Chapter 11 **Clinical Trials**

Definition

Experiments that are done in clinical research. These studies are designed so that patients are exposed to the risk factor intentionally.

Importance

To establish a causative relationship between exposure to a certain risk factor and an outcome. Also, to prove the safety and efficacy of interventions.

Types

According to randomization: randomized vs. non-randomized studies

According to the control group: single-arm vs. controlled studies

According to phase: phase I, phase II, phase III, and phase IV

According to design: pragmatic vs. explanatory

Example

Ensrud, K. E., Stock, J. L., Barrett-Connor, E., Grady, D., Mosca, L., Khaw, K., et al. (2008). Effects of raloxifene on fracture risk in postmenopausal women: The raloxifene use for the heart trial. Journal of Bone and Mineral Research, 23(1), 112-120.

This research studied the effect of raloxifene on fracture risk in postmenopausal women and found that the women who took raloxifene over the same five-year period as the women who did not reduce their risk of clinical vertebrate fracture.

Advantage

→ Control over risk assignment

Unlike the observational study designs, clinical trials enable the investigators to determine which participants are allocated to each treatment. This allows investigators to employ random allocation procedures in order to obtain nearly equal study groups.

→ Strong evidence; RCTs are the gold standard studies

Owing to their high internal validity, RCTs are regarded as gold-standard clinical research studies.

Disadvantages

→ Expensive evaluation of risk factors

A disadvantage of the clinical trials is that it is more expensive. In addition to the basic costs of running a research study, investigators of clinical trials have to pay for the costs of the treatment, assessments, and laboratory tests, follow up, and the financial compensation of the patients (if available). That's why several clinical trials nowadays are funded by a third party as governmental agencies, professional associations, or pharmaceutical industries.

→ Experimentation sometimes may be difficult, inappropriate or unethical

Despite its high internal validity, clinical trials are not possible for every research question. Experimentation can be restricted by natural, ethical, social, or religious rules. For example, to assess the risk of lung cancer among smokers, you cannot get two groups of healthy individuals and assign a group to smoke while the other group to no smoking. Although this design will be helpful to establish strong evidence on the relationship between the risk factor and the outcome, it is not ethical, not acceptable, and invalid design.

Randomized trials vs. quasi-experimental trials

Randomized trials	A comparative clinical trial where patients are allocated to the study groups in a random manner (see later, the random allocation and allocation methods).
Quasi-experimental trials	A comparative clinical trial where patients are NOT allocated to the study groups in a random manner but using a quasi-random method. (see later, the quasi-random allocation methods).

Single-arm vs. controlled trials

Single-arm study	A study includes one experimental group only
Controlled study	A study that includes more than one group (experimental vs. control).

Phases of clinical trials

	Control	Sample	Aim
Phase 1	No	10-30	▪ Investigate Safety ▪ Explore efficacy
Phase 2	Yes	100-200	▪ Investigate efficacy compared to placebo (null) ▪ Recording Side effects
Phase 3	Yes	1000-2000	▪ Evaluate efficacy against standard drug ▪ Controlling side effects
Phase 4	----	-----	▪ Post marketing evaluation

Pragmatic vs. explanatory trials

Pragmatic clinical trials	They aim to assess the safety and efficacy of an intervention in order to give a picture of the performance of this drug in clinical practice. Most of the clinical trials are pragmatic clinical trials.
Explanatory clinical trials	These trials are conducted for explanatory purpose with the aim to understand the mechanism of action of the intervention rather than estimating the efficacy of an intervention in the study population.

Random Allocation

In a randomized controlled trial (RCT), patients are randomized to the treatment groups. The random allocation is used to grantee the equal distribution of subjects to the treatment groups. While in the non-randomized controlled trial (also known as a quasi-experimental study), patients are allocated to treatment groups in a non-random manner as patient preference or physician judgment.

Proper methods of patient allocation, "True randomization."

→ Computer-generated random sequence
→ The random sequence generated by a table of randomization
→ The sequence generated by block randomization
→ The sequence generated by the minimization procedure

Quasi-random methods of patient allocation "high risk of bias."

→ Patients are allocated to the study groups according to their preference
→ Patients are allocated to the study groups according to physician opinion
→ Patients are allocated to the study groups according to the day of attendance
→ Patients are allocated to the study groups according to the study hospital

Allocation concealment

A technique used to prevent selection bias by concealing the allocation sequence from those assigning participants to intervention groups, until the moment of assignment. Allocation concealment prevents researchers from, influencing, which participants are assigned to a given intervention group.

Blinding

A condition when patients are NOT aware of the treatment group they were allocated to. In a blinded study, investigators use a placebo which should be identical to the new drug in terms of the route of administration, shape, color.

→ In single-blinded studies, patients are blinded to the study of drugs.

→ In double-blinded studies, patients and investigators (who give treatment/who assess outcomes) are blinded to the study drugs. But the data safety and monitoring board (DSMB) of the clinical trial are aware of the group medications.

→ In triple-blinded studies, patients, investigators (who give treatment/who assess outcomes) and investigators (who are in the DSMB) are blinded to the study drugs.

→ Assessor blinded trials are used when the outcome assessment is done by masked investigators. It is also recommended when the intervention itself cannot be masked as in most surgical operations.

Placebo

Inert material that is administrated by the control group in blinded studies to overcome and eliminate the psychological effect. In surgeries, blinding is not possible in all studies; most surgery interventions cannot be blinded.

Special forms of placebo

→ Placebo in the double-dummy design

If one of the treatments is parenteral and the other is capsules, the study is called (double-dummy design); we use two placebos. One of the groups will receive (true parenteral drug + Placebo of capsule drug), and the other group will receive (Placebo of parenteral drug + true capsule drug).

→ Sham intervention

Sham surgery is a faked surgical operation that skips the main therapeutic step in the procedure. Please, note that sham intervention is not possible in all surgical situations. The use of sham surgery is ethically controversial in some surgeries where control patients might be exposed to operative risks.

→ Vehicle control

Vehicle control is usually used in dermatology trials. It is used when the intervention is a topical cream, saline, or mineral oil, which is used as a vehicle for a solution of the experimental drug. In this case, the vehicle without the active drug can be applied as a control.

Intention to treat analysis vs. per-protocol analysis

Intention to treat analysis (ITT analysis)	All patients who were randomized to the study groups are included in the final analysis irrespective of any withdrawals or discontinuations. This type of analysis attempt to overcome the attrition bias (see later, the chapter of errors and bias).
Per protocol analysis	In this type of analysis includes patients who have completed the study until the end and have completely adhered to the study protocol. In this type of analysis, patients who discontinue the study drug, withdraw from the trial, or missed in the follow up are omitted from the final analysis.

How to obtain data of the missing individuals for the purpose of ITT

- → If you are running a cancer clinical trial and the primary outcome measure is mortality, search for the patient name in the death certificates of your city.
- → If your institution has a national connected healthcare system, you can attempt to track the patient to their new hospital and attempt to contact them
- → Apply the Last Observation Carried Forward analysis (LOCF); in this analysis, we consider the last observation as the last endpoint assessment of this patient. This should be used cautiously, especially with progressive chronic diseases.
- → Use multiple imputations to expect the final outcome of missing patients. Multiple imputations is a statistical method that involves multiple regression models and adding random numbers to estimate the expected final outcome of missing patients.
- → Assume the worst-case scenario and analyze the study data assuming that the improvement of all missing cases was the same as the worst case in the trial.
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