Phases of clinical trial

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Outline

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Definition

- It is an organized biomedical or behavioral research study designed to investigate new methods of preventing, diagnosing, or treating an illness or disease in humans and to answer specific questions about biomedical or behavioral interventions.

- NDCTR 2019 and ICMR guidelines requires that all researchers conducting a clinical trial must publicly document it in the Clinical Trials Registry - India.

Objectives

➢Clinical trials are specifically designed to intervene and evaluate health-related outcomes, with following objectives:

- To diagnose or detect disease
- To treat an existing disorder
- To prevent disease or early death
- To change behaviour, habits, or other lifestyle factors

Historical aspects

- The renaissance surgeon Ambroise pare conducted the first clinical trial of a novel therapy unintentionally in 1537.
- James Lind is considered as the father of clinical trials; Lind carried out trials on scurvy patient at sea on board the Salisbury in 1747.
- Placebos were first used in 1863.
- The idea of randomization was introduced in 1923 by Fisher and Mackenzie.

- Amerson et al (1931) first considered randomization of patients to treatment in clinical trial to reduce the potential bias and increase the detection of clinically significant.

- The first trial using properly randomized treatment and control groups was carried out in 1948 by Medical Research Council , and involved the use of streptomycin to treat pulmonary tuberculosis.

- 1945, the ethical impact of clinical trials has become increasingly important, resulting in strict regulation of medical experiments on human subjects.

- These regulations have been enshrined in documents such as Nuremberg codex(1947) and the Declaration of Helsinki (1964 amended in 1975,1983,1996,2000,2002 and 2004).

Need for clinical trials

- Develop drugs with maximum benefit and minimum adverse effect
- A new drug must be evaluated in human volunteers/patients for its efficacy and toxicity
- Ensure safe use in humans before market approval

Basic principles

- Clinical trial requires three important considerations:

(1) Study must examine valuable and important biomedical research questions

(2) It must be based on a rigorous methodology that can answer a specific research question

(3) Must be based on strong ethical principles to minimize the risk.

Types of clinical trials

- **Treatment trials** : Conducted to test drugs, treatments, new approaches to surgery, and novel methods.

- **Prevention trials** : study of medicines, vitamins, minerals, or exercises that may lower the risks of developing certain diseases.

- **Diagnostic trials** : Conducted to find better tests or procedures for diagnosing a particular disease or condition.

❖**Screening trials** : Conducted with the intention of testing the best way to find a disease or condition through methods such as magnetic resonance imaging (MRI), mammography, or blood tests.

❖**Quality-of-life trials** : Study the benefits of treatments (e.g., side-effect-reducing drugs) or lifestyle changes (eg. dietary changes) that may improve the quality of life.

Approach: Explanatory and pragmatic

Aspect	Explanatory Trials	Pragmatic Trials
Goal	Evaluate if and how an intervention works	Determine intervention efficacy
Criteria	Strict selection for homogenous study group	Lenient selection for heterogenous participants
Controls	Use placebo	Use active controls
Regimens	Fixed drug regimens	Flexible regimens
Analysis	Intention to treat	Include all patients who received interventions
Outcomes	Focus on “hard” outcomes (e.g. death ,tumor size)	Focus on “soft” outcomes (e.g. pain, quality of life)

Efficacy vs. effectiveness trials

Aspect	Efficacy Trials	Effectiveness Trials
Purpose	Determine if an intervention works in study subjects	Evaluate intervention effects in real-world clinical settings
Trial type	Usually explanatory	pragmatic
Design goal	Provide unambiguous evidence of intervention effects	Assess effects under daily practice circumstances
Design complexity	More complex	simpler
Selection criteria	Strict selection	Lenient selection
Regimen	Fixed regimens	Flexible regimens
Target group	Homogenous study	Heterogenous
Intervention stage	Often first stage to prove efficacy	Evaluates interventions with proven efficacy

The pathway of new drug development

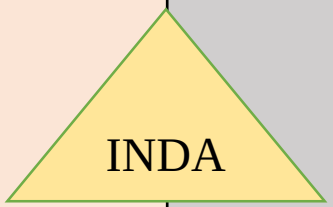
The pathway of new drug development process, there are three broad stages :

(1) Drug discovery

(2) Pre- clinical development

(3) Clinical development

DRUG DISCOVERY	PRECLINICAL PHASE	CLINICAL TRIAL PHASE			REGULATORY APPROVAL	RESTRICTED MARKETING
Compound centered or Target centered approach →Lead finding→ Lead optimization→ LEAD COMPOUND	Pharmaco-kinetics; Pharmaco-dynamics; Toxicology: Safety index PROMOISING COMPOUND FOR HUMAN TRIALS	PHASE I Non blind-open trials, 25-100 subjects. To assess safety, tolerability and safer clinical dose for human volunteers	PHASE II **Early phase II:** up to 200 subjects. Single blind. **Late phase II:** Double blind 200-400 subjects. Verification of safety, efficacy and clinical claims in homogeneous population	PHASE III Large scale multicentered trials in1000-5000 plus subjects in heterogeneous population. Double blind cross-over studies to minimize human error and bias	Submission of NEW DRUG APPLICATION for LICENSING	Post-marketing surveillance phase, Submission of PSUR regularly by the sponsor for 4 years
2-5 years	1.5-2 years	5-7 years			1.5 years	upto 4 years



Drug discovery and development

- **Target identification** : Identify and validate the target or targeted chemical moiety

- **Lead compound discovery** : Potential to bind to the identified target successfully and it’s discovered by cloning of the target protein

