Study design

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Epidemiology

Observational				Experimental		
Descriptive	**Analytic**			**Evaluative**		**Clinical epidemiology**
Cross-sectional *(trasversale)*	Cohort study	Case-control study	Echologic study	Field trial (Intervention on individuals)	Community intervention trial	Controlled (randomized) clinical trial

ECOLOGICAL STUDIES

Ecological studies investigate spatial and/or temporal relation between a determinant and a measure of occurrence,

at population level rather than at individual level (oikos = home).

Ecological studies can deal with Local Health Unit, administrative regions, municipalities.

EXAMPLES of ECOLOGICAL STUDIES

In Naples and Barcelona, epidemics of asthma were recorded when ships full of soy were unloaded.

A TEMPORAL relation exists between air pollutant concentrations and mortality or hospitalization from respiratory diseases.

GEOGRAPHIC RELATION: In England suicide rate is lower in towns having a branch of the Samaritans, an organization offering help to suicidal or equally desperate people.

Experimental *versus* observational studies

EXPERIMENT	PLANNED OBSERVATION
Researchers actively modify the course of events	Researchers just observe the course of events, without attempting to modify it
Only **positive perturbations** can be applied: 1) Preventive interventions, such as adding fluorine to tap water, or iodine to salt 2) Therapeutic measures (early thrombolysis in myocardial infarction, segmental vs total mastectomy) 3) Rehabilitation interventions	Also **etiologic factors** with **deleterious** health effects can be studied: 1) wrong lifestyle (smoking, excessive alcohol intake) 2) environmental situation (Chernobyl)
RANDOMIZATION	**SELF-SELECTION**
Participants are randomly assigned to different treatments ↓ Other risk factors (potential confounders) are balanced among groups	Potential confounders are not eliminated. For instance, it could be hypothesized that: Unknown genes → Craving for smoking Unknown genes → Increased risk of lung cancer

Observational studies

- If a diagnostic procedure (for example TC-scan), which does not modify the course of disease, is added to normal clinical practice

According to epidemiologists → This is an observational study

According to the Italian law (G.U. **31/03/2008** – AIFA - Determinazione 20 marzo 2008) → The study is NO LONGER observational

The importance of randomized clinical trials for the progress of medicine.

In favour ...

1) Hormone replacement therapy in menopause

2) Smoking as a strong risk factor for lung cancer

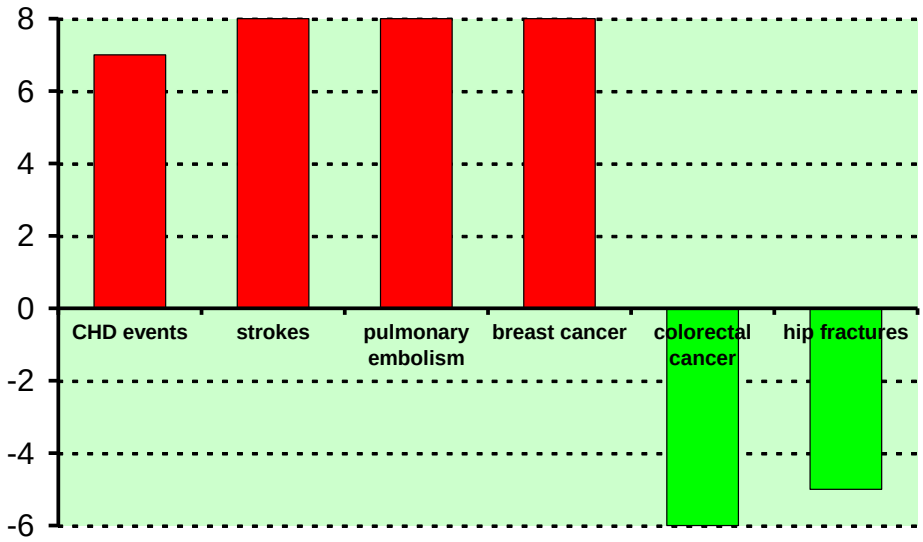
Hormone replacement therapy in menopause

"Context: **Despite decades of accumulated observational evidence**, the balance of risks and benefits for hormone use in healthy postmenopausal women **remains uncertain**.

