Design, Performance, and Monitoring of Clinical Trials

Mahdieh Hadavandkhani, Najmeh Foroughi-Heravani, Parisa Goodarzi, Moloud Payab, Hamid Reza Aghayan, Sepideh Alavi-Moghadam, Mehrnoosh Yarahmadi, Motahareh Sheikh-Hosseini, and Bagher Larijani

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11.1 What You Will Learn in This Chapter?

You will first understand the concept and definition of the clinical trials. Then, the importance and necessity of its implementation will be described. At the next step, this chapter tries to clarify the importance of phases of clinical trials (phases III and IV). In this part, you should pay attention to the type of biomedical studies including pharmaceutical, cell, gene, and tissue investigations which are mentioned. You will learn about fundamentals of clinical trials after their clarification. According to international standards and guidelines, inclusion and exclusion criteria of eligible participants will be demonstrated, and intervention includes concepts like diagnostic intervention. Furthermore, a snapshot of clinical trial monitoring, risk assessment, and its various types will be exhibited with a brief focus on registration and obstacles.

11.2 What Are Clinical Trials?

Investigational new drugs (INDs) can be available to the public after a hardworking stepwise study and proof of safety and efficacy. As a result, INDs should be evaluated in a scientific investigational setting. Accordingly, clinical trial is one of the important gold standard tests. It has a protocol for performing trials which illustrate several aspects of studies such as sex, age, etc. In the end, INDs (novel drugs and treatments) will be available to patients after passing safety and efficacy stages. Logically, all of these stages are under supervision of international, national, and regional authorized bodies (e.g., FDA, KFDA,). In summary, the purpose of conducting clinical trials is to improve medical and behavioral intervention [1, 2].

11.3 Rationale and Importance

Clinical trials play an important role in discovering novel treatments. They help scientists to identify and diagnose various diseases. On the other hand, clinical trials can provide valuable infrastructure for treatment of several diseases and decreasing the complications. In other words, factual and documented results which are extracted from clinical trials are valuable in patient care. Finally, using clinical trials, investigators and doctors can assess the risks of new drugs against their benefits and then decide to whether prescribe it or not [3].

11.4 Phases of Clinical Trial

In a clinical point of view, a novel treatment needs to pass four phases of clinical trials (Fig. 11.1).

11.4.1 Phase I

The main aim of this phase is to illustrate the best dose and method with an acceptable level of risk (safety phase). In this phase, researchers evaluate probable risks and side

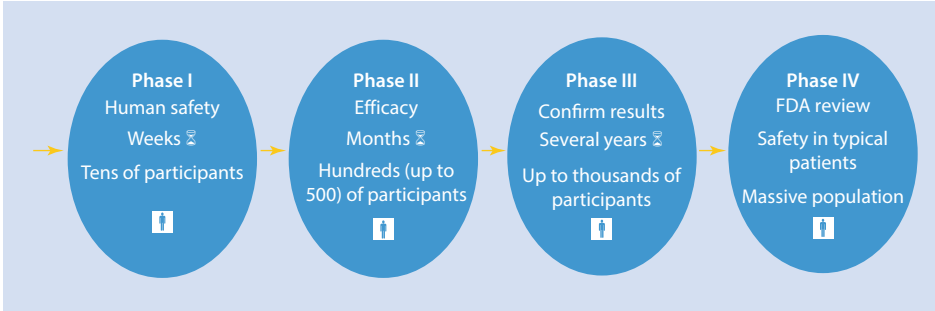

Fig. 11.1 Phases of clinical trial. Phase I: Takes weeks, aim to IND human safety, tens of participants (up to 50). Phase II: Takes months, efficacy examination, hundreds of participants (up to 500). Phase III: Takes several years, result confirmation, thousands of participants. Phase IV: Long term, health authority surveillance and observation, massive population

effects of the INDs. Enrolling participants in this phase depends on the characteristics of the studies, and the maximum number is up to 50 (e.g., in some cases such as cell-based and gene therapies, the total number of participants is around 10 people). Physicians use a few dose for a few patients at the early step of phase I. After that, the dose of INDs increases along with the number of subjects gradually. This process continues until the side effects are very intense or the desired effect is seen. Finally, phase I steps at this stage. This drug may help patients (efficacy), but the purpose of this phase is to check the human safety of the drug. If the drug or approach is sufficiently human safe, it can be tested in a clinical trial of phase II [4].

