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Introductory Chapter: Introduction to Clinical Trials

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1. Clinical research

Clinical research may be defined as the research in which an investigator directly deals with human subjects or on material of human origin. It includes mechanisms of human disease, therapeutic interventions, development of new technologies, epidemiologic and behavioral studies, and outcomes and health services research. Types of clinical research may be classified as **retrospective/prospective** that refers to the time of data collection. In prospective studies, the data are collected after the objectives are set. On the other hand, in retrospective studies, the data are collected before the objectives are set. Another classification is **cohort/cross-sectional studies**. In cohort studies, the subjects are followed over time. On the other hand, in cross-sectional study, the subjects are examined at one point of time, e.g., prevalence of a disease [1].

1.1. Types of clinical research

1. **Case reports**
2. **Observational studies:** Data are collected for a set of patients without randomization.
3. **Clinical trial:** A prospective study evaluating the effect and value of intervention(s) in human subjects under pre-specified settings.

Clinical trials are considered the heart of all medical advances and the “Gold Standard” of clinical research. They are the most definitive tool for evaluation of the applicability of clinical research with the potential to improve the quality of health care and control costs. In other words, they bridge the gap between basic science and improved human health, as they investigate new ways to prevent, detect, or treat diseases or to improve the quality of life [2].

Single center/multi-center trials: Multicenter trials enhance generalizability of the results. In multicenter studies, the use of a central lab makes data handling easier because there is only one set of reference ranges.

2. Non-comparative/comparative design

Noncomparative design is usually used to assess a treatment's safety and tolerability and also in some therapeutic confirmatory studies if long-term safety data are required.

Comparative design is used when comparing treatments: controlled clinical trials groups are studied and contrasts made between groups. Different types of controls include: Historical/Concurrent: Concurrent controls include placebo and active control (standard therapy or use another new therapy) or "sham" treatment control, e.g., sham surgery or acupuncture. The two most commonly used designs are [3]:

1. **Cross-over:** Each subject receives one treatment and then (after a wash out period) crosses over to receive the other treatment. The individual subject variability is minimized, hence the need for less number of subjects. This design should include an adequate wash out period to ensure baseline status before giving the second treatment, the diseases in question must be stable; otherwise, it will not be considered ethical.
2. **Parallel-group:** Each subject receives only one of the study treatments for a predetermined period, individual subject variability must be taken into account, hence the need for a larger number of subjects [4].

2.1. Selection criteria: Inclusion and exclusion criteria

Selection criteria define which subjects to include and which to exclude. The intention is to identify the appropriate participants in a tightly defined population, based on factors as age, gender, the type and stage of the disease, previous treatment history, and other medical conditions. Examples of exclusion criteria include concomitant therapy that may affect the course of the disease or may lead to drug interactions, women of child bearing potential, pregnant women, nursing mothers, and subjects who cannot comply with protocol (alcoholics or drug users).

3. Research bias

Selection/allocation bias occurs when researcher knows which with the possibility of being tempted to give the treatment under investigation either to subjects who had failed on previous therapy or to those who they think will do well. To eliminate selection bias, studies are conducted on a randomized fashion.

Observer bias is when the investigator knows which treatment a study subject is taking with the possibility that subjects taking a new treatment may be over-scored. To eliminate observer bias, studies are conducted blind [5].

4. Randomization and blinding

Randomization: A process based on allocation of subjects to treatment groups by chance, aiming at removing the potential bias in treatment assignment whether conscious or subconscious. This will greatly enhance the validity of the trial.

Blinding is when the investigator and/or the study subject do not know which subject is taking which treatment. The investigator, the participant, and sometimes even the evaluator are all kept unaware (blinded) of the outcomes of the trial.

1. Single-blinded study: either the investigator or the subject tested is blinded to the intervention allocation.
2. Double-blinded study: both the investigator and the subject tested are unaware about of the intervention allocation.
3. Triple-blinded study: even the evaluator is also not aware of the process.

In emergencies and life threatening situations for participants, unblinding can be done.