Objective: To assess the major health benefits and risks of the **most commonly used** combined hormone preparation in the United States."

Rossouw JE, Anderson GL, Prentice RI, et al (2002) Risks and benefits of estrogen plus progestin in healthy postmenopausal women – Principal results from the Women's Health Initiative randomized controlled trial. JAMA 288:321-333 (citato 4192 volte al 31 marzo 2008)

Hormone replacement therapy in menopause



"Absolute excess risks per 10,000 person-years attributable to estrogen plus progestin"

The importance of randomized clinical trials for the progress of medicine.

against …

1) Hormone replacement therapy in menopause

2) Smoking as a strong risk factor for lung cancer

Smoking

"For example, the studies linking smoking with lung cancer were bitterly criticized by 'conventional' researchers who were not willing to accept evidence from studies where the exposure had not been randomized".

Stolley PD (1991) **When genius errs: Fisher**, R.A. and the lung cancer controversy. *Am J Epidemiol* 133:416-25.

Pearce N (2008) Point-counterpoint. Corporate influences on epidemiology. *Int J Epidemiol* 37:46-53

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki Finland, June 64

and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West Rep.South Africa, Oct.96
and the 52nd WMA General Assembly, Edinburgh, Scotland, Oct. 2000

Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002

Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

Available on the web site: http://ohsr.od.nih.gov/guidelines/Helsinki.html

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. **It is the duty of the physician to promote and safeguard the health of the people**. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "**The health of my patient will be my first consideration**," and the International Code of Medical Ethics declares that, **"A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."**

4. **Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects**.
5. In medical research on human subjects, considerations related to **the well-being of the human subject should take precedence over the interests of science and society**.
6. The primary purpose of medical research involving human subjects is **to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease**. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve **risks and burdens**.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights.

Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized.

Special attention is also required for those **who cannot give or refuse consent for themselves**, for those who may be subject to giving **consent under duress**, for those who will not **benefit personally from the research** and for those for whom the research is **combined with care**.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. **No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.**

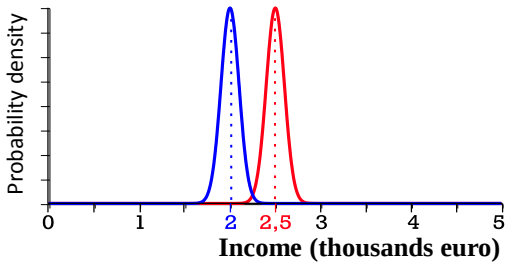
Critical issues are similar in an experiment and in a phone conversation.

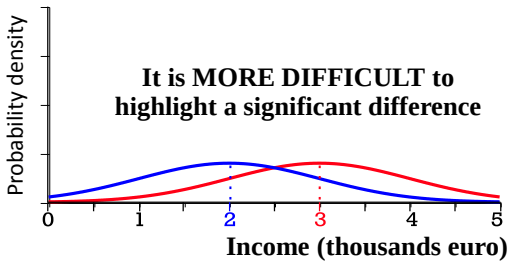
	Phone conversation	Experiment
Background noise	**Buzz and other interference**	**Known and unknown factors affecting the study outcome**
Signal intensity	**Volume of voice**	**Sample size**

Information yielded by an experiment can be increased by:
1) Decreasing background noise ⇒ decreasing random variability
2) Increasing signal intensity ⇒ ⇒ increasing sample size

$$\text{Statistical significance} \approx \frac{\text{Observed difference}}{\text{Random variability}}$$

It is EASIER to highlight a significant difference





Experimental designs can be grouped in three categories:

