Review Article

Clinical Trial - Present and Future

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Received: 02-09-2020; **Revised:** 17-11-2020; **Accepted:** 26-11-2020; **Published on:** 15-12-2020.

ABSTRACT

A Clinical trial is one of the highly important phases between preclinical trials and drugs released into a market. For drug discovery to drugs came into a market it takes much time out of that time clinical trials constitute much percentage of that time. In preclinical trials we get information about side effects, toxicity, mutagenicity, carcinogenicity in small animals at very low doses far below the therapeutic dose that might be used during clinical trials. So it's become necessary to test drugs in humans too. Because small animals are used in a preclinical trial and huge difference in human and other animal's biological systems it's necessary to evaluate the drug candidate for safety, efficacy, tolerability, toxicity, and pharmacodynamic and pharmacokinetic properties. The drug passes the trial phases in percentage is 70% in phase1,35% in phase2, 25% in phase 3 it reveals that many drugs pass preclinical phases and phase 1 of a clinical trial but then drugs fail to comply with the human biological system. In this review, we have discussed all phases of clinical trials and future chances of development in clinical trials to avoid or decrease the time, money, resources requirement in clinical trials based on advancement in technology.

Keywords: Clinical trial, pharmacodynamic, preclinical trial, pharmacokinetics, safety, efficacy.

QUICK RESPONSE CODE →

DOI: 10.47583/ijpsrr.2020.v65i02.027

DOI link: http://dx.doi.org/10.47583/ijpsrr.2020.v65i02.027

CLINICAL TRIALS

Clinical trials start after preclinical trials show supportive data to proceed[1].

Before starting clinical trials following concept consideration is of vital importance.

1) Ethical consideration – Clinical trials must be conducted only after the approval from the independent ethics committee as per GCP. A document of participant willingness to participate in a clinical trial must be obtained before the clinical trial that documents called Informed consent[2]. The ethics committee has to observe, analyze, and ensure that study not breaking any ethical principles like autonomy, beneficence, non-maleficence, and, justice[3].

2) Controlled trials – To evaluate the result of the experiment group there must be a standard group called the control group to whom the experiment group is compared for analysis of result called controlled trials. The involvement of a proper control group is highly important.

3) Randomization- Randomization is a technique through which both control and sample or experiment group get an equal opportunity to expose to the treatment so ultimately it avoids bias between the experiment or sample and control groups.

4) Blinding- Blinding refers to hiding the nature of treatment from subjects and investigators. When it's concealed from subject only called single blinds trial and when it's concealed from both subject and investigator called double-blind trial and when it's hidden from the participant, investigator and data analyst called triple blind trials[4].

5) Inclusion and exclusion criteria-The basis on which patients are selected to participate in trials must be decided in advance. Like age, sex, race, duration, and severity of illness.

6) Sample size- because a clinical trial requires major ethical and financial consideration it's not possible to involve many populations in the trial . the sample size is the number of participants that must be incorporated into the study to get a valid result. The sample size is calculated statistically so it reveals the number of subjects to be included to obtain a decisive conclusion.

7) The multicentric trial-The trial is conducted at many centers to obtain data on a diverse population called multicentric trials. For example, a multicentric trial is conducted by the national cancer institute then the data is centralized for analysis for multicentric trials. One centralized IRB review process is sufficient to analyze multicentric trial procedure[5].

PHASES OF CLINICAL TRIALS

➢ PHASE 0 (Microdosing study)

It's 1st human clinical trial of a new untested drug[6].As the name indicates a very small dose of the drug is given to the 10-15 subject to asses pharmacokinetic and pharmacodynamic properties of the drug. As we know the dose is very low it's difficult to assess pharmacodynamic properties but in the case of anticancer drugs, it reveals some dynamic properties too. Microdosing study carried out to know either drug behaves the way we want or as anticipated in preclinical trial[8]. If the drug behaves unexpectedly then the trial conducting team thinks that either "go/no go" to further trials. Because of the very low dose(1/100th), the pharmacokinetic parameter was assessed by using accelerator mass spectroscopy or LC tandem mass spectroscopy (LC-MS-MS) to measure very low drug. Phase 0 study has not developed that much extent till now. The purpose of this study is to speed up or streamline the approval procedure. In phase 0 there no chance of subject benefits because of too low dose and also fewer chances of side effect[9].

➢ PHASE 1 (Human pharmacology and safety)

This is 1st in the human study and 20-80 subjects are involved. 1st human administration carried out by clinical pharmacologist. The lowest estimated dose according to preclinical and microdosing study is given to the subject. Generally, healthy volunteers are used in this phase except for cancer and HIV medication(patients are used). Phase 1 study is an open-label. major emphasis is given on safety and tolerability no efficacy data is obtained because healthy volunteers are used not patients[10].

