Research Design of Clinical Study and Clinical Trial Research (CTR)

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Research Design for Clinical Study

Research study design depends on:

- Research questions and objectives
- Any research hypothesis
- Available resources
- Time frame allowed

Research design is a function of question, not choice

Research question

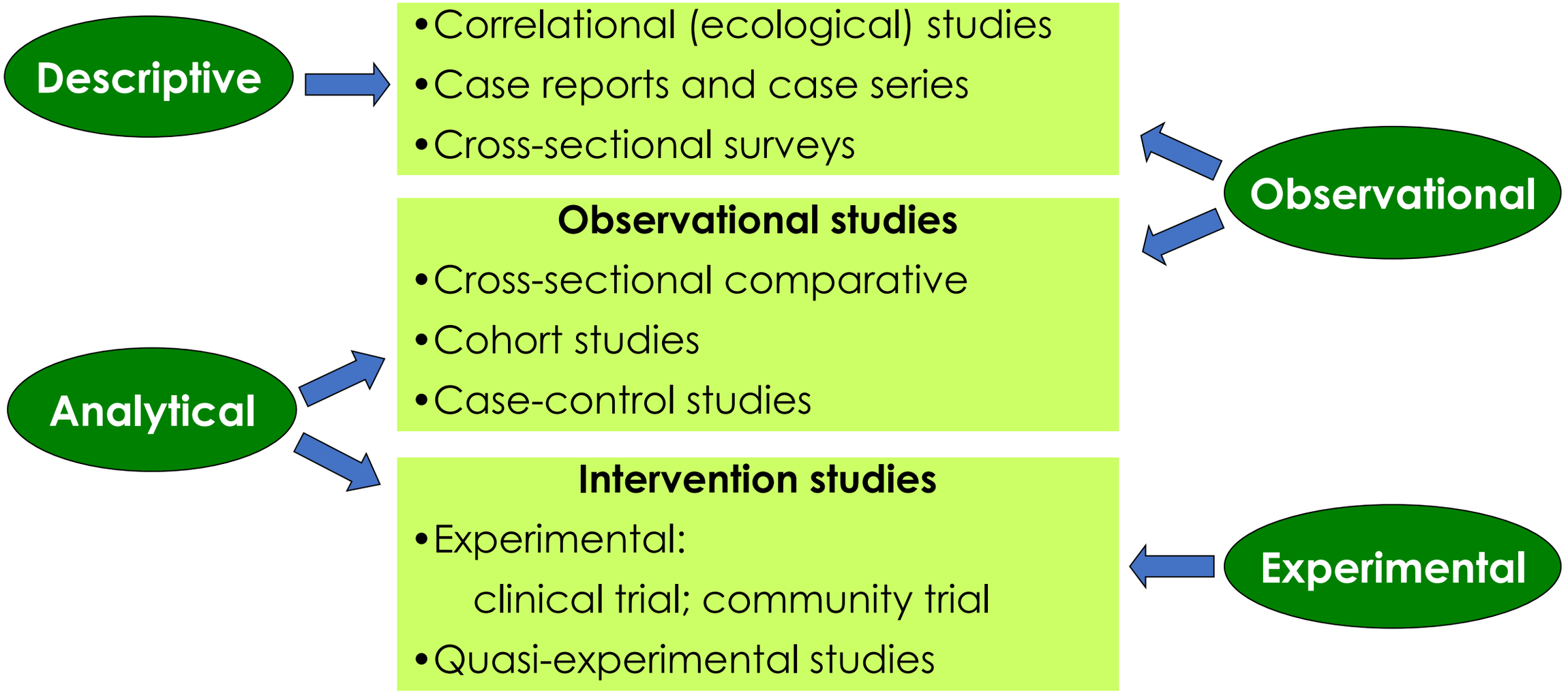
- **FINER**
  - Feasible
  - Interesting
  - Novel
  - Ethical
  - Relevant
- **PICOT**
  - Patient/Problem
  - Intervention/Exposure
  - Comparison
  - Outcome/Endpoint
  - Time

Clinical Research Studies

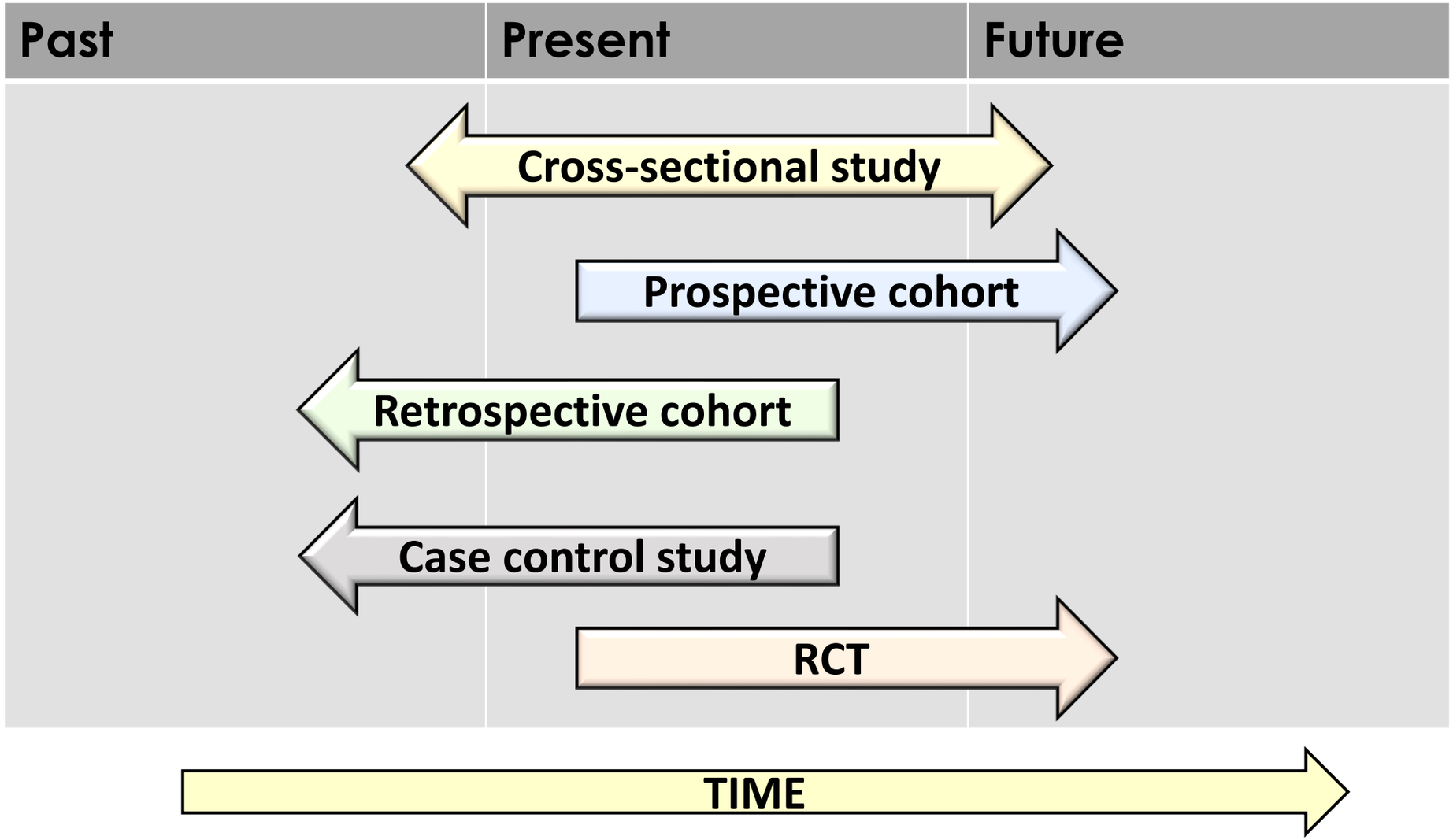
- Clinical research is medical research involving people.
- There are two types:
  - Observational studies and
  - Experimental/intervention studies

Share this infographic and help spread the word about the benefits of participating in clinical trials and studies.

Study design: Overview

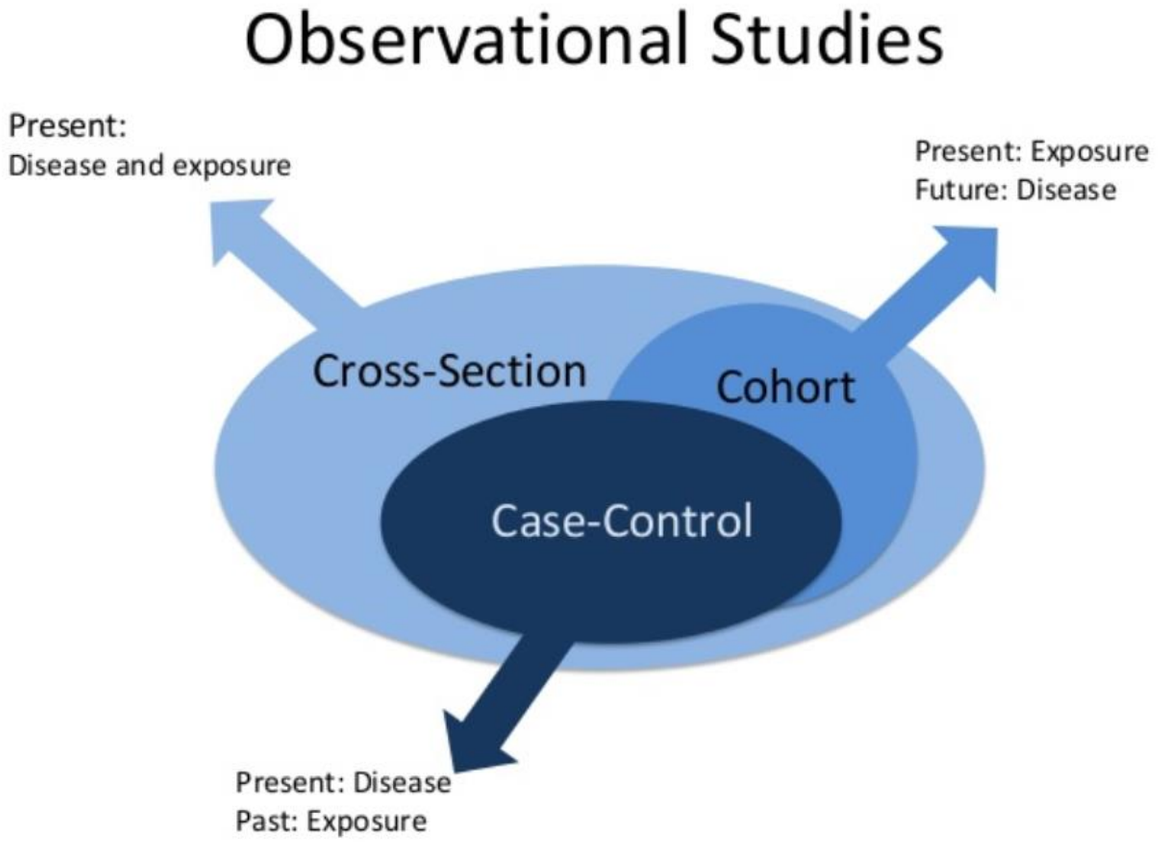


Study Design



Observational studies

- A study in which no intervention is made
- Provide estimates and examine association of events in their natural settings



Cross sectional study

- Examines the relationship between
  - diseases/other health related characteristics and
  - other variables of interest as they exist in a defined population at one time
- Exposure and outcomes both measured **at the same time**
- Quantifies prevalence, risk, or diagnostic test accuracy

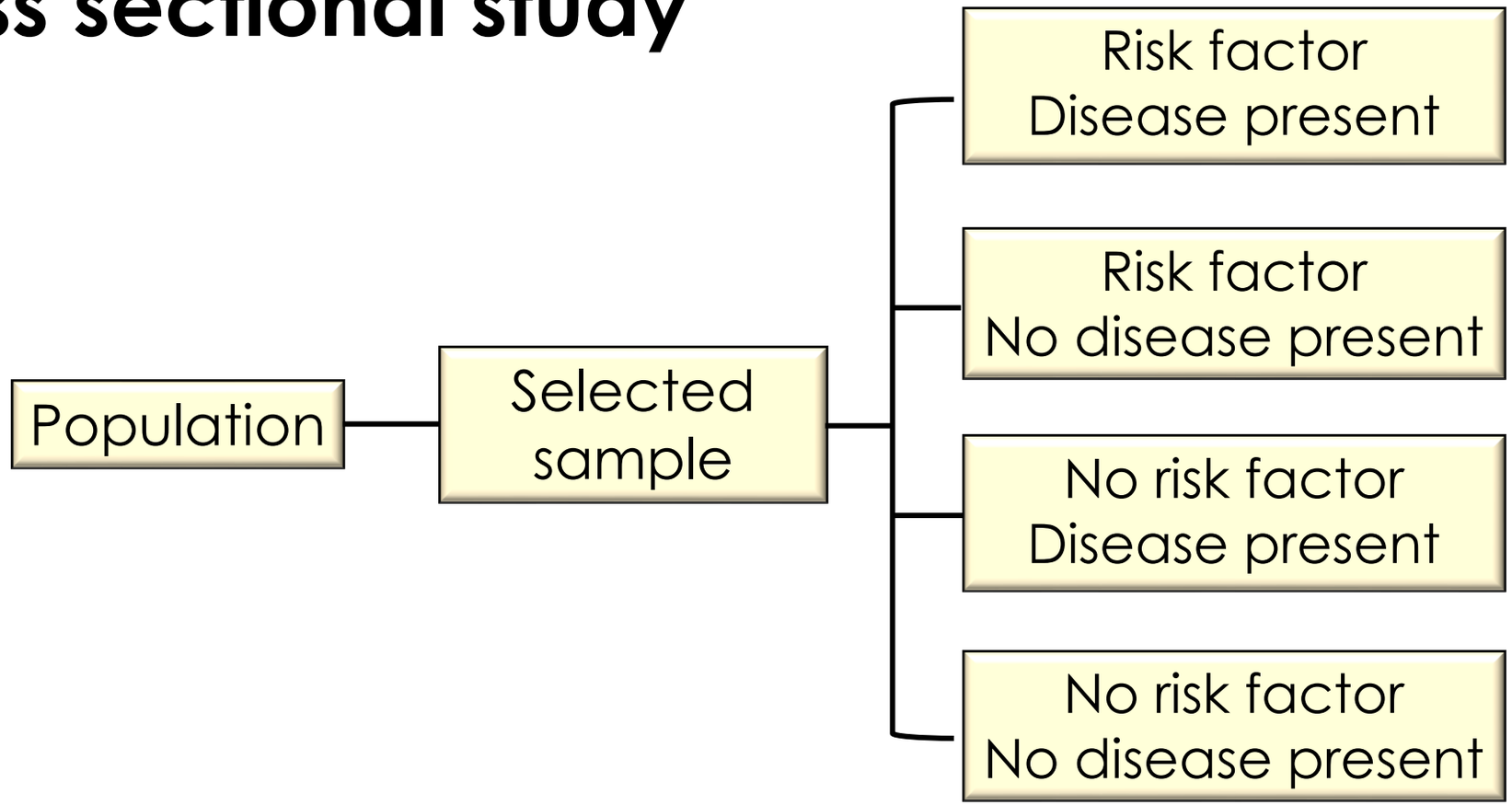
Advantages:

- cheap and simple
- Short time
- ethically safe

Disadvantages:

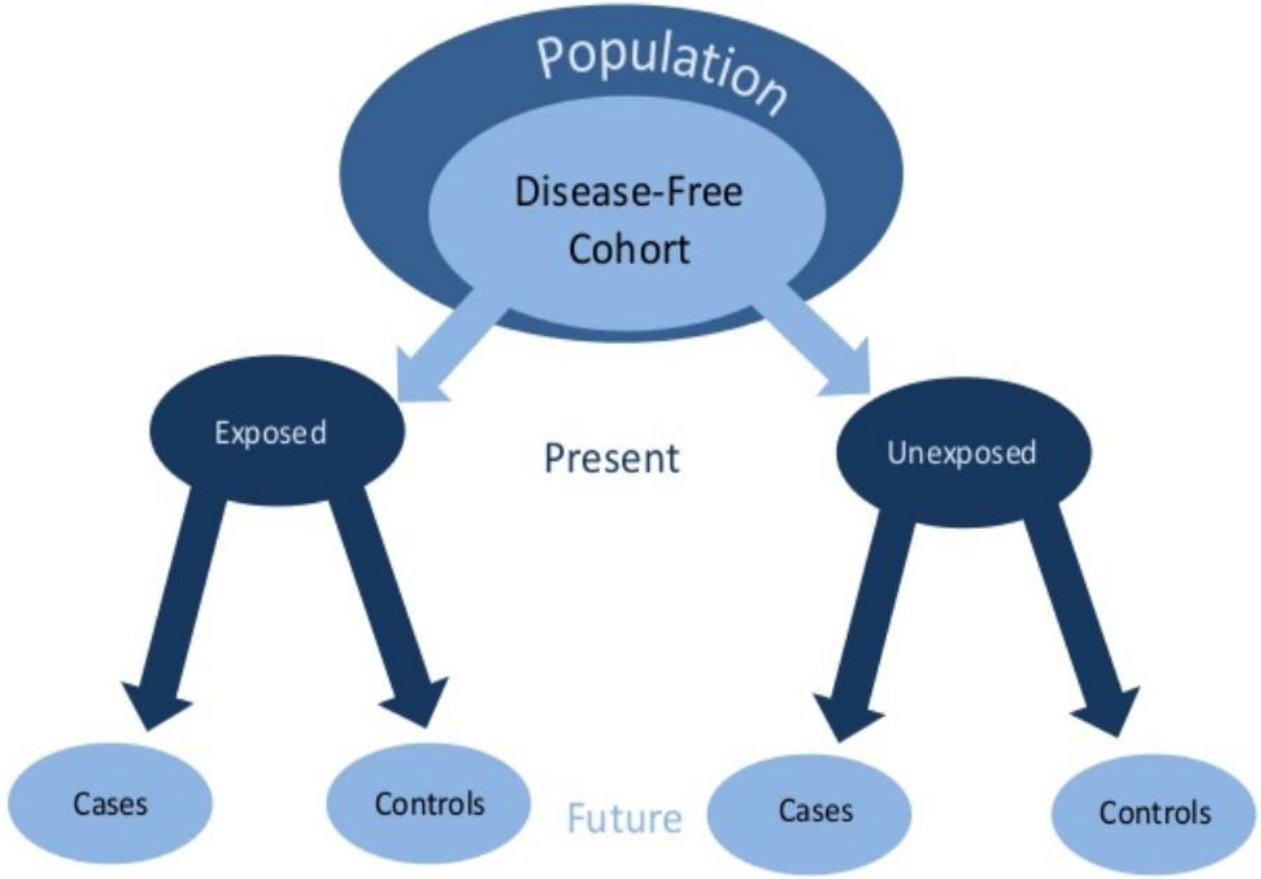
- *can not established causality*
- *group sizes may be unequal*
- *confounders may be unequally distributed*

Cross sectional study

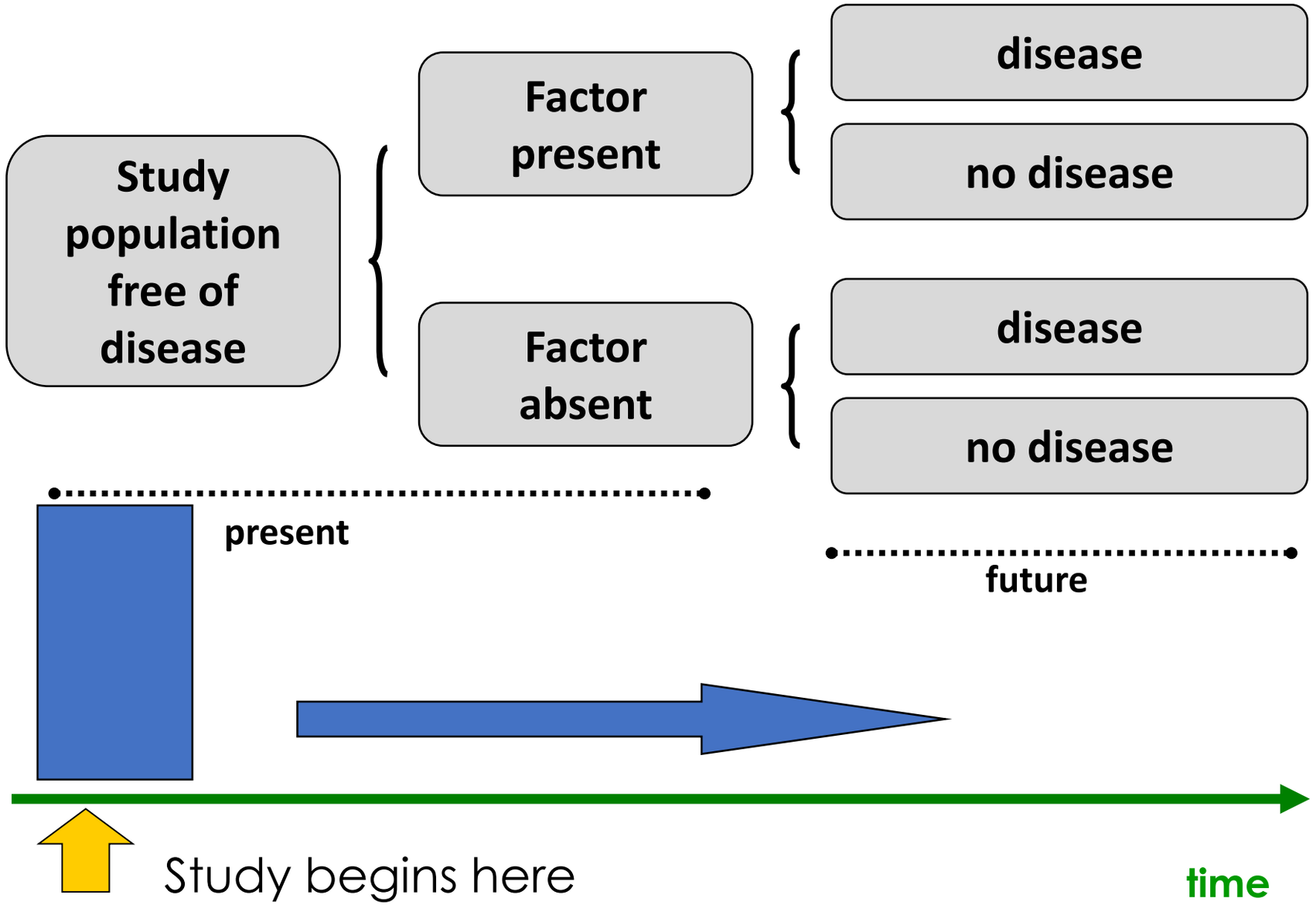


Cohort studies

- Classify on basis of **presence or absence of exposure**
- Follow up to determine the development of disease in each exposure group
- Can establish **causal association**
- Suitable for rare exposures; Not suitable for rare outcomes



Cohort Design



Cohort studies

Advantages:

- establish causal association
- participants can be matched
- eligibility criteria and outcome assessments can be standardised

Disadvantages:

- exposure may be linked to a hidden confounder
- for rare disease, large sample sizes or long follow-up necessary
- problem of loss to follow up

Case-control studies

In a case-control study, diseased people **(cases)** are compared with non-diseased people **(controls)** to determine if the two groups differ in the proportion of persons exposed to a specific factor.

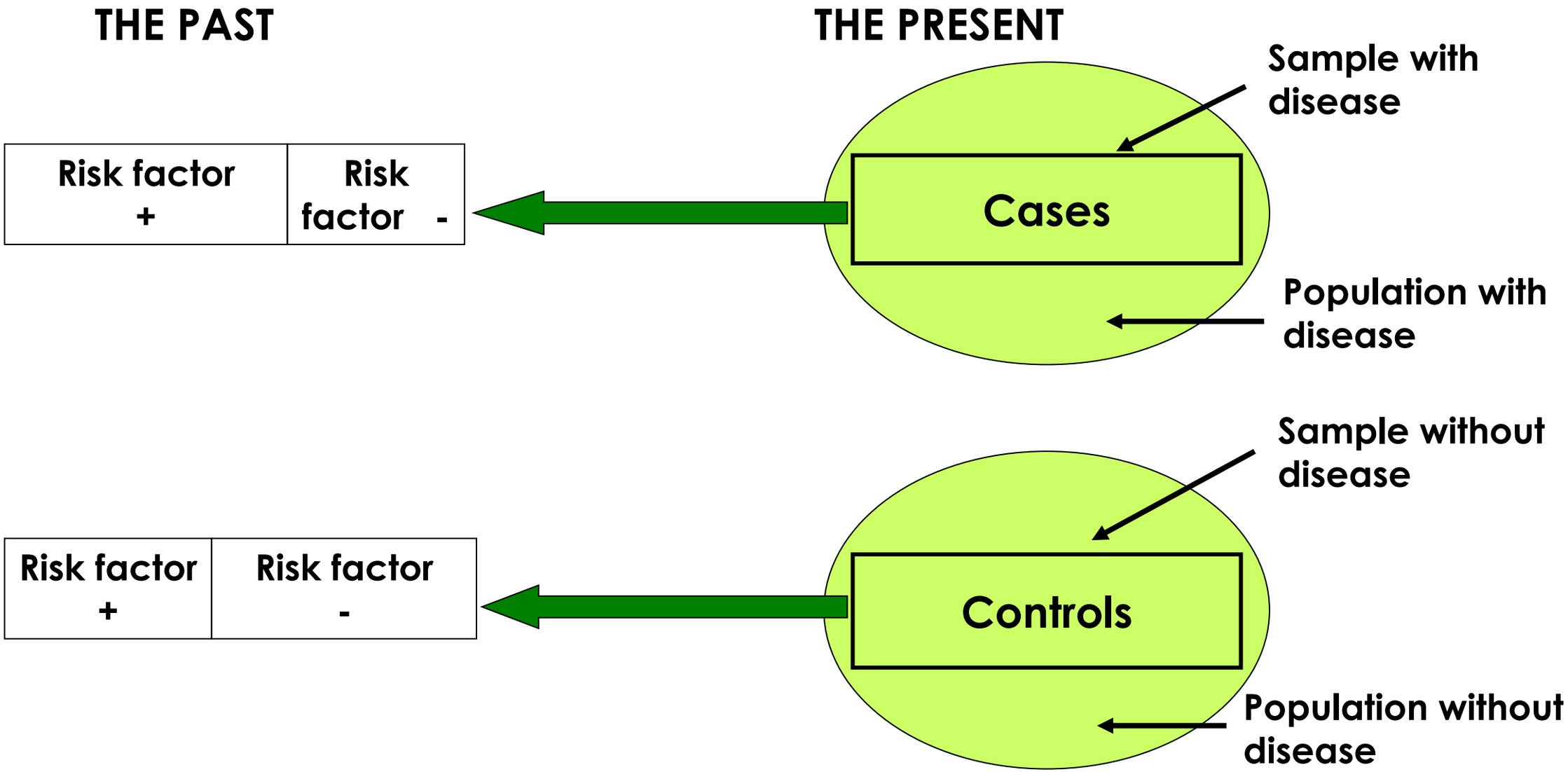
Advantages:

- quick and cheap
- only feasible method for very rare disorders

Disadvantages:

- reliance on recall or records to determine exposure status
- confounders
- selection of control groups is difficult
- potential bias: recall, selection

Case-control studies



Experimental or Intervention Studies

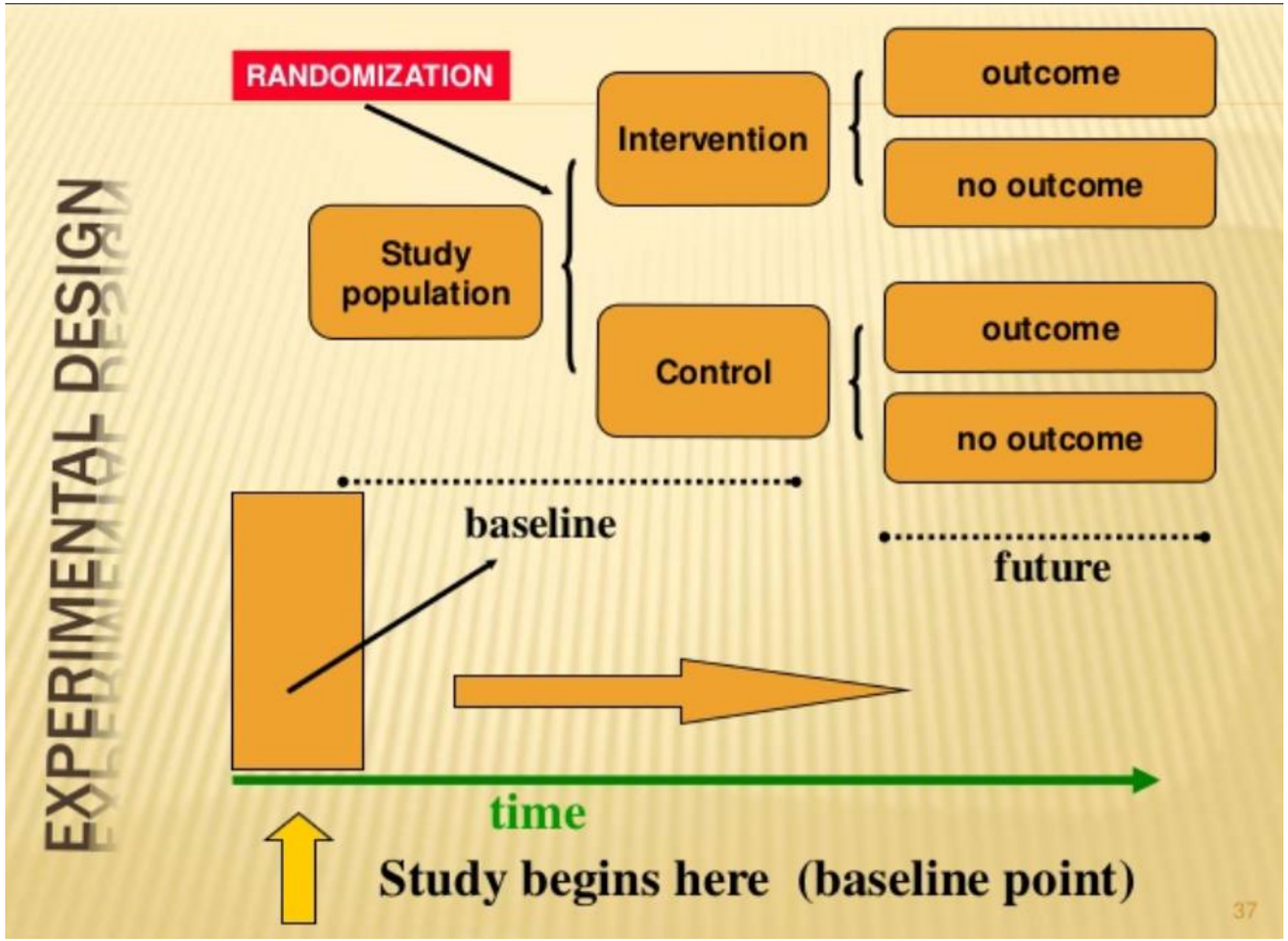
- Similar to cohort study, except that exposure is allocated by the investigator
- Investigator can control the exposure
- Subjects are followed up to determine if (when) they develop the outcome
- Allocation is best done using a randomization procedure
- **Clinical trials** are most well known experimental design
- "Treatment group" and "comparison group"

Experimental studies

Clinical trials provide the "gold standard" of determining the relationship between factor and the event

Quality of experimental study:

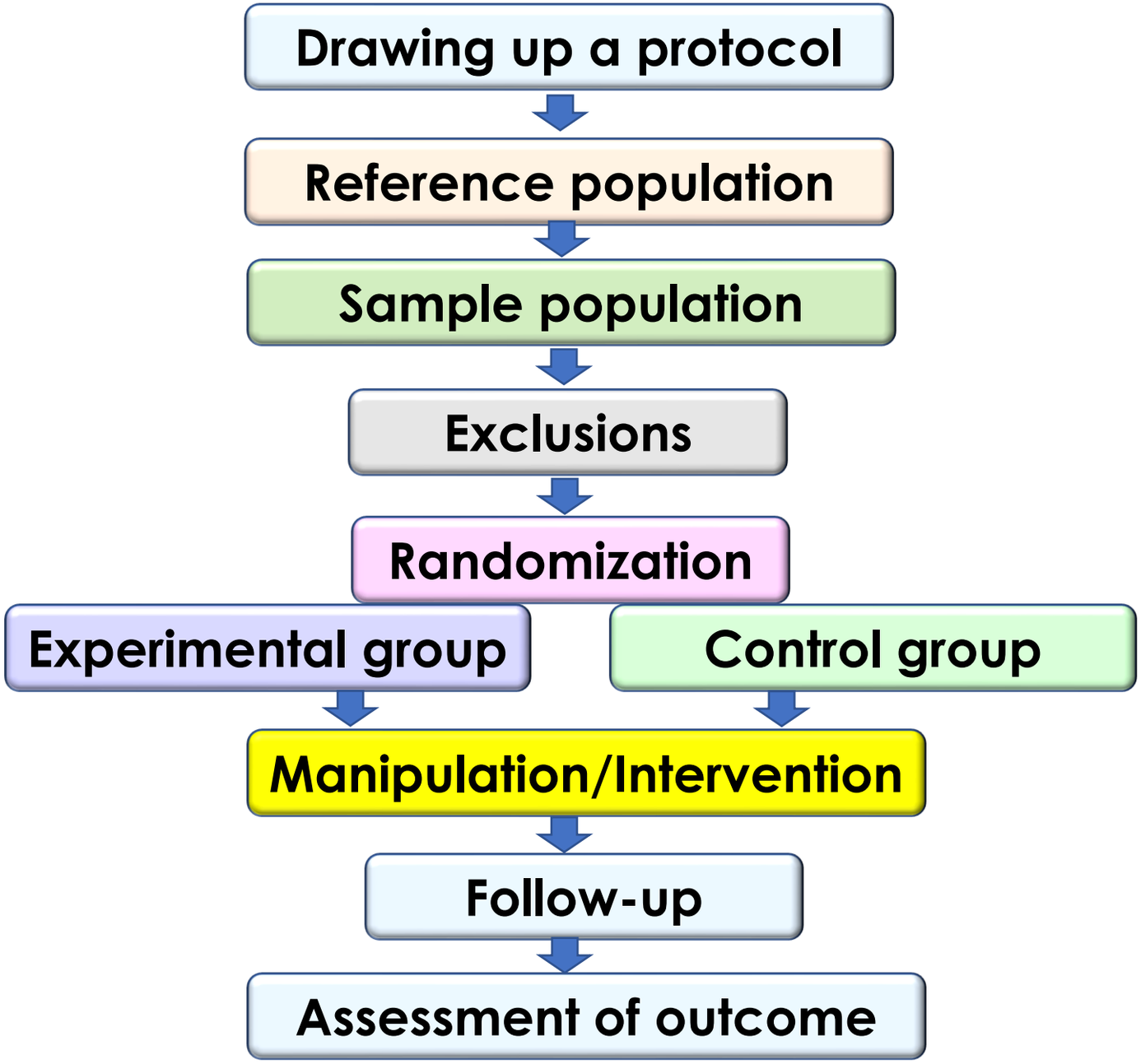
- Randomization
- Control
- Blinding
- Cross-over



Types of experimental studies

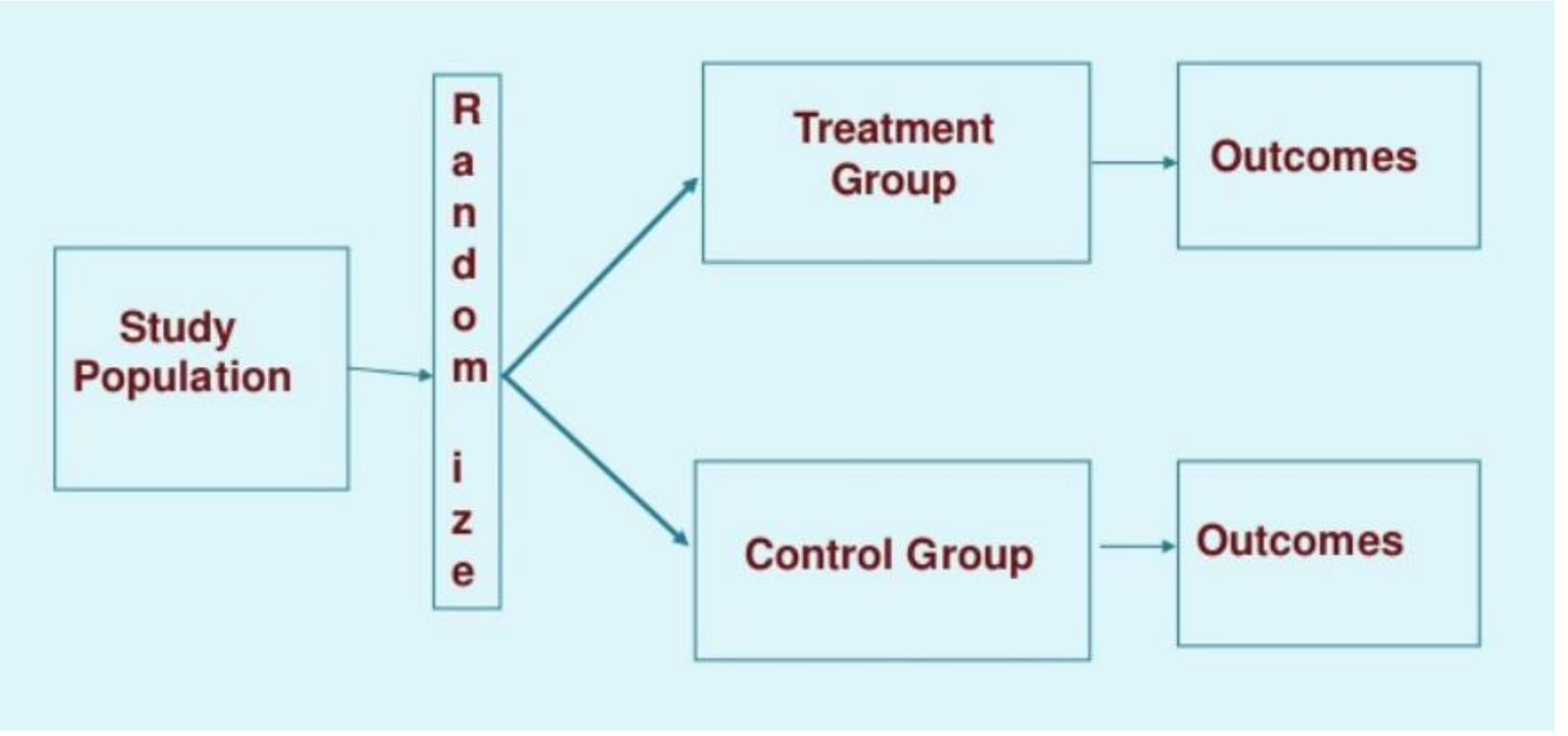
- As per randomization
  - Randomized controlled trials (RCT)
  - Non-randomized trials
- As per blinding
  - Single
  - Double
  - Triple
- As per design
  - Simple
  - Cross-over
- As per study area
  - Field trials
  - Clinical trials

Steps of experimental studies



Clinical Trials

A clinical trial is a comparative, prospective, experiment conducted in human subjects



Four Phases of Clinical Trials

- **Phase I trial:**
  - tests an experimental treatment on a small group of often **healthy people** (20 to 80)
  - to judge its **safety**, side effects and to find the correct drug dosage
- **Phase II trial:**
  - uses more people (100 to 300)
  - the emphasis in Phase II is on **effectiveness**
  - aims to obtain preliminary data on whether the drug works in people who have a certain disease or condition
  - continue to study safety, including short-term side effects; can last several years

Four Phases of Clinical Trials

- **Phase III trial:**
  - gathers more information about safety and effectiveness, studying different populations and different dosages
  - using the drug in combination with other drugs
  - number of subjects usually ranges from several hundred to about 3,000
  - If the FDA agrees that the trial results are positive, it will approve the experimental drug or device
- **Phase IV trial:**
  - for drugs or devices takes place after the FDA approves their use
  - a device or drug's effectiveness and safety are monitored in large, diverse populations
  - Sometimes, the side effects of a drug may not become clear until more people have taken it over a longer period of time

Randomized controlled trial (RCT)

- A **prospective planned experiment** designed to assess the effect of a treatment/intervention
- Compare the observed outcomes in an intervention group with those in a comparable group (control or placebo)
  - Drug vs. Placebo; Drug vs. Standard care
  - Medicine vs. Purgery; Low dose vs. High dose
- Provides most convincing evidence of relationship between exposure and effect
- Not possible to use RCTs to test effects of exposures that are expected to be harmful, for ethical reasons
- **The "gold standard" of research designs**

RCT: Choice of participants

Inclusion criteria

- Appropriate to the study question
- Reflect the potential benefit of intervention
- Ease of recruitment

Exclusion criteria

- Safety concern
- Intervention likely ineffective
- Conditions that could compete with outcomes (e.g- early death)
- Contradictions to intervention of interest
- Adherence issues

RCT: Choice of controls

- Typically, and inert agent (placebo) is ideal but might not always possible
- May want to consider and active therapy as a control (e.g-standard of care)
- Note: Placebo is not ethical in virtually all studies that involve diseases with a proven/established treatment
- Remain ethical in trials where no proven treatment is established

RCT: Choice of outcomes

- Easy to diagnose, collect or observe
- Clinically relevant
- Chosen before the start of data collection
- The sample size calculation should be carried out to detect a clinically relevant effect of the intervention on the primary outcome
- The choice of the most suitable outcome should be based on the research question and the corresponding hypothesis

RCT: Choice of outcomes

- Outcomes:
  - **Primary:** variable that most relevant to answer the research question
  - **Secondary:** additional outcomes to help interpret the results of the primary outcome
  - **Surrogate:** biomarkers intended to substitute for a clinical outcome
  - **Composite:** made up of multiple variables

Table 1. Types of outcomes.

Outcome	Patient-centered	Composite	Surrogate
Asthma	Asthma control (questionnaire)	Hospitalization or a > 20% decline in asthma control	FEV_1, peak flow, eosinophils
PAH	2-year survival	Lung transplantation or death	6MWD, PASP
ARDS	Hospital survival	Time to extubation or tracheotomy	PaO_2/FiO_2 ratio, ventilator-free days

PAH: pulmonary arterial hypertension; 6MWD: six-minute walk distance; and PASP: pulmonary artery systolic pressure.

J Bras Pneumol. 2017;43(1):5-5
http://dx.doi.org/10.1590/S1806-37562017000000021

RCT: Randomization

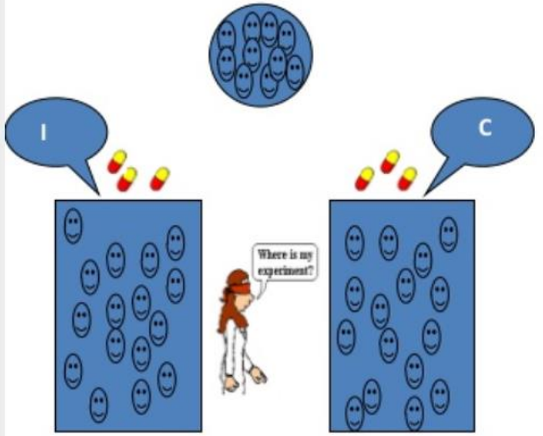
- Purpose of **assigning participants** to treatment and control
- Assuming that each participant has **an equal chance** of being assigned to any group
- Assignment of participants to treatment by a random process such that neither the investigator nor the participants knows the treatment to be assigned at the start of the study
- Study participants are assigned to treatment groups by chance (not by choice)

RCT: Randomization

Why randomization is important?

- In a clinical trial, comparability is needed among study groups and best way to assure comparability is by randomization
- **Features:**
  - Balance patient baseline characteristics to all arms of the study
  - Equal distribution of all known and unknown confounding variables
  - Allows for an unbiased comparison between groups

RCT: Blinding/Masking



- Refers to masking treatment assignment from patients, investigators and/or end point assessors
  - Single blind: participants are not aware of assignment
  - Double blind: both participants and health staff unaware
  - Triple blind: patients, health staff and investigators

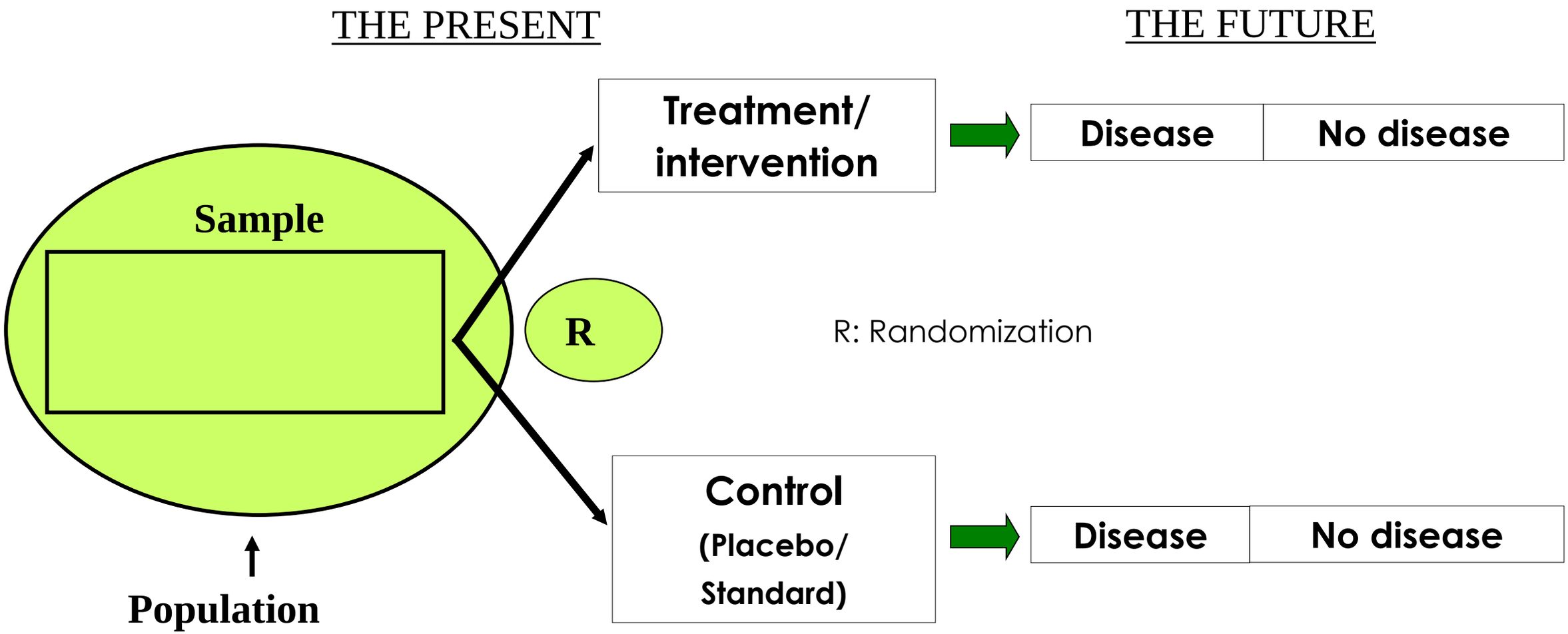
Why blinding?

- If an outcome can be affected by patient/investigator expectations, then maintaining blinding is important
- Maintains balanced groups during follow-up and minimized outcome ascertainment (participant) and measurement (investigator)

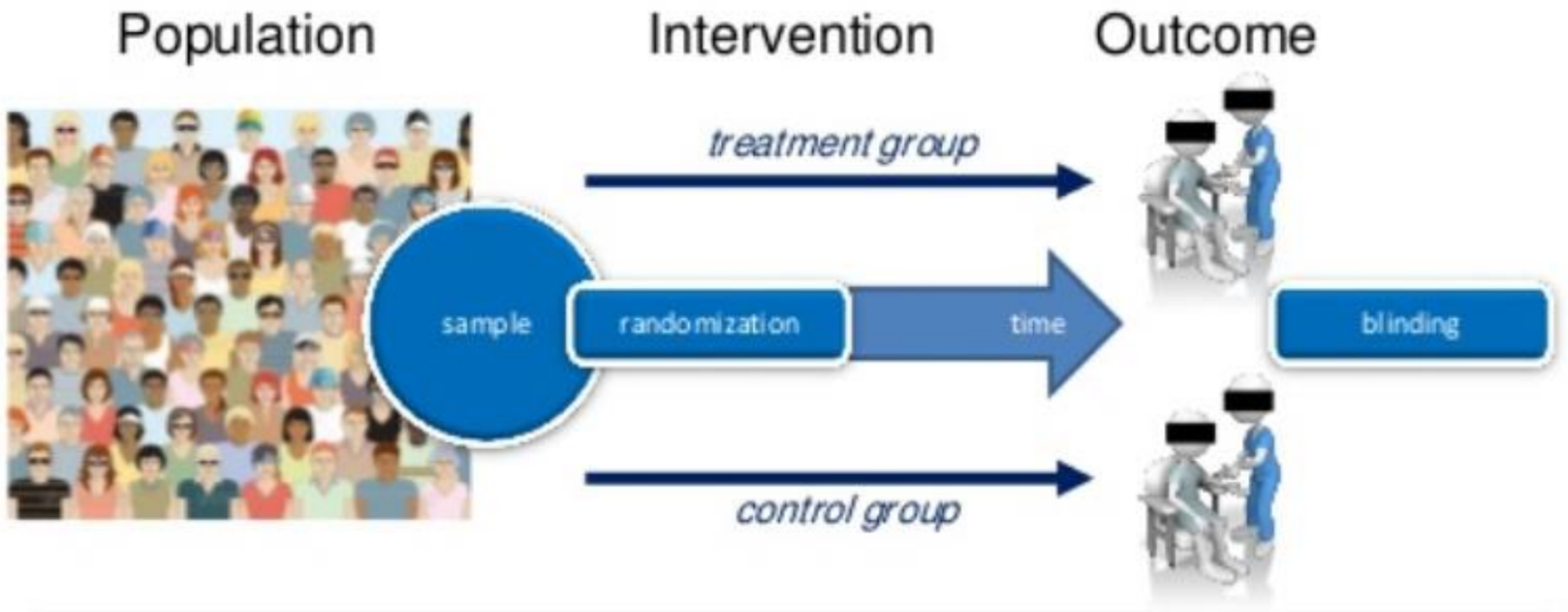
RCT: Types

- Before and after comparison
- Comparison with placebo
- Comparison of two medicines/procedures/tests
- Comparison of more than two medicines/procedures/tests

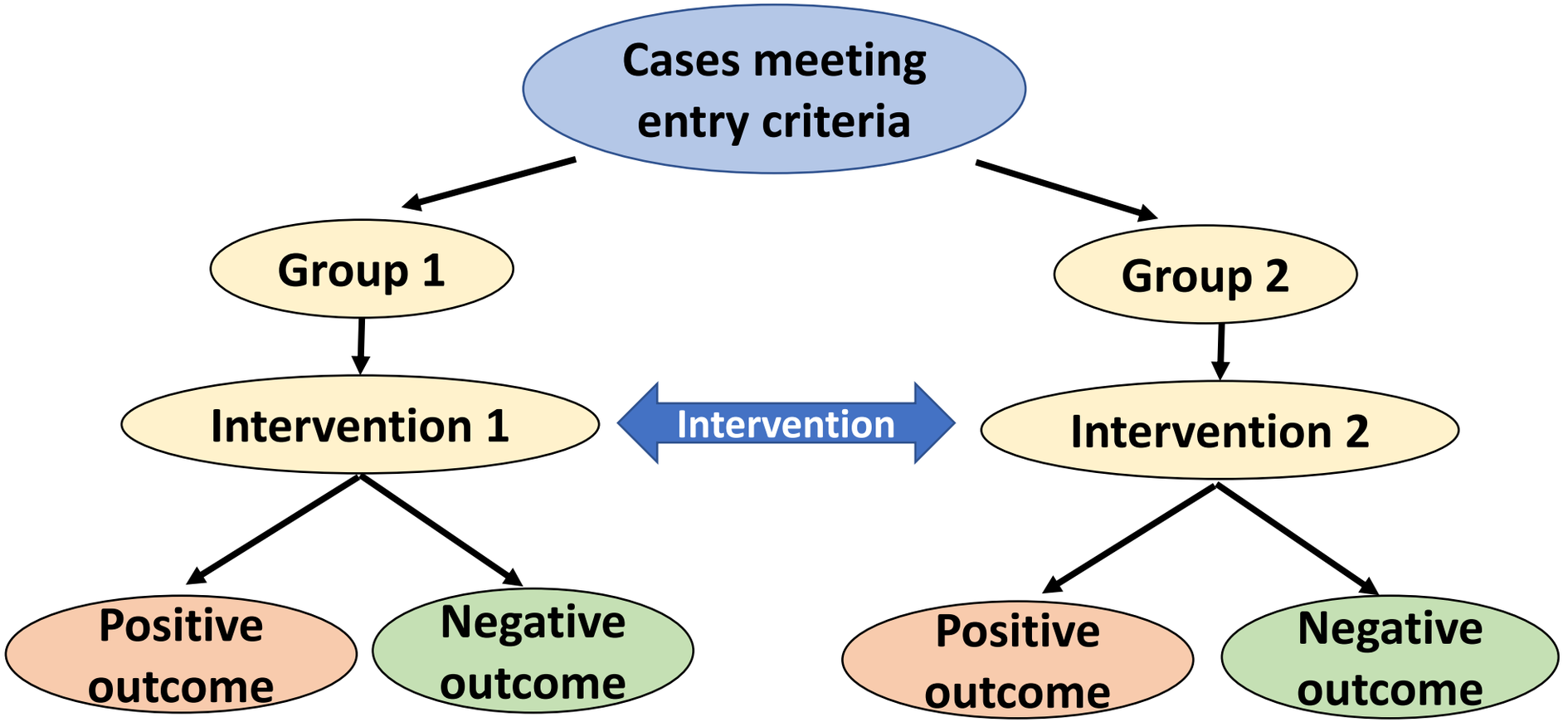
RCT: Basic design



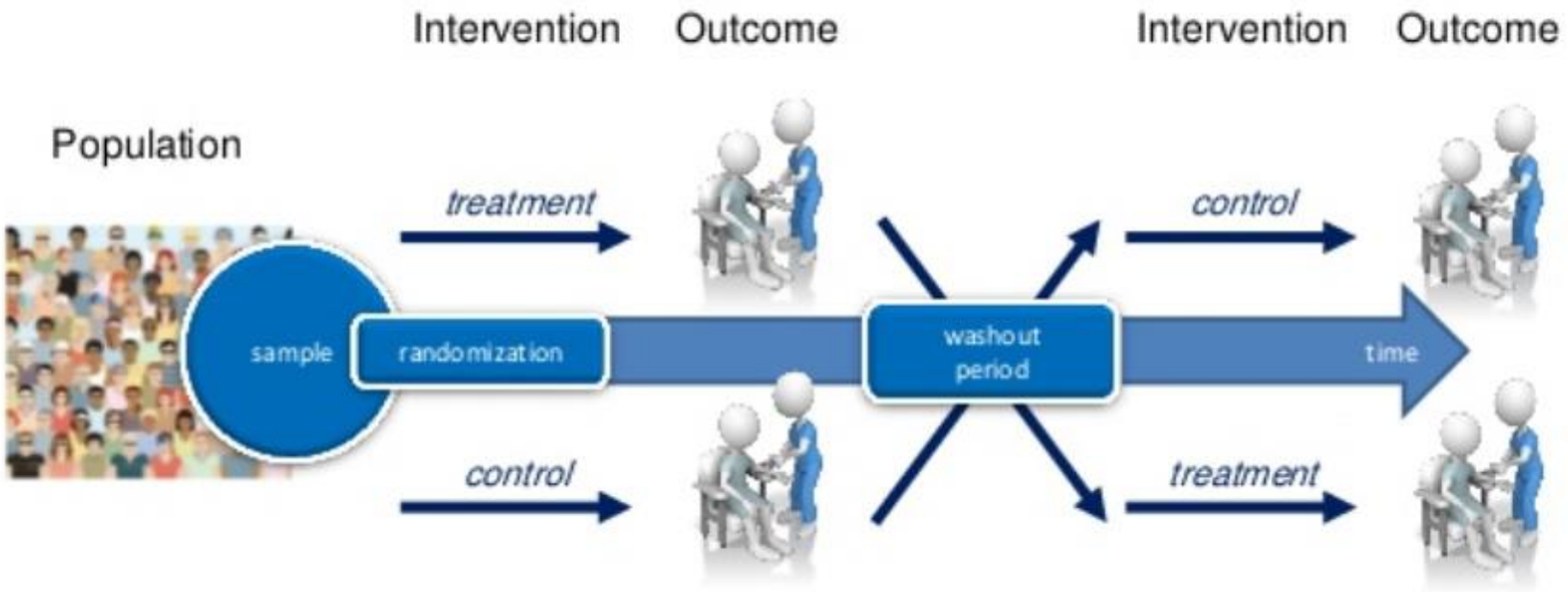
RCT: Comparison with placebo/control



RCT: Comparison between two types of intervention



RCT: Crossover design



Advantages

- Good for chronic or repeating conditions (e.g- epilepsy)
- Gain in power because each patient is their own control

Disadvantage

- Wash out and sequence effect consideration (e.g- long drug half life)
- Very susceptible to patient drop outs