1) Completely randomized desigs
Parallel group designs

2) Designs reducing background noise:
Randomized block designs
Cross-over designs
Latin squares and Greek-Latin squares

3) Designs which increase the amount of information (signal intensity), as they allow to estimate not only main effects but also interactions:
Factorial designs, Latin squares and Greek-Latin squares
Hierarchic designs (split-plot o split-unit)

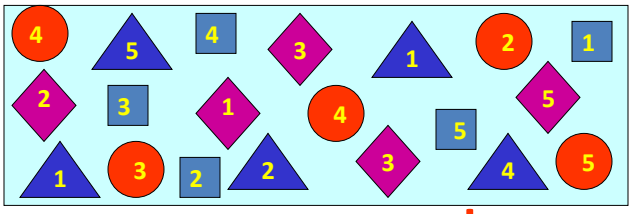
Is it feasible to reduce random variability?

Yes

By restricting study base: studies usually have several inclusion and exclusion criteria

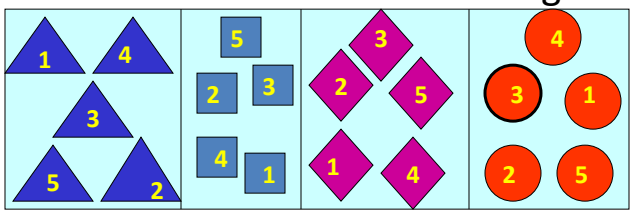
By stratifying or blocking: for instance, a parallel group design is replaced by a cross-over design

Completely randomized study



y = mean + treatment effect + **random variability**

Randomized block design

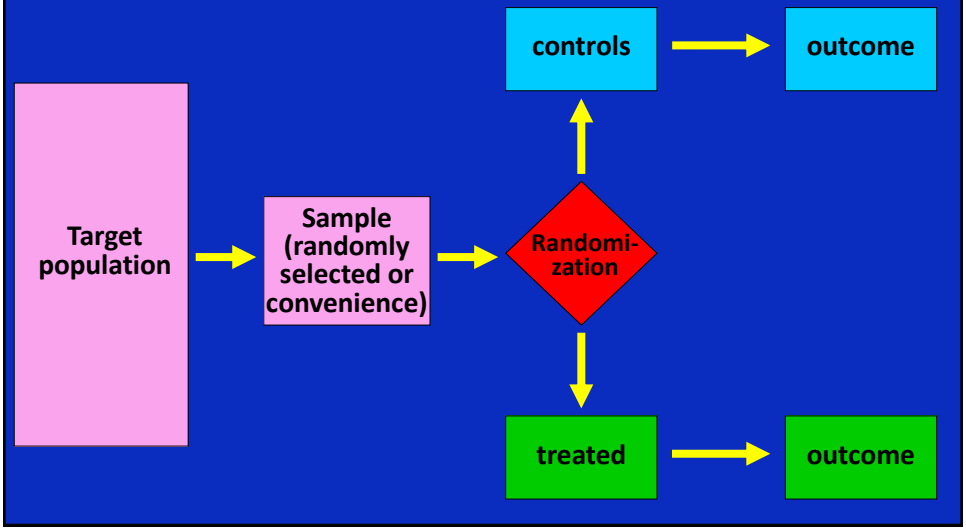


y = mean + block variability + treatment effect + random variability

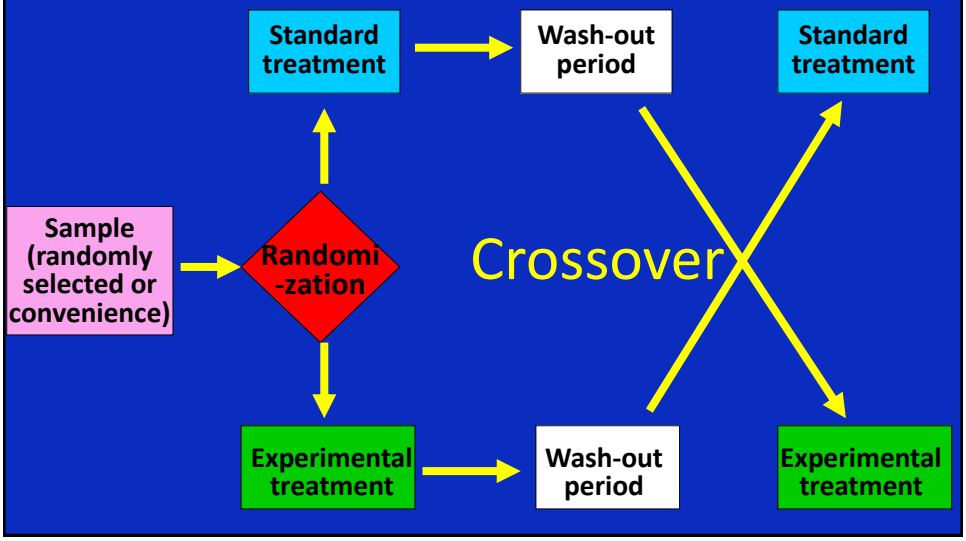
Randomized clinical trials (RTC), also named controlled clinical trials:

1) Parallel-group design
2) Cross-over design
3) Sequential design

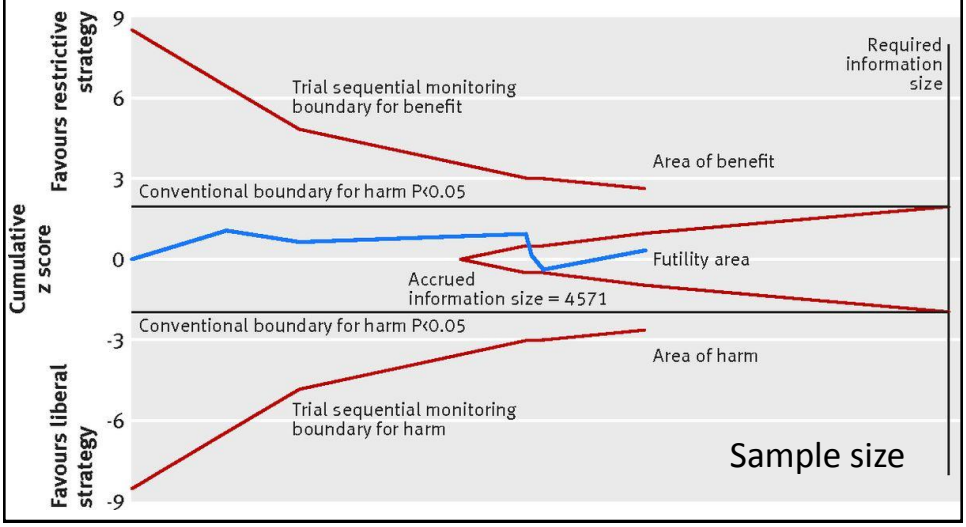
Parallel-group randomized clinical trial:
one group receives only the standard treatment (or placebo), while the other group receives only the experimental treatment.



Crossover randomized clinical trial.
Both groups receive both treatments in sequence.
The sequence of administration is randomized.



Sequential design = the enrolment can be interrupted before completing the planned sample size, if the treatment achieves a predefined efficacy or futility.



Disegni particolarmente utilizzati nelle sperimentazioni cliniche controllate

Disegno a gruppi paralleli = due o più trattamenti vengono valutati in gruppi di soggetti distinti

Disegno incrociato (cross-over) = ogni soggetto riceve in sequenza due o più trattamenti con attribuzione randomizzata

Disegno sequenziale = il reclutamento può essere interrotto anticipatamente se il trattamento raggiunge un'efficacia o un'inefficacia prestabilita

Evaluation of randomized clinical trials (Jadad score)

Jadad score ranges between 0 (very bad study) and 5 (very good study)

+1) The study is **randomized**

+1) The randomization method is **described** and it is **appropriate** (e.g. computer-generated random numbers)

-1) Randomization method is **wrong** (e.g. alternate allocation according to date of birth or day of the week)

+1) The study is **double blind**

+1) The method of blinding is **described** and it is **appropriate** (for instance, placebo cannot be distinguished by drug)

-1) the method of blinding is **wrong** (for instance, placebo is orally administered and the drug intravenously)

+1) Withdrawals and dropouts are described

PRAGMATIC approach: analysis by Intention To Treat (ITT)

All enrolled patients are considered in the final statistical analysis, even if they did not receive the treatment assigned according to the study protocol. Patients are **grouped according to the initial randomized assignment,** even if they switched to the other treatment during the study.

This approach better reflects the **real situation found in everyday practice**.

ETIOLOGIC/EXPLANATORY approach: analysis Per Protocol (PP)

Only patients who received the full treatment according to the study protocol are considered in the final statistical analysis.

This approach is suited to address **cause-effect relationship**.

Enrolled population = all patients enrolled in the study

Full Analysis Set (FAS) = all patients randomized

Intent-to-treat (ITT) = all randomized patients. Even if the patients do not take the assigned treatment, do not receive the correct treatment, or otherwise do not follow the protocol, they will be analyzed according to the treatment group to which they were assigned.

Per Protocol Set (PPS) = all randomized patients, without any validity findings impacting the primary efficacy variable.

Safety Analysis Set (SAF) = all patients who took at least one dose of the study medication and who had at least one post-baseline safety assessment. Subjects will be analyzed as treated.

Pharmacokinetic-Per Protocol Set (PK-PPS) = all patients who took at least one dose of the study medication and who provided at least 1 measurable post-dose plasma sample.

Efficacy evaluation

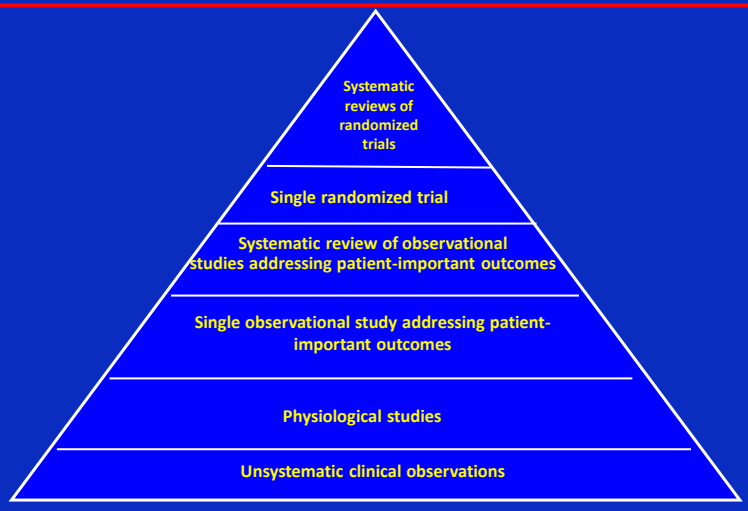
Phase 2 trial: main analysis on both ITT (Intent-To-Treat) Set and PP (Per-Protocol) Set.

Phase 3 trial: primary analysis on ITT (Intent-To-Treat) Set. Secondary analysis on PP (Per-Protocol) Set.

