PLANNING RESEARCH

Planning Research: Key Questions

- What is the subject of research?
- Which is the plan for research?
- What is the clinical significance of research?

Subject of Research - Examples:

- What is the incidence (or prevalence) of a disease?
- What is the cause of a disease?
- What is the effect of a given risk factor?
- What are the characteristics of disease course and its prognosis?
- How effective is a given therapy regimen?
- How reliable is a given diagnostic test?
- What is the significance of a given symptom?

The aim of research defines its strategy:

- Description, assessment (of the situation in a population, prevalence of disease, etc.).
- Comparison (of the effectiveness of two drugs).
- Association (of a risk factor and disease).

The key to the planning research is THE HYPOTHESIS

- **The fact: some menopausal women take estrogens for prevention of osteoporosis.**
- Hypothesis: Synthetic estrogens may prevent development of osteoporosis.
- Deductive analysis of the hypothesis: provide AIM of the study:
    - How many women take estrogens? How many women have osteoporosis? (description)
    - Do women who take estrogens have less osteoporosis? (comparison)
    - Can synthetic estrogens prevent the onset of osteoporosis? (causative association, prevention)
    - More ideas?

Planning Research

- Literature search (first look for systematic reviews).
- Definition of the problem – HYPOTHESIS.
- The hypothesis defines TYPE OF THE STUDY.
- Practical issues (*finances, time, equipment, technical expertise, authorships, ethical issues*).

Literature Search

- What has been investigated so far, and how?
  - Population(s) (e.g., asthma patients from one hospital).
  - Type of they study (descriptive, observational, interventional?).
  - Statistical methods (which methods were utilized?).
  - Mechanisms , regimens, methods…
- What has NOT been investigated so far?
  - Identify limitations of published reports (sample imperfections, biases, methods, outcome measures, pertinence of the conclusions).
  - Unanswered questions (associations, mechanisms, different outcomes, side effects).
- Secondary research – systematic reviews and meta-analyses.

A Problem Well Defined is a Problem Half Solved

- Foundation and formulation of the hypothesis
  - Hypothesis is founded on the existing knowledge and, whenever possible, on the own preliminary research.
  - Hypothesis is formulated as a short statement, in one sentence.
  - Planned research is actually testing of the hypothesis, ie, its deductive consequences.
- Is the planned research qualitative or quantitative in its nature?
  - Qualitative
    - How? (mechanism of the effect/s)
    - Why? (explanation of association/s)
  - Quantitative
    - How many? (number, quantity)
    - Fractions, ratios, probabilities…
- Advise/review of the experts – before starting the investigation.

Key Phases of Research

- Type of the study (deduction from the hypothesis).
- Definition of the sample (deduction from the target population).
- Experimental and control group/s.
- Methods (main outcome measure, measurements, units).
- Collection of data.
- Data analysis and interpretation.

Formation of the Sample

(selection of members of a population in the planned research)

- Instrumental characteristics of the sample:
  - Representativeness (reflects characteristics of the population).
  - Size (determined by data variability, expected difference between experimental and control group, and the desired power of the study to detect the difference at the given *P*-level.
- Types of samples:
  - Random sample (equal probability).
  - Systematic sample – selection after a given rule (eg, consecutive).
  - Stratified sample – selection after a criterion of difference.
  - Convenient sample – members are at hand (eg, my patients).
  - Dependent samples – samples of the repeated measurements .

