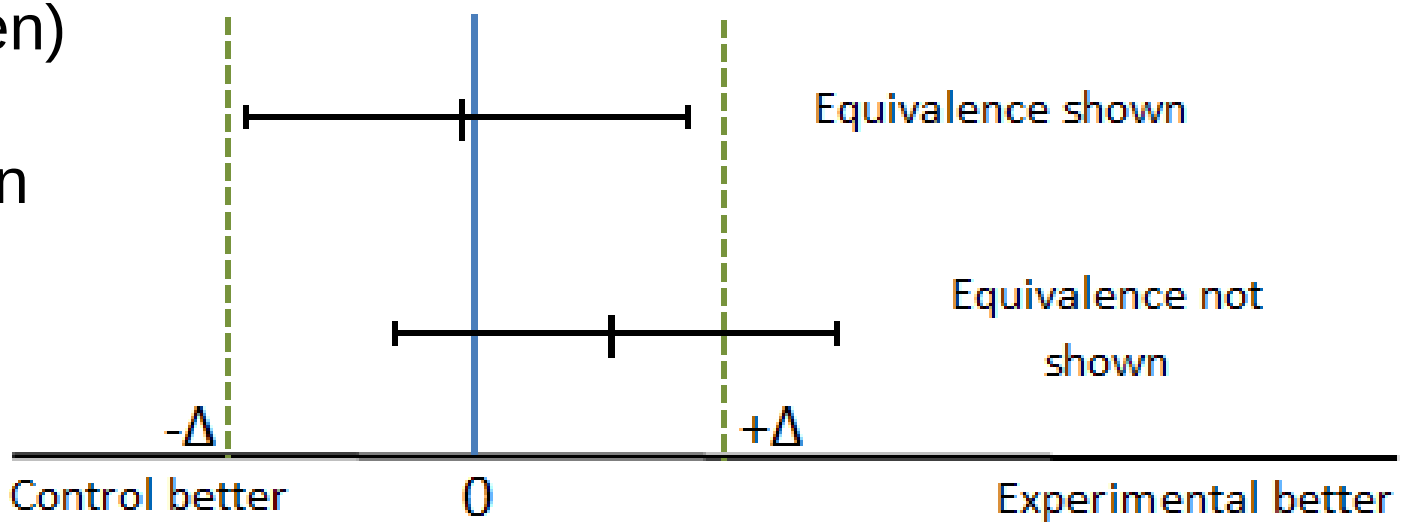
EPFL

EQUIVALENCE

to confirm the **absence of a meaningful difference** between products

$$H_0: \mu_E - \mu_C \leq -\Delta \text{ or } \mu_E - \mu_C \geq \Delta$$
$$H_A: -\Delta < \mu_E - \mu_C < \Delta$$

H_0 is rejected (equivalence proven) if and only if the (two-sided) 95% CI for $\mu_E - \mu_C$ is contained in (-Δ, +Δ)



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Study Type – FIXED or ADAPTIVE?

Fixed design

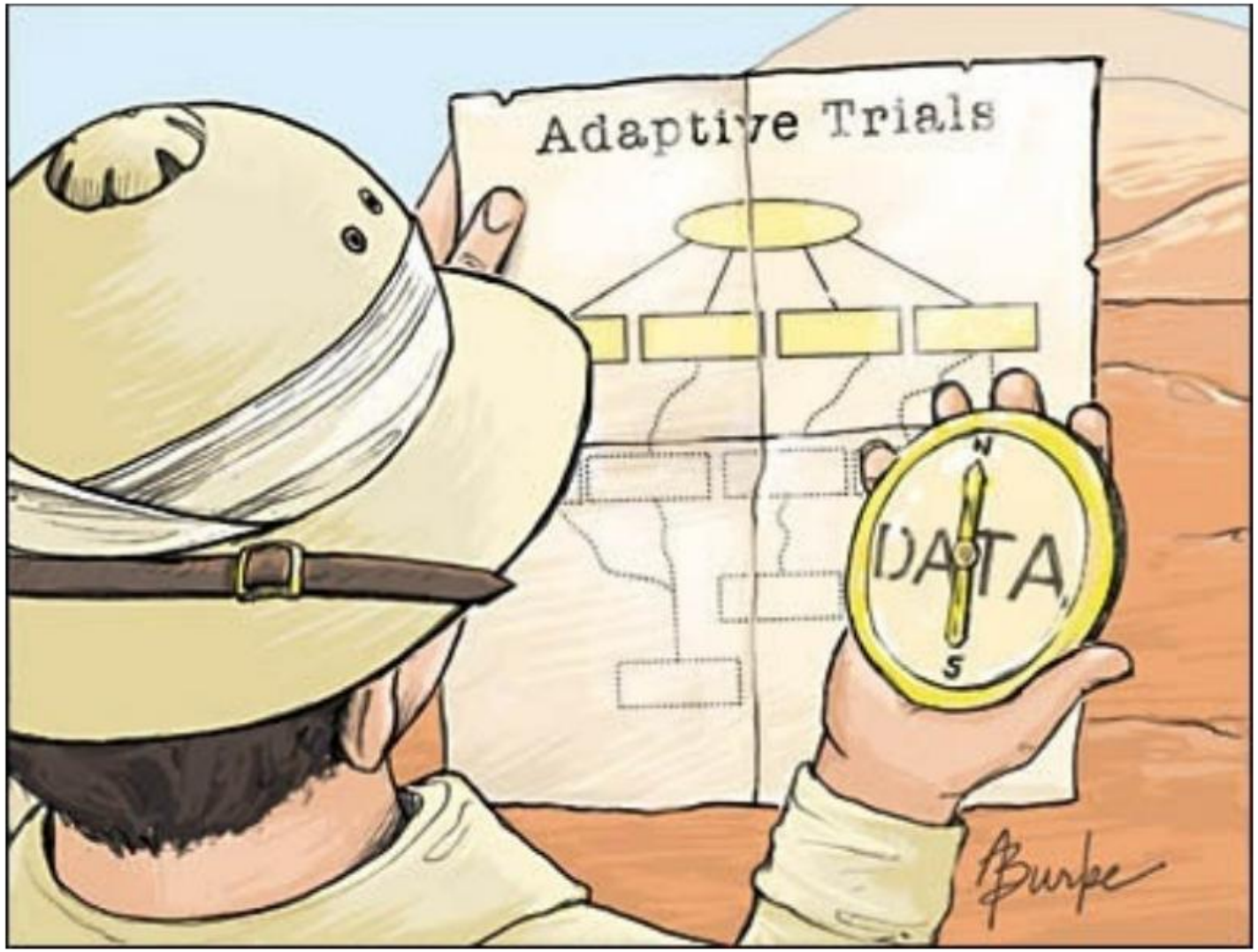
- Conventional study design of a **fixed** sample size that does not use any design adaptive elements

Adaptive design

- Design that uses accumulating data to decide on how to **modify** aspects of the study during the conduct, without undermining the **validity** and **integrity** of the trial and **following pre-specified rules**.

EPFL

ADAPTIVE TRIALS



JAMA 2006;296:1955-1957.

ADAPTIVE DESIGNS

Motivation:

- Substantial **uncertainty** regarding the experimental intervention:
  - Optimal dose
  - Duration
  - Target population

- Avoid getting the wrong answer (incorrect conclusions)

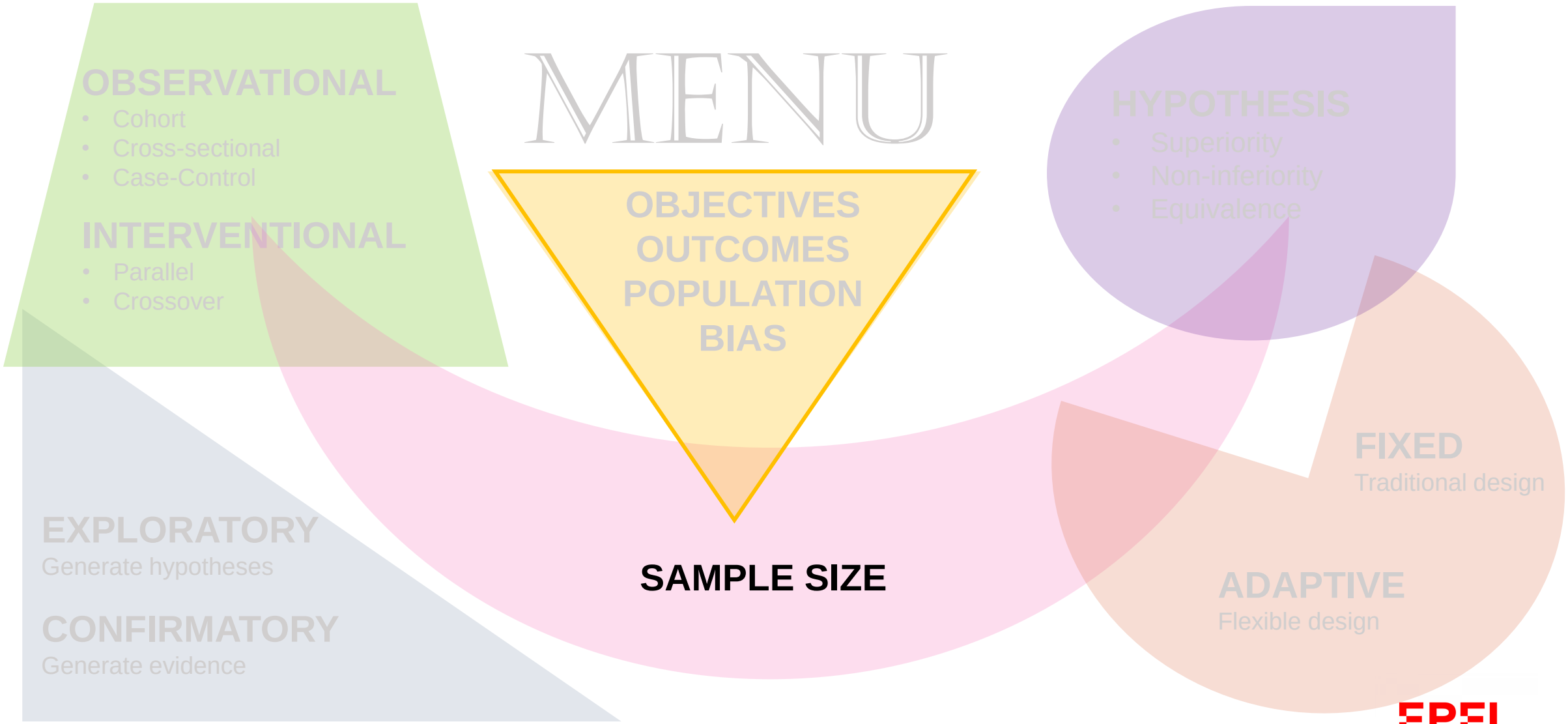
- Avoid taking **too long** to draw the right conclusion

Remarks:

- An adaptive design is **not** the solution for saving a **poorly designed** trial or ineffective intervention
- Improper adaptations can lead to **biased** studies

Type of ADAPTATIONS

- **Prospective** (by design):
  - Adaptive randomization
  - Stoping a trial due to efficacy, futility or safety
  - Dropping the loser
  - Sample size re-estimation
- **Concurrent**
  - Inclusion/exclusion criteria
  - Treatment duration
- **Retrospective**
  - Statistical analysis plan, prior to unblinding the treatment codes


MENU
OBSERVATIONAL
• Cohort
• Cross-sectional
• Case-Control
INTERVENTIONAL
• Parallel
• Crossover
OBJECTIVES
OUTCOMES
POPULATION
BIAS
HYPOTHESIS
• Superiority
• Non-inferiority
• Equivalence
FIXED
Traditional design
ADAPTIVE
Flexible design
EXPLORATORY
Generate hypotheses
CONFIRMATORY
Generate evidence
SAMPLE SIZE

Sample Size

- **WHY**
  - Scientific/Statistical rational
  - Study operational planning
  - Ethical Committee approval & regulatory requirement

- **WHEN**
  - At the study planning stage

- **WHO**
  - Biostatistician (with support from the clinical team)

Sample size – key components

- **Outcome(s)/Endpoint(s)**
  - Primary / Key outcome of interest identified

- **Effect size** (most critical and challenging)
  - Expected magnitude of difference (response on two groups) equal and above which is considered clinically relevant and biologically meaningful / plausible
  - Estimated from previous studies

- **Variability**
  - Usually obtained from previously conducted pilot or other studies

Sample size – other considerations

➢ **Other Considerations**

- Study type (confirmatory, exploratory,…)
- Study design (parallel, crossover,…)
- Statistical hypothesis (superiority, non-inferiority, equivalence)
- Data type (quantitative, qualitative,…)
- Type I (false positive α) & type II (false negative β) rates
  Standard: α = 5%, β = 20%
- Multiplicity (multiple outcomes/timepoints, interim analysis,…)
- Drop-out rate

Sample size – formula for a 2-samples t-test

$$n_g \doteq 2(z_{\alpha/2} + z_{\beta})^2 \left(\frac{\sigma}{\mu_1 - \mu_2}\right)^2$$

n_g – sample size / group
σ – variability in the outcome of interest (assume the same variability in both groups)
μ_1-μ_2 – effect size (expected difference between the 2 groups)
$Z_{\alpha/2} = 1.96$ when $\alpha=0.05$ (type I error)
$Z_{\beta} = 0.8416$ when $\beta=0.20$ (type II error)

$$n_g \doteq 16 \left(\frac{\sigma}{\mu_1 - \mu_2}\right)^2$$

(when rounding)

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Sample size – cheat sheet ☺

Effect size	↓	►	Sample size	↑
Variability	↑	►	Sample size	↑
α	↓	►	Sample size	↑
β	↓	►	Sample size	↑
(Power 1- β	↑	►	Sample size	↑)

Always consider several scenarios for discussions within the team

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Oleuropein example

REMINDER

Objective

- Evaluate the efficacy of oleuropein-based dietary supplement versus placebo on muscle energy after 36 days of supplementation in healthy male aging population

Outcome(s)

- Muscle energy metabolism measured through PDH activation in skeletal muscle biopsy

Estimate

- The difference between Oleuropein group and placebo group in PDH activation in skeletal muscle biopsy after 36 days

Sample size calculations

Background knowledge on the PDH activation was extracted from an animal study, where a reduction of 40% (standard deviation of 29%) was observed in the Oleuropein group, compared with the placebo.

In order to show a **difference of 40%** in the PDH activation with a **standard deviation of 29%** as statistically significant at an **alpha level of 5%** and a **power of 80%,** n/group=9 subjects are needed. Assuming **5% dropout rate**, 20 subjects need to be enrolled in the trial*.

** In the actual trial, an additional element was considered, the **design effect** to account for the transfer from animal to human. The design effect of 2.37, led to a final sample size of 40 subjects.*

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Clinical trials are key to assess health benefits of products / ingredients in the relevant population