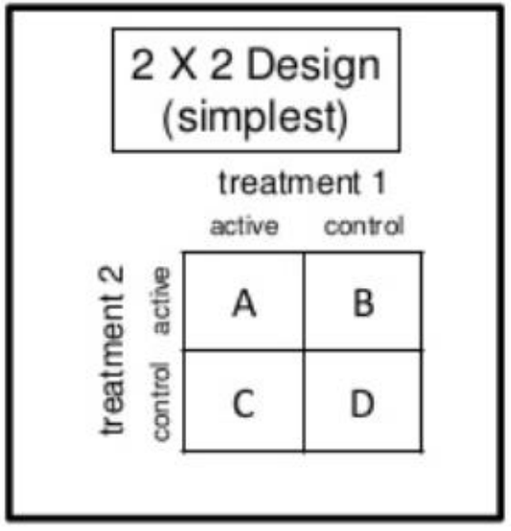
RCT: Factorial design

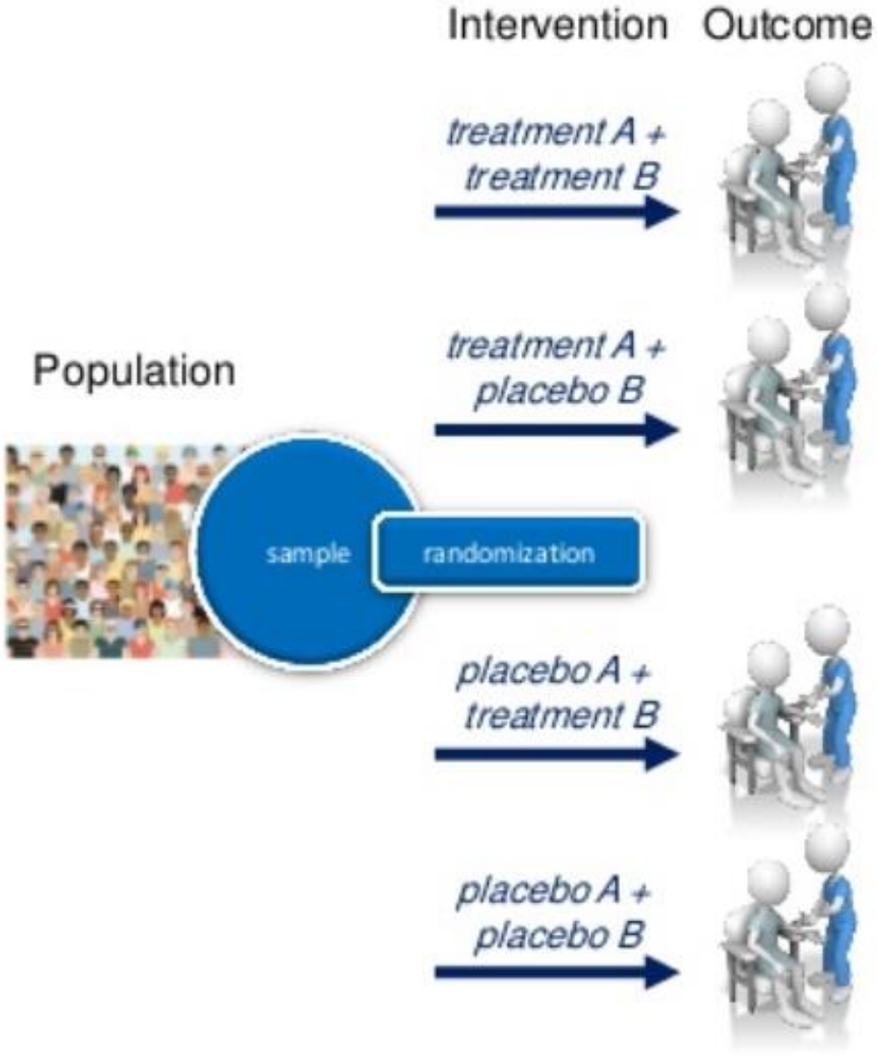
Advantages

- Can examine main effects & interaction effects

Disadvantage

- May be difficult to disentangle the interaction effect and interpret results

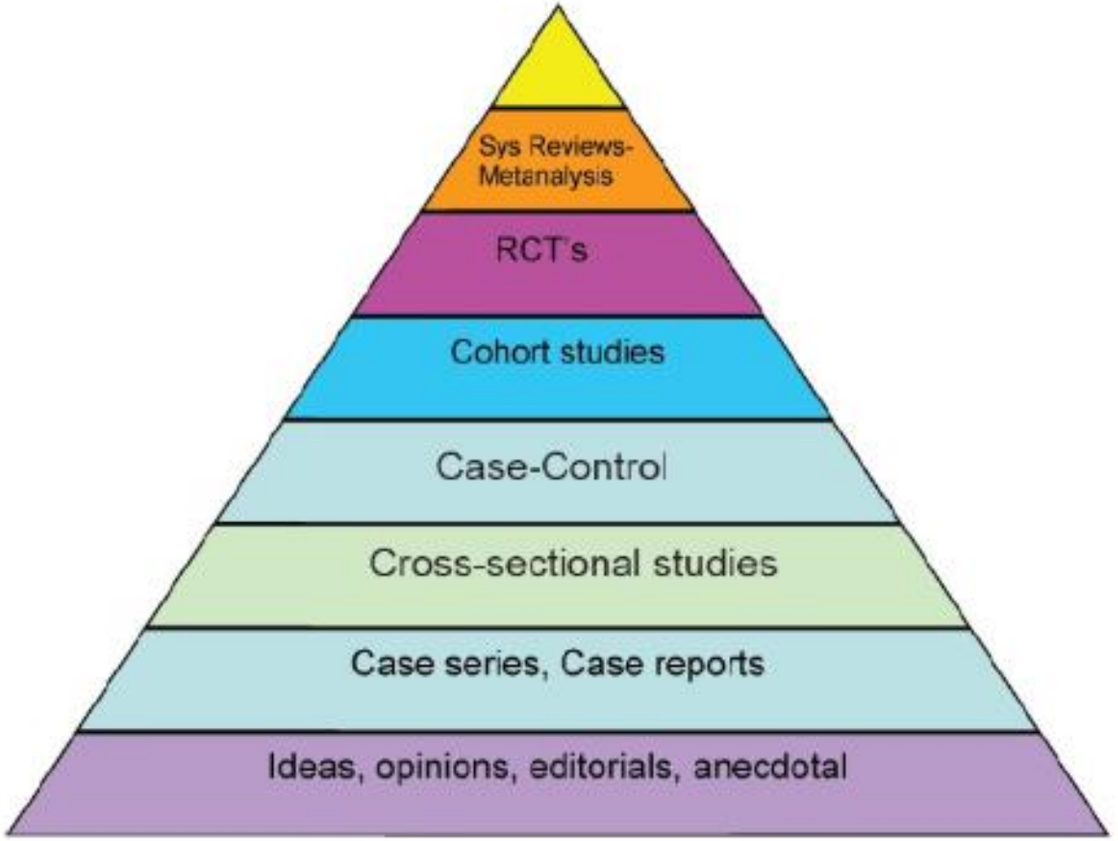


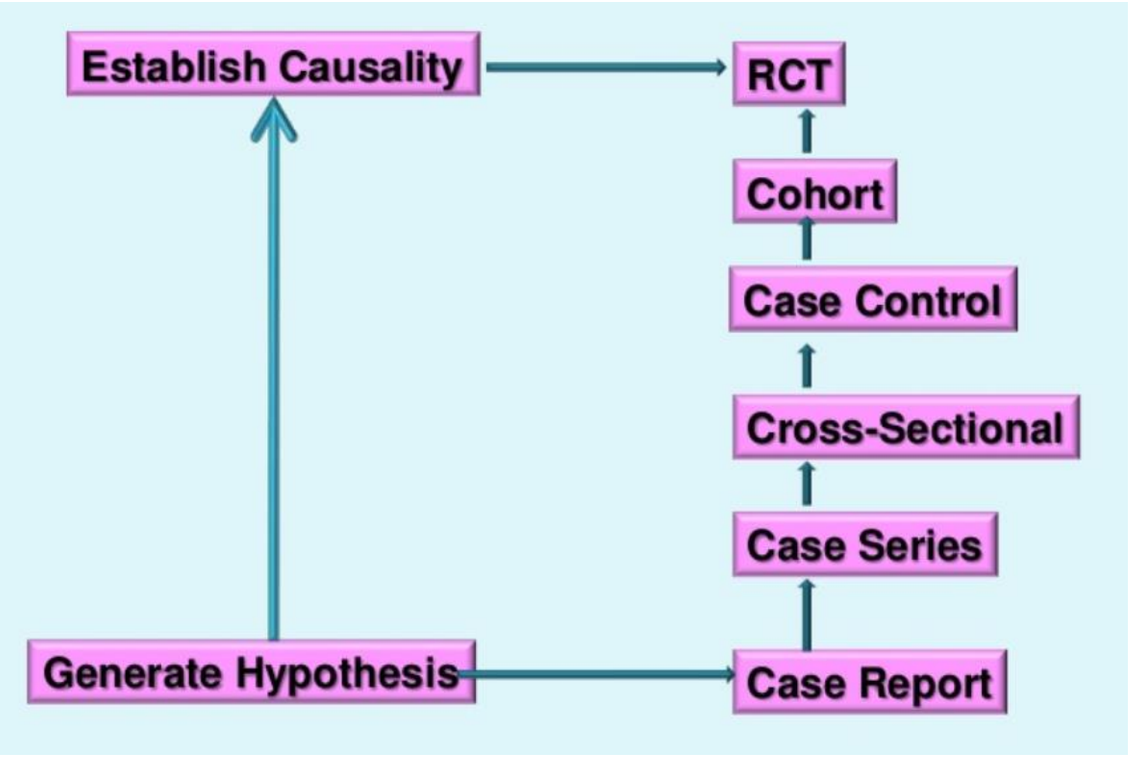


RCT vs. Observational Studies

	RCTs	Observational studies
Selection bias	If randomization is done properly, negligible	Likely to occur
Measurement bias	If blinding is done properly in double blinded studies, less likely	Possible especially with subjective outcomes
Statistical analysis	Simpler- usually unadjusted simple analysis is sufficient (t-test or ANOVA)	More complicated- adjusted analysis is necessary with logistic/linear regression or cox proportional hazard models
Unmeasured confounders	Usually balanced if sample size is appropriate	Usually imbalanced
External validity	Usually limited as restrictions of patients who can participate in the trial	The real world scenario makes this design more externally valid
Ethical issues	Placebo use can be an ethical issue	Minimal ethical issues usually
Cost	High	Usually lower

Evidence Hierarchy





Crd: Dr. Kusum Gaur

Linking research question with research design

Type of question	Appropriate study design
Burden of illness	Field survey
Prevalence	Cross sectional survey
Incidence	Longitudinal survey
Causation, risk & prognosis	Case control, Cohort, RCT
Treatment efficacy	Randomized controlled studies (RCT)
Diagnostic test evaluation	Randomized controlled studies (RCT)
Cost effectiveness	Randomized controlled studies (RCT)

Linking research question with research design

Type of Question	Study Design
Therapy	RCT > Cohort > Case Control > Case Series/Reports
Diagnosis	Prospective, blind comparison to a gold standard or Cross-Sectional
Harm/Etiology	RCT > Cohort > Case Control > Case Series/Reports
Prognosis	Cohort > Case Control > Case Series/Reports
Prevention	RCT > Cohort > Case Control > Case Series/Reports
Clinical Exam	Prospective, blind comparison to a gold standard
Cost-Analysis	Economic analysis

Questions on therapy, etiology and prevention that can best be answered by an RCT, can also be answered by a systematic review or meta-analysis.

Harm/Etiology studies can be answered by RCTs if ethical issues allow it.

Schardt, 2013

Linking research question with research design

Research question	RCT	Controlled longitudinal studies	Cross sectional surveys	Qualitative research
Effectiveness: does it work, Does A work better than B?	++	+	-	--
Explanation: how does it work, why does it work?	--	-	+	++
Context: in what circumstances does it work, for whom?	--	-	+	++
Safety: will it do more good than harm?	++	+	+	+
Acceptability: will the target group accept the intervention/ new method of working?	--	-	+	++
Prevalence: how often is this intervention/method applied/implemented?	--	--	++	--
Appropriateness: is this the right intervention/method for this target group?	--	-	+	++

https://www.cebma.org/faq/what-are-the-levels-of-evidence/

Linking research question with research design

Research question	Study design
Therapy	Randomized controlled trial
Diagnosis	Cross-sectional study
Screening	Cross-sectional study
Prognosis	Cohort
Etiology	Cohort or case-control
Side effects	Case series

(Source: Panda, 2015)

Summary and Synthesis: How to Present a Research Proposal - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/Research-questions-vis-a-vis-study-designs_tbl1_326232753 [accessed 8 Mar, 2020]

Characteristics, strengths and weaknesses of study designs used in clinical research

Study design	Characteristics	Strengths	Weaknesses
Case report & case series	One or few subjects Detailed description of (a) case(s) without a control group	First form of publication Fast, inexpensive Hypothesis generation	Very limited potential to establish causal effects Selection bias
Cross-sectional study	Exposure & outcome measured at same point in time Subjects with and without outcome are compared	Useful to describe the prevalence of disease Fast, inexpensive Hypothesis generating	Very limited potential to establish causal effects Selection bias Survival bias

Characteristics, strengths and weaknesses of study designs used in clinical research

Study design	Characteristics	Strengths	Weaknesses
Case-control study	Cases are compared with controls with respect to exposure	Efficient; Suitable to study rare outcomes & multiple exposures Relatively inexpensive Hypothesis generating	Potential to establish causal effects Can only study outcome Choice of control group can be difficult Selection and Recall bias
Cohort study	A cohort of subjects free of the outcome is followed and compared based on the exposure	Suitable to study multiple exposures, rare exposures, & multiple outcomes Hypothesis generating High generalizability	Potential to establish causal effects Can take a long period Can be expensive Selection bias

Characteristics, strengths and weaknesses of study designs used in clinical research

Study design	Characteristics	Strengths	Weaknesses
RCT	Randomization: allocation of subjects to experimental or control group by chance	Gold standard in establishing causal effects in studies on therapy Suitable to study more than one intervention	Very expensive Can take a long period Not suitable to study rare events Can be unethical Often low generalizability due to strict selection criteria

Mixed Methods Research Designs

1. Convergent Parallel	QUAL	AND	*QUAN*		
2. Explanatory Sequential	*QUAN*	THEN	QUAL		
3. Exploratory Sequential	QUAL	THEN	*QUAN*		
4. Embedded	QUAL/ *QUAN*	WITHIN	*QUAN* /QUAL		
5. Transformative	*QUAN*	THEN	QUAL	WITHIN Framework	
6. Multiphase	QUAL	THEN	*QUAN*	THEN	QUAL/ *QUAN*

Ozawa S , and Pongpirul K Health Policy Plan. 2014;29:323-327

References

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Thank you