SHORT COMMUNICATION

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Clinical Trial: important phases

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Abstract

Clinical trials are an advance level of research designs used in biomedical research. Every year several clinical trials are conducted across the world. Presently, developed countries are moving faster than before in planning and registering high quality clinical research. Increase in research funds, advancement in biotechnology and easily available research participants are attraction for many clinicians for their involvement in clinical research. This paper aimed to provide brief information on important phases of the clinical trials.

Key words

Clinical trial, developing countries, drug, phases, randomization

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Background

Every year several clinical trials are conducted for various reasons such as development of a new medicine, therapeutic, and preventive procedure [1]. Presently, 201,149 clinical trials are registered in all of the 50 states of USA and 190 countries in the Clinical Trials registry of the National Institute of Health (NIH). Registration of new studies is increasing rapidly. Developing nations are moving faster than before in conducting clinical trials. Now a day, participants in clinical trials are also being recruited more from developing countries. Among the total participants recruited in all clinical trials, 51% represent Asian countries, 43% USA and remaining 6% from USA and rest of the world together [2].

The developed nations are more experienced and equipped with the research knowledge, infrastructure, and advancement in research and medicine. Many universities and research organizations based in developed countries are collaborating with academic and research organizations in developing countries for clinical trials. This collaboration brings opportunity to many medical professionals to participate in clinical trials. Thus interest in clinical research is growing immensely among the medical professionals.

The medical schools are promoting research in their medical graduates by adding research components in the curriculum and giving them opportunity to present and publish. However, such efforts are limited. The knowledge and information among medical community in developing nations is limited [3-8]. Medical professionals in low and middle income countries (LAMI) also have limited opportunities to access freely available research material from various sources [9-10].

Presently many developed nations are recruiting research participants in developing nations. It may also be helpful in generalizing the findings of the research; so far the population from LAMI nations has been underrepresented in medical research [11]. Many clinical trials are planned in developed nations but carried out globally. This approach is helpful because the population of LAMI nations is underrepresented in research [11]. Now a day, India is an attractive site for many clinical trials because of its diverse population, cheap infrastructure, availability of well qualified medical professionals and patients with countless diseases [12]. It is recognized that the population in such nations is vulnerable due to many factors such as poor literacy rate, poverty, lack of research knowledge, infrastructure, trained staff and well equipped healthcare systems [13]. It is projected majority of clinical trials would be done in the future to more hospitable countries to mitigate the economic damage [14]. Thus it is very important to increase knowledge and awareness level on clinical research methods among medical professionals in LAMI nations.

Method

Information from text books on clinical trial, peer reviewed articles, websites, guidelines set by NIH, WHO, and peer reviewed monographs & presentations are referred to describe the phases of the clinical trial.

Result

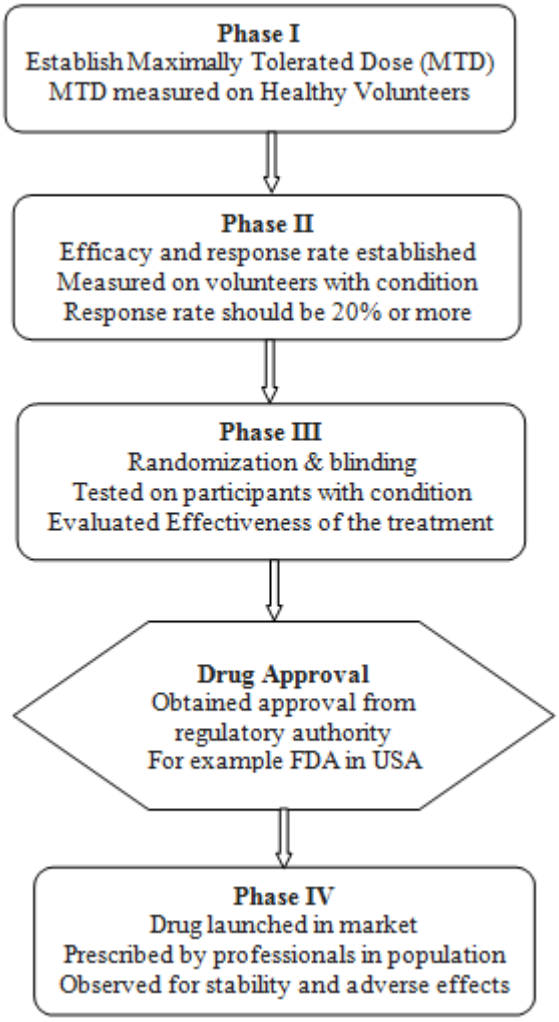

Figure 1- important phases of the clinical trial

Clinical trial: Clinical trial is an advance level of research design which studies new methods to prevent, rehabilitate, diagnose and treat disease and condition. Friedman *et al*. (2010) defines a clinical trial as a prospective study comprising the effect and value of intervention(s) against a control in human beings [15]. Phase wise process of clinical trial is discussed next (Figure 1).