Different ways of phase 1 study

SAD-Single Ascending Dose Studies this means a small group of subjects receive the dose of the drug if it's well tolerated then the next high dose is administered to the next group until the MTD (maximum tolerated dose) is reached.

MAD-Multiple Ascending Dose Studies this means assessment of pharmacokinetic and pharmacodynamic properties by giving multiple small doses to the patient and by taking blood sample drug level in the systemic circulation is measured[11].

This trial (phase1) normally taken into consideration dose escalation to find optimum therapeutic dose[12].This phase takes 3-6 months and the success rate is 70%.

➢ PHASE 2 (Therapeutic Exploratory)

This study is 1st inpatient study and involved 50-300 subjects. Both efficacy and safety are determined in this phase and also dose range and ceiling effect in a controlled setting. Phase 2 is done in a double-blind manner. Drug toxicity and its interaction are recorded in this phase. This study is generally carried out at 2-4 center[13].phase2 reveals the therapeutic efficacy or usefulness of the drug candidate. It takes 6 months to 2 years and the success rate is 35%. Drug candidates fail here if it does not shows clinical efficacy.

➢ PHASE 3 (Therapeutic Confirmatory)

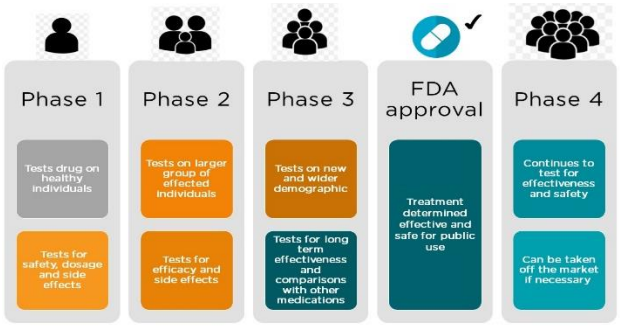
This phase of a trial is conducted generally on a large population (500-3000) and due to this, it's carried out in a multicentric fashion. The safety of the drug is determined more broadly. This trial confirms the therapeutic efficacy observed in phase 2.Main aim of this phase is to determine the benefits to risk ratio. The adverse effect is determined by giving questionnaires to participants and responses are recorded[14]. Phase 3 is the last step after completion of this NDA is filed. if this phase is succeeded the drug is released into the market. Approximately 25-30% of the drug able to pass this phase and the length of study is 1-4 years.

➢ PHASE 4 (Post-marketing surveillance)

In this phase generally act as participant subject. Those side effects not observed in these phases may be observed in this phase such as an idiosyncratic reaction and individual-specific side effect. Not related to how patients have studied during phase1,2,3 phase 4 acts as the best non-interventional, naturalistic to assess drug safety[15].This phase remains alive until the drug in the market.

➢ PHASE 5

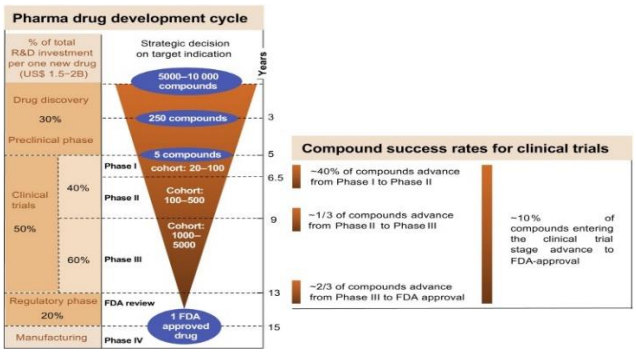
This translational research is designed to "move from bench to bedside"[16]. The drug for which new use is discovered along with existed one come under phase 5 drug in phase 5 can't be removed or withdraw from the market.



FUTURE OF CLINICAL TRIAL

Because we know that many drugs were discovered but out of those small percentage of drugs able to pass clinical trial phases.

To know about see diagram below:



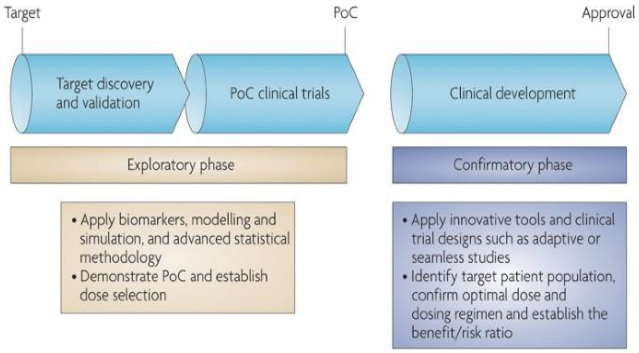
In the future, there will be only 2 phases one exploratory phase and a confirmatory phase.