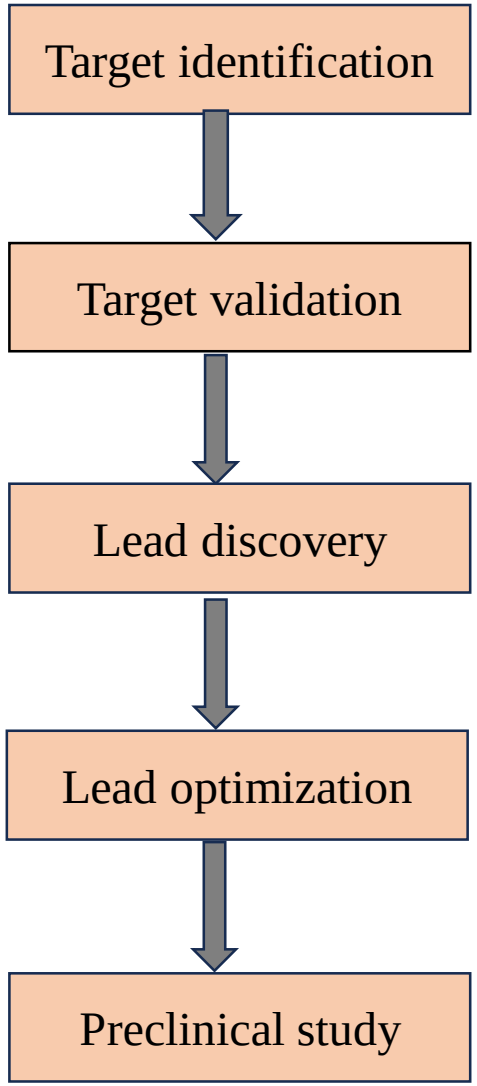
- **Lead compound optimization** : Increase potency regarding selectivity, metabolic stability, pharmacokinetics and toxicological effects on target

- **Preclinical studies** : Conduct studies to gather data on safety and efficacy before human trials

- **Regulatory approval** : Obtain approval from Drug Regulation Authority(DRA) (e.g. FDA in the US , CDSCO/DCGI in India)

- **Clinical trials** : Begin trials after approval and filling an Investigational New Drug application (INDA)

Pre DRA phases



Preclinical development

- **Aim** : An investigational drug is tested extensively in the laboratory under in vitro and in vivo conditions to ensure that it would be safe to administer to humans.

- It is important to have the information about the pharmaceutical composition of the drug, its safety, how the drug will be formulated and manufactured, and how it will be administered to the first in human.

- It includes the study of following :

  Pharmacokinetic study : study of ADME of potential drug candidate in animals.

  Toxicological study : Conducted to identify potential risks to humans.

- Preclinical animal studies are as per “Good Laboratory Practice”(GLP) guideline.

- The aim of GLP is to ensures reliability and reproducibility of laboratory data and minimizes human errors.

- Studies during the pre clinical phase usually require 1.5 to 2 years for completion.

- Investigational New Drug application (INDA) in India, US, and Clinical Trial Authorization (CTA) in Australia and UK, which are submitted to appropriate regulatory authorities for permission to conduct investigational research.

The Investigation New Drug Application (INDA):

The application to request permission to begin human testing is commonly referred to as an IND application.

(1) Introductory statement and study plan

(2) Investigator’s Brochure

(3) Preclinical study data

(4) Chemistry, Manufacturing and Control data

(5) Clinical plan and Protocol

(6) Physician Information

DRA phases

Pre-clinical study

↓ DRA Submission

Exploratory IND application

↓ DRA approval

Clinical trial: phase 0

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Phase 0 results: help identify most promising candidate

↓ DRA submission

IND application for promising candidate

↓ DRA approval

Clinical trials: phases I- III

↓ DRA Submission

Drug application(NDA)

↓ DRA approval

Phases IV post marketing surveillance

Clinical Trials

- Clinical trial includes various phases that include phase 0 (micro-dosing studies), phase 1, phase 2, phase 3, and phase 4.

- Phase 0 and phase 2 are called exploratory trial phases, phase 1 is non-therapeutic phase, phase 3 is known as the therapeutic confirmatory phase, and phase 4 is called the post-approval or the post-marketing surveillance phase.

Types of clinical trials

Type of clinical trial	Definition
Randomized trial	Study participants are randomly assigned to a group
Open-label	Both study subjects and the researchers are aware of the drug being tested
Blinded (single-blind)	In single-blind studies, the subject has no idea about the group (test/control) in which they are placed
Double-blind (double-blind)	In the double-blind study, the subjects as well as the investigator have no idea about the test/control group
Placebo	A substance that appears like a drug but has no active moiety
Add-on	An additional drug apart from the clinical trial drug given to a group of study participants
Single center	A study being carried out at a particular place/location/center
Multi-center	A study is being carried out at multiple places/locations/centers

Phase 0 (micro-dosing)

- Exploratory
- Examines too low (1/100th) concentrations (micro-dosing) of the drug for less time.
- Study the pharmacokinetics and determine the dose for phase I studies.
- Previously done in animals but now it is carried out in humans.

➢ Limitations

- Nonlinear pharmacokinetics, if exists can create problems in dose extrapolation
- False negative results can lead to discontinuation of promising candidates
- Every drug may not be suitable candidate for phase 0 trial

Phase I

- Nontherapeutic trial
- 25-100
- Healthy volunteers, occasionally patients with advanced or rare disease
- Non-blinded or open label study
- Done by trained clinical pharmacologist
- Usually single-center studies.
- Month to 1 year study duration

➢ **Prerequisites :**

- