Clinical trial : A Review

Apurva Patel*, Kirti M Patel**

Abstract :

Randomized clinical trials are scientific investigations that examine and evaluate the safety and efficacy of new drugs, devices, tests, or lifestyle interventions using human subjects. The results that these clinical trials generate are considered to be the most robust data in the era of evidence-based medicine. The primary aim of most clinical trials is to provide an unbiased evaluation of the merits of using one or more treatment options for a given disease or condition of interest. Ideally, clinical trials should be performed in a way that isolates the effect of treatment on the study outcome and provides results that are free from study bias.

Key Words : Randomized clinical trials, ethics, phase, Institutional Review Boards

Introduction

Randomized clinical trials are scientific investigations that examine and evaluate the safety and efficacy of new drugs, devices, tests, or lifestyle interventions using human subjects. The results those these clinical trials generate are considered to be the most robust data in the era of evidence-based medicine.[1] The primary aim of most clinical trials is to provide an unbiased evaluation of the merits of using one or more treatment options for a given disease or condition of interest.[2] Ideally, clinical trials should be performed in a way that isolates the effect of treatment on the study outcome and provides results that are free from study bias.

A large proportion of clinical trials are sponsored by pharmaceutical or biotechnology companies that are developing new disease management interventions. Disease specific charities may also fund investigators to conduct studies and large central government bodies interested in health care will also sponsor scientifically valid studies. Clinical trials usually involve a program of studies from initial exploratory studies on a handful of subjects to large trials involving hundreds or thousands of subjects, requiring considerable financial investment usually into the millions of dollars over several years. Given this investment, there is often an expectation of a return from this investment. The more commercial the source of funding, the greater the expectation for financial success and the greater the pressure on those involved to produce positive results.

Historical Minute First Clinical Trials

Clinical Trials have a long history [3] even if not acknowledged as Clinical trials

Formal record of clinical trials dates back to the time of the *Trialists :*

Dr. Van Helmont's proposal for a therapeutic trial of bloodletting for fevers [1628]

Dr. Lind's, a ship surgeon, trial of oranges & limes for scurvy [1747]

* Associate Professor, Department of Medical Oncology, GCRI, Civil hospital, Ahmedabad, India

** Dean, GCS Medical College Hospital & Research Centre, Ahmedabad, India

Correspondence : apurvapatel04@gmail.com

Historical Highlights of Drug Trials

1909: Paul Ehrlich - Arsphenamine

1929: Alexander Fleming - Penicillin

1935: Gerhard Domagk - Sulfonamide

1944: Schatz/Bugie/Waksman Streptomycin

By 1950, the British Medical Research council developed a systematic methodology for studying & evaluating therapeutic interventions.

Ethics of Clinical Trials Protection of Participants

Three ethical principles guide clinical research: 1) Respect for Persons: Treatment of person as autonomous, 2) Beneficence: Issue re: potential conflict between good of society vs. individual, 3) Justice: Treatment of all fairly & all equally shares benefits & risks.

Ethical Norms of Clinical Trials: Sound study designs take into account: Randomization or sharing of risks, proper use of placebo, processes to monitor safety of treatment benefit and its toxicity (rx/tx) competent investigators, informed consent, equitable selection of participants, compensation for study related injuries.

Ethical Issues: Protection of Human Subjects, Rely on integrity of Investigator but outside groups also have oversight, Participants' rights protected by Institutional Review Boards [IRBs]. An IRB is defined as[4]"any board, committee or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of biomedical research involving human subjects." IRB responsible for such tasks: Review research to ensure that potential benefits outweigh risks, develop and issue written procedures, review research for risk/benefit analysis & proper protection of subjects, issue written notice of approval/disapproval to the Investigator, review and respond to proposed protocol changes submitted by the Investigator, review reports of deaths, and serious and unexpected adverse events received from the Investigator, conduct periodic continuing review of the study, study risks, selection of subjects, privacy of subjects, confidentiality of data, and the consent process.

Historical Minute 10 Key Points: Voluntary informed consent, experiment must be for the good of society, &

results not obtainable by other means. Experiment should be based upon prior animal studies, physical & mental suffering & injury should be avoided, no expectation that death/disabling injury will occur from the experiment. Only scientifically qualified persons to be involved, Subject can terminate her/his involvement.

Design and analysis of clinical trial

New drug development: from bench to bedside

Pre-clinical studies: bench refers to laboratory experiments to study new biochemical principles and discover novel treatments. [5] The experiments with promising results are followed by pre-clinical animal studies. After understanding the effect of the treatment on animals, proceed to clinical trials. Clinical trials involving human subjects are conducted in phase I-IV reflect the sequential nature of the experiments involved and finally analysis of Clinical Trials in the phase 3 is obtained.

Pharmacology : The science dealing with interactions between living systems and molecules, especially those from outside the system. [6]

Clinical pharmacology: To prevent, diagnose and treat diseases with drugs. [7]

Pathogenesis of disease due to chemicals in the environment.

Drug: It is the small molecule that alters the body's function when introduced into the body. [8]

Pharmacokinetics (PK): [9] *Pharmacokinetics* is currently defined as the study of the time course of drug absorption, distribution, metabolism, and excretion. Clinical *pharmacokinetics* is the application of pharmacokinetic principles to the safe and effective therapeutic management of drugs in an individual patient. Primary goals of clinical pharmacokinetics include enhancing efficacy and decreasing toxicity of a patient's drug therapy. The development of strong correlations between drug concentrations and their pharmacologic responses has enabled clinicians to apply pharmacokinetic principles to actual patient situations.

Drug administration can be divided into PK and PD (pharmacodynamics) phase, both of which are important to the design of a dosage regimen to achieve the therapeutic objective. Since both the desired response and toxicity are functions of the drug concentration, the therapeutic objective can be achieved only when the drug concentration lies within a therapeutic window , in which it is effective, but not toxic. Drug concentrations are typically measured at the plasma. Optimal dosage regimen: maintains the plasma concentration of a drug within the therapeutic window.

PK models: 1) Mechanistic a) Physiologic model - consider qualitative features shared by different tissues or organs, and use a prior knowledge of physiology, anatomy, and biochemistry

b) Compartmental model - the body is viewed in terms of kinetic compartments between which the drug distributes and elimination occurs. The kinetics is often described by a linear system of ordinary differential equations

PD models - describe and quantify the steady-state relationship of drug concentration (C) at an effectors site to the drug effect (E)

One way to compare potency of two drugs that are in the same pharmacologic class is to compare EC50. The drug with a lower EC50 is considered more potent.

Phase 1 clinical trial design: Typical Phase I studies [10] give drug to healthy volunteers, which is initiated at low doses and subsequently escalated to show safety at a level where some positive response is achieved. In cancer studies, patients are used as study subjects, and given the hoped-for benefit, aims at an acceptable level of toxic response in determining the maximum tolerated dose (MTD),3-plus-3 design, Treats group of 3 patents sequentially, starting with the min dose. Escalate if no toxicity is observed in all 3 patients; otherwise an additional 3 patients are treated at the same dose level If 1/6 patients has toxicity, escalate; if 2/6 patients have toxicity, declare the current dose as the MTD; if more that 2/6 patients have toxicity, use the lower dose as the MTD. up-and-down [11] sequential design continual reassessment method (CRM) - use parametric modeling of the dose-response relationship and a Bayesian approach to estimate the MTD. Escalation with overdose control (EWOC) [12,13] - even though the response rates are low and that a large number of patients are treated at non-therapeutic dose, it is still widely used because of ethical issues. [14] Bartroff and Lai (2010a,b; Stat. Sci., Biometrics):provide a mathematical representation of the dilemma between safe treatment of current patients in the dose-finding cancer trial and efficient experimentation to gather information about the MTD for future patients a stochastic optimization problem that leads to a class of hybrid designs a two-stage design whose first stage is a modified version of the 3-plus-3 design that generate data to check the parametric assumptions in the model-based hybrid design used in the second stage. [15,16]

Phase 2 and 3 clinical trial: Phase II trials use the information collected and the dosage regimen determined from Phase I studies to evaluate the efficacy of the drug from particular indications in patients with the disease. [17] Phase III trials demonstrate effectiveness of the drug for its approval by the regulatory agency and also collect safety information from the relatively large samples of patients accrued to the trial.

Phase II cancer trials [18]: 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. 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. Some Phase II trials are designed as case series, demonstrating a drug's safety and activity in a selected group of patients. Other Phase II trials are designed as randomized clinical trials, where some patients receive the drug/device and others receive placebo/standard treatment. Randomized Phase II trials have far fewer patients than randomized Phase III trials.

Phase III [18]: Phase III studies are randomized controlled multicenter trials on large patient groups (300 3,000 or more depending upon the disease/medical condition studied) and are aimed at being the definitive assessment of how effective the drug is, in comparison with current 'gold standard' treatment. Because of their size and comparatively long duration, Phase III trials are the most expensive, time-consuming and difficult trials to design and run, especially in therapies for chronic medical conditions. It is common practice that certain Phase III trials will continue while the regulatory submission is pending at the appropriate regulatory agency. This allows patients to continue to receive possibly lifesaving drugs until the drug can be obtained by purchase. Other reasons for performing trials at this stage include attempts by the sponsor at "label expansion" (to show the drug works for additional types of patients/diseases beyond the original use for which the drug was approved for marketing), to obtain additional safety data, or to support marketing claims for the drug. Once a drug has proved satisfactory after Phase III trials, the trial results are usually combined into a large document containing a comprehensive description of the methods and results of human and animal studies, manufacturing procedures, formulation details, and shelf life. This collection of information makes up the "regulatory submission" that is provided for review to the appropriate regulatory authorities in different countries.

Phase 4 clinical studies

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.

Conclusion and summary

Despite the sequential nature of Phase I-III trials, the trials are often planned separately, treating each trial as an independent study whose design depends on results from previous phases .Advantage: the reproducibility of the results of the trial can be evaluated on the basis of the prescribed design, without worrying about the statistical variability of the results of earlier-phase trials that determine the prescribed design Disadvantage: the sample sizes are often inadequate because of the separate planning; inconclusive results at each phase. Adaptation and sequential experimentation approach.

References

1. McFadden E. Management of data in clinical trials. New York: Wiley, 1997.
2. Green S, Benedetti J, Crowley J. Clinical trials in oncology, 2nd ed. Boca Raton, FL: Chapman & Hall/CRC, 2003.
3. Curtis L. Meinert, Susan Tonascia (1986). *Clinical trials: design, conduct, and analysis*. Oxford University Press, USA. P3
4. The Office of Human Research Protection. Institutional Review Board Guidebook. "Chapter 3, Section A: Risk/Benefit Analysis. pp. 1-10
5. Curtis L. Meinert, Susan Tonascia (1986). *Clinical trials: design, conduct, and analysis*. Oxford University Press, USA. P65-70
6. Vallance P, Smart TG (January 2006). *"The future of pharmacology"*. *British Journal of Pharmacology*. 147 Suppl 1 (S1): S304 7. doi:10.1038/sj.bjp.0706454. PMC 1760753. PMID
7. Clinical Pharmacology forwarded from http://en.wikipedia.org/wiki/Clinical_pharmacology; Last accessed on 23rd June 2014.
8. Brater DC, Daly WJ (May 2000). "Clinical pharmacology in the Middle Ages: principles that presage the 21st century". *Clin. Pharmacol. Ther.* 67 (5): 447 50. doi : 10. 1067 / mcp. 2000. 106465. PMID 10824622
9. Concepts in clinical pharmacology ; Lesion 1: Introduction to pharmacokinetics and pharmacodynamics; forwarded from http://www.ashp.org/doclibrary/bookstore/p2418-chapter1.aspx; last accessed on 23rd June 2013
10. Eisenhauer EA, O'Dwyer PJ, Christian M, Humphrey JS. Phase I clinical trial design in cancer drug development. J Clin Oncol 2000;18(3):684.
11. Moller S. An extension of the continual reassessment methods using a preliminary up-and-down design in a dose finding study in cancer patients, in order to investigate a greater range of doses. Stat Med 1995;14:911.
12. Simon R, Freidlin B, Rubinstein L. Accelerated titration designs for phase I clinical trials in oncology. J Natl Cancer Inst 1997;89:1138.
13. Dancey J, Freidlin B, Rubinstein LV. Accelerated titration designs. In: Chevret S, ed. Statistical methods in dose-finding experiments. New York: Wiley, 2006:91.
14. Babb J, Rogatko A, Zacks S. Cancer phase I clinical trials: efficient dose escalation with overdose control. Stat Med 1998;17:1103.
15. Goodman SN, Zahurak ML, Piantadosi S. Some practical improvements in the continual reassessment method for phase I studies. Stat Med 1995;14:1149
16. O'Quigley J, Pepe M, Fisher L. Continual reassessment method: a practical design for phase I clinical trials. Biometrics 1990;46:33.
17. Bryant J, Day R. Incorporating toxicity considerations into the design of two-stage phase II clinical trials. Biometrics 1995;51:1372.
18. Forwarded from: http://www.genetherapynet.com/clinical-trial-phases.html. last accessed on 23rd June 2013.

Further reading

19. Conaway M, Petroni G. Designs for phase II trials allowing for a trade-off between response and toxicity. Biometrics 1996;52:1375.
20. Zee B, Melnychuk D, Dancey J, Eisenhauer E. Multinomial phase II cancer trials incorporating response and early progression. J Biopharm Stat 1999;9:351.
21. Simon R, Wittes RE, Ellenberg SS. Randomized phase II clinical trials. Cancer Treat Rep 1994; 69:1375.