11.4.2 Phase II

In phase II, the main focus is on evaluating efficacy. There are significant differences between this phase and phase I which include the following: (1) phase II is longer and it takes months. (2) The number of participants of phase II is more than phase I. Of course, the number of patients depends on the type of biomedical study (e.g., pharmaceutical or cell-based study). At this stage, the new developed products are compared with standard of care ones. Then, it will enter phase III if the efficacy and safety are acceptable [5].

11.4.3 Phase III

In phase III, the side effects and efficacy of INDs are assessed. In this phase, lots of drugs and methods which were considered successful do not pass due to the detrimental side effects and lack of therapeutic effects. In phase III, clinical trial investigators compare INDs with the standard of care to determine which ones work better [6].

11.4.3.1 Basic Principles

This phase has several conditions and includes the following:

1. Participants in study are alike, and there is no difference between them. They should be adjusted based on age, gender, etc.
2. The research is randomized and patients are chosen incidentally.
3. The level of efficacy is associated with either single- or double-blind process.
4. Every patient should be observed precisely [7].

11.4.3.2 Features of the Participants in Trial Groups

Phase III has 2 significant features:

- The large amount of participants (up to thousands)
- Control group such as scheme group

For election of scheme (control group), some components including objective, amount of participants, and steps multiplicity play important roles. The essential purpose of phase III is providing new and better approach for prevention, management, and treatment of diseases. The number of patients included in phase III varies based on the type of study. In pharmaceutical studies, more than 1000 patients can be enrolled, whereas in cell-, gene-, and tissue-based studies, this number significantly drops [8].

11.4.3.3 Premature Termination

The study terminates before the deadline under two conditions:

1. If the adverse events of them in one or more groups are too intense
2. If one or more groups culminate in much better results [9].

11.4.4 Phase IV

After phase III, new drugs and treatments enter the market. If they have unknown adverse effects, they will be excluded. Phase IV trials evaluate the safety of INDs in typical patients approved by the health authorities. The drug is tested in large amount of patients in long-term surveillance, which allows finding diverse effects in large groups of people. Moreover, it is helpful for doctors to know more information about the IND's works [3].

11.5 Statistics in Clinical Trial Design

Clinical trial design needs careful planning with statistical methods including the following:

11.5.1 Alternative Hypothesis

Alternative hypothesis claims that researchers would like to make it at the end of the trials. It is stated to evidence something (e.g., the IND is more effective than the conventional

treatments), so a complement (called the null hypothesis) is assumed true and then they seek contraindicatory evidence. If the contraindicatory evidence is observed, the desired claim (the alternative hypothesis) will be proved, and the compliment will be disproved [10].

11.5.2 Null Hypothesis

This claim is enounced when there is no connection between groups. Null hypothesis and alternative hypothesis are opposites (pay attention to "alternative hypothesis") [10, 11].

11.5.3 Intent to Treat (ITT)

It is useful for running a randomized clinical trial (RCT) and analyzing data. The plan implies careless of adherence or treatment received. It can afford unbiased comparisons among the trial groups [10, 12].

11.5.4 Type I Error (α)

It is known as the likelihood of incorrect rejection of the true null hypothesis or false-positive conclusion. For example, INDs should cure a disease, but substantially it does not [10].

11.5.5 Type II Error (β)

It is defined as the acceptance of false null hypothesis or false-negative finding. For example, in ascendancy trials, it means the likelihood of failing to recognize a treatment effect when indeed a true treatment effect exists [10].

11.6 Eligibility Criteria and Intervention

11.6.1 Inclusion and Exclusion Criteria

The inclusion and exclusion criteria can direct the enrolment of participants based on relevant standards. These criteria contain several items such as gender, age, race, ethical principles, type of disease, medical history, mental status, and other medical situations. They play an important role in assuring patient safety during trials, justification of subjects, decrease cost, and side effects of new treatments [2].

11.6.2 Intervention

The intervention in clinical trials aims to evaluate the safety and efficacy of INDs. Accordingly, there are several categories of interventions including the following [3, 13]:

11.6.2.1 Treatment

Examination of INDs for various therapeutic purposes

11.6.2.2 Prevention

Investigation of new methods for improving lapse or relapse of diseases (e.g., vaccines, lifestyle change, etc.)