Formation of Research Groups

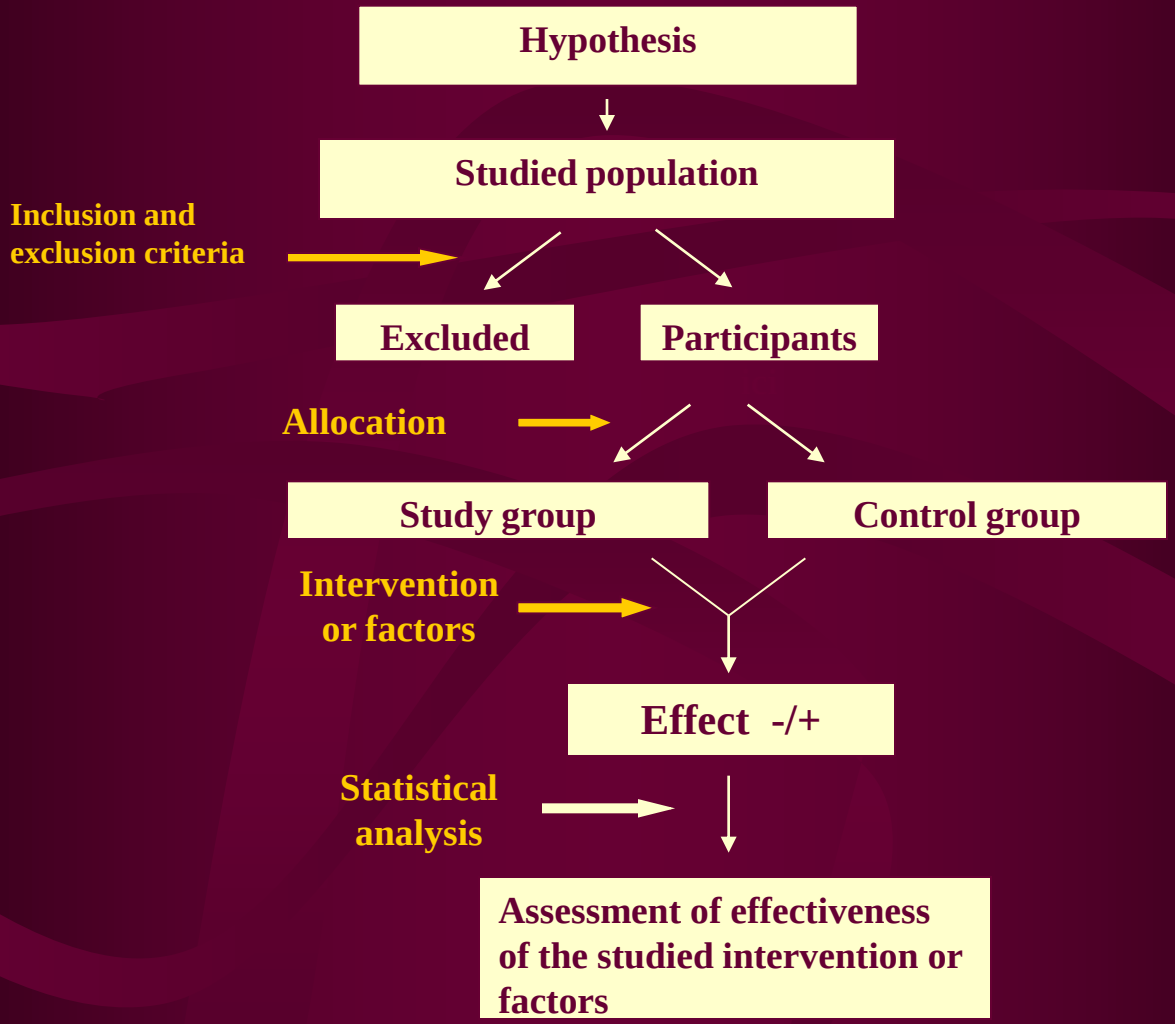
(allocation of members of the sample to groups)

- Experimental and control group should be identical in all aspects except in the feature investigated.
- Formation of the groups (allocation) depends on the design (type) of the study:
  - Allocation based on the feature investigated.
  - Pairing appropriate individuals.
  - **Randomization** – subjects are allocated to groups randomly (do not confuse with random selection of the sample).

Collection of Data

- Methods: a form or measuring instrument.
- Principles:
  - *Validity* – adequate procedures applied.
  - *Reliability* – repeated measurement yield reasonably same data.
  - Consistency – always measured in the same way, with same accuracy (units, decimals).
  - Completeness – all questions answered, measurements done with all samples/groups.
  - Objectivity – different investigators obtain the same results, masking/blinding.
- Archiving, security, confidentiality.
- Preparation for data analysis and interpretation.

Bleueprint of the Research Plan



Variables that Cause Bias – Distort the Results

- *Bias* is an additional effect which makes the observed result different from the real one.
- *Confounding variable* (*confounder*) is a variable associated with the risk factor, but independently of it contributes to the risk of disease.

“Bias”

Biases are possible at all levels of investigation.

Examples:

- “Sampling bias”
- “Allocation bias”
- “Different treatment bias”
- “Follow-up bias”
- “Measurement bias”
- “Detection bias”
- Etc.

Sampling Bias

- Inclusion and exclusion criteria are not clearly defined; the investigator does not obey these criteria strictly enough.
- Too small a sample (it is often difficult to obtain desired sample size – caution).
- Patients and control subjects are recruited from different populations (so they differ in other criteria beside the investigated one).

Always check:

- Are inclusion and exclusion criteria unequivocally defined and applied.
- Is the sample representative of the studied population (and thus allows generalization of the results to that population).
- Is the sample large enough to detect the differences expected (always calculate its minimal size).

Different Treatment Bias

Other factors than the studied one (lifestyle, other drugs) in either the test or control group may modify effects of the treatment that is being tested or affect some subjects' health parameters.

THAT IS WHY WE ALWAYS ALLOCATE THE SUBJECTS RANDOMLY TO THE 2 GROUPS – TO MATHEMATICALLY EQUALY ALLOCATE THE UNKNOWN COUNFOUNDING FACTORS TO THE 2 GROUPS.

Always check:

- Did the subjects know in which group they were allocated?
- Did the researchers know in which group the patients were?
- Did the study design made sure that the subjects did not differ in any other risk factor (parameter) but in the tested one(s)?