EXPLORATORY PHASE– apply biomarkers, modeling, simulation, advanced statistical methodology.

PROOF OF CLINICAL TRIAL – demonstrate POC then dose selection

CLINICAL DEVELOPMENT- Apply innovative tools and clinical trial design also use the various algorithm and genetic record of participant

DRUG APPROVAL- finally drug will approved[17].



INNOVATIVE SOLUTIONS TO INCREASE SPEED OF CLINICAL CYCLE

- Adaptive clinical trial -The name itself suggests that such a method allows flexibility in clinical trial design based on interim data.
- Master protocol-this means the evaluation of more than one IND by keeping the overall trial structure unchanged.
- Synthetic control arms-these devices collect data from a previous clinical trial, electronic health records, fitness records, disease registries so this will reduce time, cost, and increases trial speed.
- Pharmacogenetic testing – in 2018 55% of trials were initiated by using selective pharmacogenetic biomolecule for patient selection to predict efficacy and safety[18].

CONCLUSION

After the preclinical study, a highly important step is a clinical trial. The clinical trial consists of 4 core phases and each step has its significance and importance. each phase requires a different population and involves determining if highly important parameter like safety, efficacy, tolerability, toxicity, and the other pharmacokinetic parameter which plays a vital role in drug development in the clinical trial. And as advancements in technology and an increase in demand to treat novel diseases and disorders, it's of great demand to increase the speed of clinical trial by replacing traditional way through advanced technological tools.

REFERENCES

1. Kulkarni S.K. Handbook of Experimental pharmacology,3rd edition Vallabh Prakashan New Delhi 2004,Page-21.
2. E6(R2)Good clinical practice: Integrated addendum to ICH E6(R1), Page No.18
3. TRIPATHI KD MD Essential of Medical Pharmacology ,7th edition, Page No.74,75,79,80
4. www.publichealthnotes.com What is Blinding in Research? What is it's Types?
5. Guidance For Industry: Using a centralized IRB Review Process In Multicenter clinical trial, Page :7.
6. Dr. Mandal M. Ananya D Reviewed by Sally Robertson BSc, www.newsmedical.net
7. Gupta Umesh Chandra, Bhatia Sandip, Garg Amit, Sharma Amit, Choudhary Vaibhav, Phase 0 clinical trials in oncology new drug development, Article in perspective in clinical research: march 2011 page:14. DOI:10.4103/2229-3485.76285.
8. www.healthonline.com What happens in clinical trials? Medically Reviewed by Deborah Weatherspoon Ph.D. Written by Jill Seladischulman Ph.D. Updated on JUNE 21,2019.
9. www.cancer.org American Cancer Society.
10. Gobind Rai Garg, Sparsh Gupta, Review of the pharmacology 12th edition,12.
11. Frampton Chris, Holt Shawn, Clinical trial- An Overview, Research Review Education Series, 2012 ,www.researchreview.co.nz, Page no-2.
12. Thorat S.R, Banarjee S.K., Gaikwad D.D., Jadhav S.L., Thorat R.M. Clinical Trial: A Review, 1(2), March-April 2010, Article 019, Page-102.
13. Barar FSK Essential of pharmacotherapeutics, revised edition, S. Chand publication, Page no.60.
14. Bourin Michel, Neurobiology of the mood the University of Nantes, Phase 3 clinical trials What Methodology, SOJ pharmacy and pharmaceutical sciences, Published: August 26,2017 Page-1,3 DOI-10.15226/2374-66/4/400165
15. Dr.Suvarna Viraj, Phase 4 of drug development, J. Indian society for Clinical research year vol.1, 2010 page- 4.
16. Mahan Vicki L. Department of pediatric cardiothoracic surgery, st.Christophers hospital for children Philadelphia, J. international journal for clinical medicine, Clinical Trial Phases, 2014, published online Dec 22, 2014, 1380. Doi.10.4236/ijcm.2014.521175
17. Orloff John J, Douglas Frank L, Pinheiro Jose, Levinson Susan, The future of drug development: Advancing clinical Trial Design, Journal: Nature, October 2009 Page :2 DOI.10.1038/nrd3025.
18. Intelligent clinical trial, Deloitte. Insights 6,7.
19. Image, Clinical trial FAQs- NephCure Kidney International, nephcure.org/research/clinical research.
20. Harrer Stefan Image, Artificial intelligence for clinical trial design, Trends in Pharmacological sciences, 40, August 2019, Doi.10.1016/jtips.2019.05.005 sciencedirect.com

Source of Support: None declared.

Conflict of Interest: None declared.