11.6.2.3 Diagnostics

Discovering higher methods for diagnosing type and stage of diseases

11.6.2.4 Supportive Care

Exploration of high quality and comfortable lifestyle for subjects with a long-term chronic condition

11.6.2.5 Health Services Research

Enhancing the delivery, process, management, organization, or financing of healthcare system

11.6.2.6 Basic Science

Focusing on the function of interventions

11.7 Clinical Trial Monitoring

Although there are several standards and regulations for harmonizing the framework of clinical trials, the performance of the experiments may be different according to the specific circumstances of each study. Monitoring objectives focus on the safety and welfare of the participants and also the protection of patients' rights at all stages of testing, collecting, and analyzing data. Furthermore, monitoring has several types such as on-site, oversight, and off-site methods [14].

11.7.1 Risk Assessment

Risk assessment is made of the following several steps [15]:

11.7.1.1 Risk Identification

The first step for beginning the risk assessment is answer to the questions educed from ICH Q9 including the following:

- "What might go wrong?"
- "What is the probability it will go wrong?"
- "What are the consequences (severity)?"

11.7.1.2 Risk Analysis

It includes examination of the likelihoods, causes, and results of risk occurrence.

11.7.1.3 Risk Evaluation

For evaluation, the risks of clinical trial researchers should answer ICH Q9 questions as follows:

- "What is the acceptable level of risk for the clinical study?"
- "Is the risk above an acceptable level?"
- "What can be done to reduce or eliminate risks?"
- "Are new risks introduced as a result of the identified risks being controlled?" [16, 17].

11.7.2 Clinical Trials Registration

The first clinical trials registration was started in 1994 in the WHO's International Clinical Trials Registry Platform (ICTRP) databases. After that, it was improved between 2004 and 2015 noticeably. Registration is essential for clearness of information and enhancing the scientific and ethical profits. Nowadays, several aspects of clinical trials can be found in registration databases (e.g., "primary registry and trial identifying number, date of registration in primary registry, secondary identifying numbers, source(s) of monetary or material support, primary sponsor, secondary sponsor(s), contact for public questions, contact for scientific queries, public title, scientific title, countries of recruitment, health condition(s) or problem(s) studied, intervention(s), key inclusion and exclusion criteria, study type, date of first enrolment, recruitment status, primary outcome(s), and key secondary outcomes" are the most important data based on WHO Trial Registration Data Set (TRDS)). Additionally, target sample size, status of clinical trials, and conditions of enrolment are other features that should be registered by investigators [18, 19].

11.8 Challenges and Future Direction

11.8.1 Eligible Patient Enrollment

One of the significant barriers is about enrolling the patients. The process of choosing patients with the acceptable conditions to engage in the researches is very difficult, and institutions or universities play an important role in facilitating this process. Afterwards, more barriers will arise. Since some of appropriate participants are reluctant to take part in the study, they will be excluded during the trial [20].

11.8.2 During the Trials

11.8.2.1 Cost of Trials

The provision of welfare and medical facilities for patients, the cost of providing tools, equipment, and staff salaries may be more than the budget for the study purposes [21].

11.8.2.2 Long Time Span

Accordingly, long time span (an average of 5–7 years) poses the studies to financial and safety management. During the trials, participants must be observed; hence, long-term observation needs a lot of staff and equipment [22–24].

Take-Home Messages

- Clinical trials are the gold standard tests for evaluating INDs.
- The goals of phases I and II are examination of human safety and efficacy.
- In phase III clinical trials, investigators compare INDs with the standard of care.
- Phase IV trials evaluate the safety of INDs in typical patients approved by the health authorities.
- Careful planning with statistical methods helps the researchers to decrease the errors.
- The types of intervention include treatment, prevention, diagnostics, supportive care, health service research, and basic science.
- Clinical trial should be done in a standard framework so it needs monitoring, risk assessment, and registration.
- Clinical trials like other kinds of researches have some barriers and challenges. Note that if the side effects are irreparable, it must be terminated.

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Further Reading

Online Resources

FDA: https://www.fda.gov
The ICH-GCP guideline: https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice

Books

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