Safety evaluation

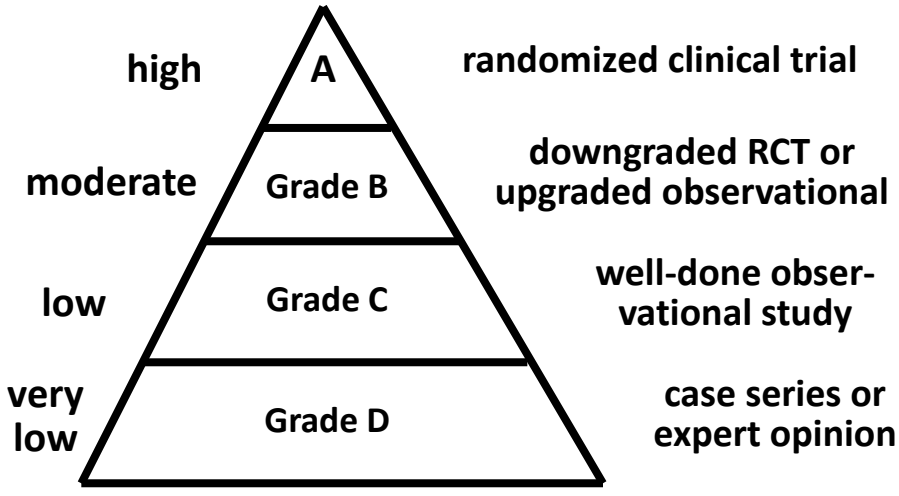
Analysis on Safety Analysis Set

A Hierarchy of Strength of Evidence in Interventional Clinical Trials



Adapted from: Guyatt et al (2000) for the Evidence-Based Medicine Working Group. *JAMA* 284:1290-6

Pyramid of evidence



Four phases of drug development

Phase 1 trials

These are the earliest trials in the life of a new drug or treatment. When laboratory testing shows that a new treatment might help treat cancer, phase 1 trials are done to find out:

- The safe dose range
- The side effects
- How the body copes with the drug
- If the treatment shrinks the cancer

They are usually small trials, recruiting anything up to about 30 patients, although often a lot less. The trial may be open to people with any type of cancer.

The first few patients to take part are given a very small dose of the drug. If all goes well, the next group have a slightly higher dose. The dose is gradually increased with each group. The researchers monitor the effect of the drug, until they find the best dose to give. This is called a *'dose escalation study'*.

http://www.cancerhelp.org.uk/help/default.asp?page=73

Phase 2 trials

Not all treatments tested in a phase 1 trial make it to a phase 2 trial. Phase 2 trials aim to find out:

- If the new treatment works well enough to test in a larger phase 3 trial
- Which types of cancer the treatment works for
- More about side effects and how to manage them
- More about the best dose to use

Although these treatments have been tested in phase 1 trials, you may still have side effects that the doctors don't know about. Drugs can affect people in different ways.

Phase 2 trials are often larger than phase 1. There may be up to 100 or so people taking part. If the results of phase 2 trials show that a new treatment may be as good as existing treatment, or better, it then moves into phase 3.

Phase 3 trials

These trials compare new treatments with the best currently available treatment (the standard treatment). These trials may compare:

- A completely new treatment with the standard treatment
- Different doses or ways of giving a standard treatment
- A new radiotherapy schedule with the standard one

Phase 3 trials usually involve many more patients than phase 1 or 2. This is because differences in success rates may be small. So, the trial needs many patients to be able to show the difference.

For example, 6 out of 100 more people (6%) get a remission with a new treatment compared to standard treatment. If there were 50 people in the new treatment group and 50 people in the standard treatment group, there may be 3 more people in remission in the new treatment group. The 2 groups would not look that different. But if the researchers gave each treatment to 5,000 people, there could be 300 more remissions in the new treatment group.

Sometimes phase 3 trials involve thousands of patients in many different hospitals and even different countries.

Phase 4 trials

Phase 4 trials are done after a drug has been shown to work and has been granted a license. These trials look at drugs that are already available for doctors to prescribe, rather than new drugs that are still being developed.

The main reasons pharmaceutical companies run phase 4 trials are to find out:

- More about the side effects and safety of the drug
- What the long term risks and benefits are
- How well the drug works when it's used more widely than in clinical trials