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Discussion

Phases of Clinical Trials: Clinical trials undergo through a rigorous procedure which also follow a high level ethical protocol. Mainly, four phases are involved in a clinical trial. These phases are named as phase I, II, III & IV. Clinical trial often moves in an ascending order from phase I to phase IV. In some literature, an inception / preclinical or phase 0 (zero) has also been described [16]. Phase 0 primarily deals with the discovery of drug, treatment, or procedure and literature review. All of that occurs before the conceptualizing and designing of the clinical trial of phase I.

Phase I: In this phase, drug is tested for its tolerability, and pharmacokinetics and pharmacodynamics characteristics in human. How large dose of a drug can be tolerated without experiencing unacceptable toxicity [15, 17, 18]? This phase is also known as Maximally Tolerated Dose (MTD). There are different methods to test the MTD. The most common and traditional approach is discussed here. MTD is tested on healthy volunteers. Three healthy volunteers are given the dose; if no toxicity occurs, the dose is escalated at the next level, and that dose is given to this group. If toxicity occurred, the other group of three volunteers is given the same dose. If toxicity is not occurred, the dose is escalated to the next level on the same group of participants. If the escalated dose creates an unaccepted toxicity among the participants, the dose escalation is terminated and either that dose or the preceding dose is set as the MTD. The assumption behind it is that the MTD is the dose when one third of the participants should experience unacceptable toxicity [15].

Phase II: In this phase, the efficacy of the drug is tested on patients so this phase is also considered explanatory trial. Participants of this phase are patients and have a condition of interest [15, 19]. Efficacy determines what pharmacological agent (intervention) does under ideal conditions [20]. Mainly biological activities and effect of drug on condition is evaluated [15]. Although MTD has been established in the previous phase, but still, there may be dose-response uncertainty, therefore, more doses may be tested in four to five intervention arms [15]. Similar to the phase I, phase II also have several methods of testing the efficacy of the drug [21-24]. The method originated through Gehan's (1961) work in cancer research is commonly used for this stage of clinical trial [15, 25]. In this model, the investigator uses two pronged approach. In the first approach, the investigator rules out the drug that has less than 20% biological activity in participants. If the drug response is so little or below 20%, the investigator may not continue further trial on that MTD. On other hand, if that drug yields 20% or a higher response rate in selected participants, than the investigator may add more participants in order to calculate better estimation of the response rate of the pharmacological agent in that condition [15, 25].

Phase III: Once the MTD shows a response rate over 20%, the drug is tested in the real word, and it is evaluated for its effectiveness. This phase is also considered as pragmatic trial, in which the effect of the drug is evaluated in the real world, not like in ideal conditions as in phase II [26]. In this phase, participants are randomized in two or more groups as per the design of the study. Randomization provides equal chance to all participants to be selected in any group of the research. Randomization is a key feature of a clinical trial that reduces the bias and the effect of known and unknown confounders. Randomization can be done in a variety of ways. Simple, block, and stratified randomization are common methods those applied in this phase [27-29]. Single, double, and triple blinding is used to keep participants and investigators unaware of the treatment that who is receiving what. Here, the investigator referred to a professional who give intervention to the participants [30, 31]. Drug may be tested against the previous drug, device, and placebo or with different doses [15]. Usually there is an attempt to plan this phase for shorter period. Effectiveness and safety of the intervention is evaluated by applying appropriate parametric and non-parametric bio-statistical methods [32-34].

Phase IV: This phase deals with legal stuff of acquiring approval on the tested drug or agent. Once the drug or intervention is found effective and safe on a set criterion, then, the researching agency applies to the drug regulatory authority, Food and Drug Administration (FDA) in USA and similar agency in other country where clinical trials have been conducted. There are different laws and regulations pertaining to the approval of the drug. FDA does not only look for a well-designed and executed clinical trial. It also reviews other supporting evidences [15, 35]. In this final phase of clinical trial, the drug is launched in the market and prescribed by the professionals to real patients, and carefully and closely watched for its adverse effect and the stability of the intervention in the population [36, 37].

Conclusion

Clinical trials are complex research methods, but extremely important for the medical community, and researchers specially in developing nations where information is limited. Knowledge on clinical trial will enable researchers in conducting such researches and improve the health quality of the population.

Abbreviations

Food and Drug Administration (FDA), low and middle income countries (LAMI), Maximally Tolerated Dose (MTD), National Institute of Health (NIH).

Competing interests

None

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