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CLINICAL TRIALS: A REVIEW

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ABSTRACT

A clinical trial is a research study in human volunteers. It progressively assigns human to one or more health related interventions. Preclinical development starts before clinical trials. If preclinical studies show that the therapy is safe & effective, clinical trials are started. Clinical trials include phases 0, I, II, III, IV & V clinical studies. This will improve the number of therapies coming to market for patients.

KEYWORDS: clinical trials, preclinical studies, clinical studies, phases.

INTRODUCTION [1-4]

Clinical trials may be defined as the process designed to determine the safety and efficacy of a particular drug or device on humans. A clinical trial is a research study that tests a new medical treatment or a new way of using an existing treatment to see if it will be a better way to prevent and screen for diagnose or treat a disease. The overall purpose of a clinical trial is to learn, not to treat patients.

For any new drug to enter in clinical trial, it must pass preclinical studies. Preclinical studies involve in vitro (i.e. test-tube or Laboratory) studies and trials on animal populations. Wide range of dosages of the study drug is given to animal subjects or to an in-vitro substrate in order to obtain preliminary efficacy, toxicity and pharmacokinetic information.

OBJECTIVES OF CLINICAL TRIAL: [4]

1. To assess the safety and effectiveness of a new medication or device on a specific kind of patients. (e.g. patients who have been diagnosed with Alzheimer's disease).
2. To assess the safety and effectiveness of a different dose of a medication that is commonly used (e.g.10mg dose instead of 5mg dose).

3. To assess the safety and effectiveness of an already marketed medication or devices for new indication.
4. To assess whether the new medication or device is more effective for the patient's condition than the already used, standard medication or device.

TYPES OF CLINICAL TRIALS: [5-6]

Clinical trials are used to study many aspects of health care

a. **Prevention Trials:-**It looks for better ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may be including medicines, vitamins, vaccines, minerals, or lifestyle changes.
b. **Screening Trials:-**To test the best way to detect certain diseases or health conditions.
c. **Diagnostic Trials:-**Conduct to find better tests or procedures for diagnosing a particular disease or condition.
d. **Treatment Trials:-**To test experimental treatments, new combinations of drugs or new approaches to surgery or radiation therapy.
e. **Quality of Trials:-**It is to explore ways to improve comfort and quality of life for individuals with a chronic illness.

PHASES OF CLINICAL TRIALS

Pre-clinical studies: [7]

Before pharmaceutical companies start clinical trials on a drug, they conduct extensive pre-clinical studies.

Pre-clinical studies involve in vitro (i.e., test tube or laboratory) studies and trials on animal populations. Wide ranging dosages of the study drug are given to the animal subjects or to an in-vitro substrate in order to obtain preliminary efficacy, toxicity and pharmacokinetic information and to assist pharmaceutical companies in deciding whether it is worthwhile to go ahead with further testing.

Phase 0: [8-10]

Phase 0 is a recent designation for exploratory. First in human trials conducted in accordance with the U.S. Food and Drug Administration's (FDA) 2006 Guidance on Exploratory Investigational New Drug (IND) Studies. Phase 0 trials are designed to speed up the development of promising drugs or imaging agents by establishing very early on whether the drug or agent behaves in human subjects as was anticipated from preclinical studies.

Distinctive features of Phase 0 trials include the administration of single sub therapeutic doses of the study drug to a small number of subjects (10 to 15) to gather preliminary data on the agent's pharmacokinetics (how the body processes the drug) and pharmacodynamics (how the drug works in the body).

Surprisingly, Phase 0 studies do not provide any specific data about the safety and efficacy of the test drug. Furthermore, the drug development companies have been noted to perform Phase 0 studies for ranking the drug candidate in order to decide the pharmacokinetic parameters on humans for further development.

Phase I (Human pharmacology): [11-14]

Phase I trials are the first stage of testing in human subjects. Normally, a small (20-80) group of healthy volunteers will be selected. This phase includes trials designed to assess the safety (pharmacovigilance), tolerability, pharmacokinetics, and pharmacodynamics of a drug. These trials are often conducted in an inpatient clinic, where the subject can be observed by full-time staff. The subject who receives the drug is usually observed until several half-lives of the drug have passed.

Phase I trials also normally include dose-ranging, also called dose escalation, studies so that the appropriate dose for therapeutic use can be found. The tested range of doses will usually be a fraction of the dose that causes harm in animal testing. Phase I trials most often include healthy volunteers. However, there are some circumstances when real patients are used, such as patients who have end-stage disease and lack other treatment options. This exception to the rule most often occurs in oncology (cancer) and HIV drug trials. Volunteers are paid an inconvenience fee for their time spent in the volunteer centre.

There are different kinds of Phase I trials

1. Single Ascending Dose studies

Single Ascending Dose studies are those in which small groups of subjects are given a single dose of the drug while they are observed and tested for a period of time. If they do not exhibit any adverse side effects, and the pharmacokinetic data is roughly in line with predicted safe values, the dose is escalated, and a new group of subjects is then given a higher dose. This is continued until precalculated pharmacokinetic safety levels are reached, or intolerable side effects start showing up at which point the drug is said to have reached the Maximum tolerated dose (MTD).

2. Multiple Ascending Dose studies

Multiple Ascending Dose studies are conducted to better understand the pharmacokinetics & pharmacodynamics of multiple doses of the drug.

Generally, in this study, a group of patients have been administered the multiple low doses of the drug, while samples are collected at various time intervals and analyzed in order to collect information regarding the processing of drug inside the body. Later on, the dose of the test drug is increased for further groups up to a certain level in such studies.

Phase II (Therapeutic exploratory trials): [14-15]

Once the initial safety of the study drug has been confirmed in Phase I trials, Phase II trials are performed on larger groups (20-300) and are designed to assess how well the drug works, as well as to continue Phase I safety assessments in a larger group of volunteers and patients. Genetic testing is very much common if there is enough proof of variation in metabolic rate. When the development process for a new drug fails, this usually occurs during Phase II trials when the drug is discovered not to work as planned, or to have toxic effects. Phase II studies are sometimes divided into Phase IIA and Phase IIB. Phase IIA is specifically designed to assess dosing requirements (how much drug should be given), whereas Phase IIB is specifically designed to study efficacy (how well the drug works at the prescribed dose(s)). Some trials combine Phase I and Phase II, and test both efficacy and toxicity.

Phase II trials are performed at special clinical centers like that of universities and hospitals.

Phase III: [16-19]

Phase III clinical trials have been suggested to be designed in order to analyze the efficacy of new drug and its therapeutic effect in clinical practices. Phase III trials have been conducted randomly on large number of patients (300-3000 or more), having the target to achieve the definite assessment of the new drug, by comparison with the standard drug treatment. Also, due to their longer duration and size, the Phase III trials have been considered as the most expensive, time consuming and difficult to design and run. In phase III trials, the chronic diseases having a period of evalution related to the time period of the intervention can be used in practice. In common practice, some trials of Phase III are continued until the regulatory submission is pended at the appropriate regulatory agency.

Once the drug satisfaction has been achieved after Phase III trials, the report is combined by having the comprehensive description of the methods and result of manufacturing technique,

detail of formulation and its half life. Moreover, the collected information is submitted to the "regulatory submission" so that the hope transpires to the sponsor in order to get the approval of marketing the drug. Also, if any adverse effects have been reported anywhere, the specific drug is recalled immediately from the market.

Phase IV: [4]

Phase IV trial is also known as Post Marketing Surveillance Trial. Phase IV trials involve the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it receives permission to be sold.

Phase IV studies may be required by regulatory authorities or may be undertaken by the sponsoring company for competitive (finding a new market for the drug) or other reasons (for example, the drug may not have been tested for interactions with other drugs, or on certain population groups such as pregnant women, who are unlikely to subject themselves to trials). The safety surveillance is designed to detect any rare or long-term adverse effects over a much larger patient population and longer time period than was possible during the Phase I-III clinical trials. Harmful effects discovered by Phase IV trials may result in a drug being no longer sold, or restricted to certain uses.

Phase V: [20-21]

Phase V, a new term used in the literature, is also termed as "translational research" to refer the effectiveness and community based research studies. It is used to find the interrogation of a new clinical treatment into a large number of public health practices. Generally, the Phase V trials have been considered as the "field research" and it is particularly designed to test generalization of the mechanism to a large sample.

CONCLUSION

Clinical trials are conducted in human volunteers for confirmation of useful properties of new drug. After preclinical development, investigational new drug passes through clinical phases I, II, III and IV.

The drug-development normally proceeds through various phases over many years. These phases provide in detail explanation of pharmacokinetic, pharmacodynamic profile and side effect which may be harmful or beneficial, adverse effect and post marketing surveillance.

REFERENCES

1. Nayak C, Oberai P, Varanasi R, Baig H, Ch R, Reddy GR, et al. A prospective multicentric open clinical trial of homeopathy in diabetic distal symmetric polyneuropathy. Homeopathy, 2013; 102: 130-8.
2. Bykerk VP, Keystone EC, Kuriya B, Larché M, Thorne JC, Haraoui B. Achieving remission in clinical practice: lessons from clinical trial data. Clin Exp Rheumatol, 2013; in press.
3. Information about clinical trial. Available from: URL http://www.temple.edu/pascope/about trials.html
4. Clinical trial wikipedia, the free encyclopedia. Jan 28 2008. Available from: URL http://en.wikipedia.org/wiki/clinical_trial. 28 Jan 2008.
5. Guideline for Good Clinical Practice, (2002), European Medicines Agency, ICH Topic E 6 (R1), 5-48.
6. Turner JR., (2007), New drug development: Design, Methodology and analysis, John Wiley & Sons, Inc., NewJeney, 41-201.
7. Kulkarni S. K., Hand Book of Experimental Pharmacology, 3rd ed, Vallabh Prakashan New Delhi, 2004; 21.
8. Chow SC, Liu JP. Design and Analysis of Clinical Trials: Concepts and Methodologies, John Wiley and Sons; New York. 1998.
9. The Lancet (2009). Phase 0 trials: a platform for drug development?. Lancet, 2009; 374: 176.
10. DeMets D, Friedman L, and Furberg C. Fundamentals of Clinical Trials. Springer 4th Edition, 2010; ISBN 978-1-4419- 1585-6.
11. CDER. "Exploratory IND Studies". Guidance for Industry, Investigators, and Reviewers. Food and Drug Administration, 2010.
12. Adil E.S. The Myth of Equipoise in Phase 1 Clinical Trials. Medscape J Med., 2008; 10: 254.
13. Guidance for Institutional Review Boards and Clinical Investigators. Food and Drug Administration, 2007.
14. http://www.pdtrials.org/en/about_PDtri als_what. Assesses on March 20, 2013.
15. http://www.mlanet.org/resources/hlth_tutorial/mod4c.html. Assessed on March 31, 2013.
16. Paul J, Seib R, Prescott T. The Internet and Clinical Trials: Background, Online Resources, Examples and Issues. J Med Int Res., 2005; 7: e5.

17. Melinda C. Experimental Labour – Offshoring Clinical Trials to China East Asian Science, Technology and Society. An Int J., 2008; 2: 73-92.
18. Poole V, Peterson AM. Pharmacotherapeutics for Advanced Practice: A Practical Approach, 2005; Lippincott Williams & Wilkins. ISBN 0- 7817-5784-3.
19. John H. Fixing a broken drug development process. J Comm Biotech, 2013; 19: 588.
20. Rogers MA. What are the phases of intervention research?. American Speech- Language-Hearing Association, 2013.
21. Brantner CP. Estimating the Cost of New Drug Development: Is It Really $802 Million? Health Affairs, 2006; 25: 420-8.