Standard operating procedures (SOPs) ensure that the specific tasks in the trial are carried out in a consistent manner. Topics for SOPs for investigators:

1. Ethics: initial and continuing review by ethics committees, informed consent, consent forms, and information sheets
2. Study setup: review of investigator brochures, protocols, protocol amendments, CRFs, and agreements (e.g., responsibility, financial, confidential, and insurance/indemnity agreement)

5. Basic documents and materials of clinical trials

5.1. Protocol

The protocol is a written agreement between investigators, participants, and the scientific community. The protocol must inform (study staff) about how the study treatments will be assigned, how the subjects are to be treated, and what assessments are to be performed. It is the reference comprehensive operational manual that describes **who** is conducting the trial, **who** is sponsoring it, **where** is it to be conducted, and **on whom** it will be conducted, **what** is being tested?, **why** is this research needed, **what** are the risks?, **what** are the procedures?,

how will data be collected, **how many** patients you will need?, and **what** is to be done in any eventuality? It specifies the standard operation procedure (SOP). It describes the background, objective(s), design, methodology, statistical considerations, and organization of the trial. It represents a guideline for the conduct, quality control of a clinical trial, and guidelines to the monitoring groups. It is considered as a legal document for regulatory bodies and may be used to procure funding. It should contain the right amount of detail necessary for the reader of each section to be able to understand exactly what is required to conduct the study [5].

6. Specific objectives

6.1. Primary objective

It defines one question the investigators are most interested in answering and is capable of being adequately answered. It should define the **primary endpoint**, which is a defined measurement or assessment. If possible, end-points need to be objective measurements rather than subjective outcomes. However, many diseases necessitate measurements of subjective symptoms, e.g., pain, discomfort, irritation, etc. Ideally, a clinical trial has just one end point, and this is the primary end point. Common failing is too many end points. The best designed trials keep it simple as this makes a clear answer more likely and easier to achieve.

6.2. Secondary objectives

Secondary objectives should be based on subgroup hypotheses that are respectively defined and based on reasonable expectations and should not distract from the primary objective.

Methods include hypothesis, patient population, inclusion criteria, exclusion criteria, and trial design.

Protocol amendment: A written description of a change(s) to or formal clarification of a protocol. Must be approved by IRB prior to implementation may be partial or complete.

7. Phases of clinical trials

Phase 0: Preclinical animal studies.

Phase I: First-time test of intervention in a small group of people (20–80) to evaluate safety, determine appropriate dosage, and identify side effects. Follows successful pharmacological and toxicological studies in animals start with 1/5th or 1/10th maximum tolerated dose in the most sensitive animal species.

Phase II: Intervention given to a larger group (100–300) to evaluate effectiveness and safety. First administered to patients. Phase IIa (early phase II) potential benefits and side effects

establish dose range for phase IIb. Phase IIb (late phase II) establishes efficacy in specific disease. Compare efficacy and side effects with other drugs for same conditions.

Phase III: Randomized, controlled, double-blinded. A sufficient sample size for statistical evaluation of efficacy and safety. Intervention given to large groups (1000–3000) to confirm effectiveness, monitor side effects, compare to other treatments, and collect information that will allow it to be used safely. Successful phase III trial leads to request permission to market new drug.

Phase IV: After drug obtained marketing license, post marketing studies determine additional information including risks, benefits, and optimal use of an intervention [6].

8. Ethical considerations

Every possible precaution should be taken to ensure the safety of research participants including uncoerced and truly informed consent ensuring that the research staff conducts the study honestly and thoroughly.

8.1. Evolution of research ethics guidelines

1. Nuremburg “Doctor’s Trial”: 1946 in response to Nazi atrocities of using concentration camp prisoners for human experiments.
2. Nuremburg: 1947
3. UN Universal Declaration of Human Rights: 1948
4. Declaration of Helsinki: 1964
5. Belmont Report: 1979
6. International Ethical Guidelines for Biomedical Research (CIOMS): 1993 (Updated 2002)

The Declaration of Helsinki: A set of principles defining the standards that should apply to biomedical research worldwide. It remains the cornerstone ethical reference for global medical research. It is a statement of clinical principles to provide guidance to physicians and other participants in medical research involving human participants.

Informed consent: It is a process by which the participant voluntarily confirms the willingness to participate in a particular clinical research trial, after having been informed of all aspects of the trial that are relevant to the subject’s decision to participate. It consists of two parts: a written information describing the clinical trial and a form which the subject signs to document that he/she has given consent to take part in the study and obtained from the participants in the study population after explaining them fully about the purpose, duration, required procedures, expectations, risks and benefits, adverse effects of the trial if any, participants’ rights and compensation and/or treatment available to subject in the event of trial-related injury. It is a process not just signing a form communication document not having a

legal binding on the patients. The consent should state that the subject's participation is voluntary and that he/she may refuse to participate or withdraw from the trial at any time [5, 7].

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