Follow-up Bias

"Control", 100 subjects treated with the "old" drug	**"Cases",** 100 subjects treated with the "new" drug
2 died **8 stopped taking "old" and switched to "new" drug** **10 moved away** **10 left the study**	**4 died** **26 stopped taking "new" and switched to "old" drug** **10 moved away** **13 left the study**
70 completed the study **7 cured, 10%**	**47 completed the study** **7 cured, 15%**

Always check:

- Are all "lost" subjects included in analysis of data.
- Is the analysis performed "objectively" (no bias).

Measurement (Detection) Bias

- Imprecise follow up protocols (different follow ups, check-up periods, numbers of performed tests).
- Different procedures or instruments of measurements of outcome measures.
- Study was not done as “blind” (researchers and subjects knew to which group the subjects belong).

Always check:

- Is the probability of diagnosis equal for all subjects? Are all subjects followed equally long time?
- Did the person who does the measurements know to which group individual subjects belong?
- Did the person who analyzes the data know to which group individual subjects belong?

Other Frequent Types of Bias

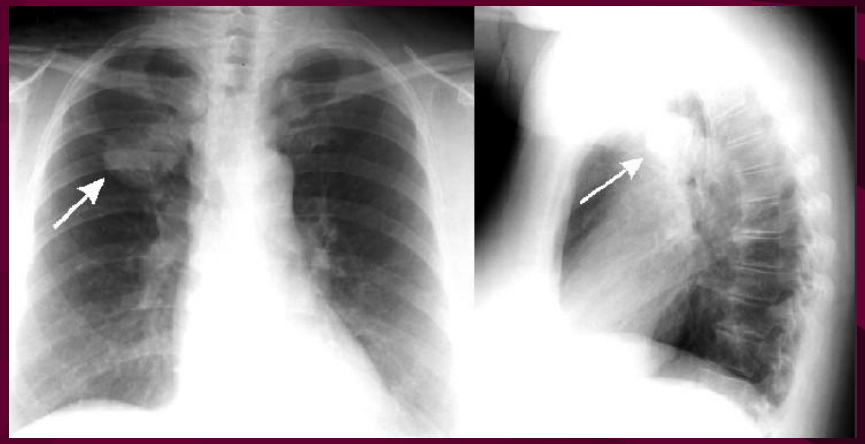
Bias	Description
Response bias	There was a systematic difference between subjects who accepted to participate in the study and those who declined.
Surveillance bias	There was a systematic difference in the frequency and quality of the follow up of exposed and unexposed subjects.
Confounding bias	Bias is the consequence of confounding factors on the measured outcome, but we did not recognize nor controlled for them.
Recall bias	Patients better remember and recall information than controls (healthy subjects).
Data collection bias	Unreliable, incomplete or subjective data collection.
Ascertainment bias	Subjective interpretation of results, especially when the masking/blinding was not applied.
Attrition bias	Subjects lost from the study differ from those who remain in the study.

Confounding Factor

- *Confounding factor is* (too late recognized) association between the disease and that unrecognized risk factor (which affects the disease in a manner that is not controlled for), which causes or aggravates the disease.

If we noticed an association, is that due to an indirect effect of some other, unrecognized factor?

Facotr/parameter analyzed (effect of coffee)



Confounding factor (“smoking with coffee” is what causes the disease)

Control of Confounding Factors

- Study design
  - Increase criteria of inclusion and exclusion.
  - Pairing of subjects/groups in accord to confounding factors.
  - Randomization (adequate!) of subjects to the study groups excludes effects of unknown confounding factors.
  - All nonrandomized trials are sensitive to confounding factors, for example historic controls, age differences; environmental factor differences, additional diseases of therapies).
- Data analysis
  - Stratification of the sample (to study groups) with respect to the confounding factors (careful selection, pairing).
  - Balancing study groups with respect to the confounding factors.
  - Multivariate statistical analysis.

Assessment of the Validity of the Study

- *Internal validity* is determined by the relevance of the main outcome measure for adequate testing of the given hypothesis. (For the assessment of the severity of asthma – is it better to rely on (measure) quality of life or number of hospitalizations?)
- *External validity is determined* by the appropriateness of the main outcome measure ("Operation successful, the patient died."), i.e., how generalizable are the findings of the study (the result of a Croatian study is not valid in Germany).
- *Power of the study* is determined by its potential to detect a difference (association, correlation) that does exist in the population. (Primarily depends on the sample size and quality.)

Summary: Key points of Planning a Study

- Clearly and concretely define hypothesis and then variables.
- Use study design which can answer the question(s) deduced from critical analysis of the hypothesis (as well as adequate statistics).
- Plan statistical analysis before beginning of the study.
- Analyze acquired data and consider them all.
- Avoid mistakes in measurements and analysis of the data.
- Consider clinical relevance of the study.
- Consult experts.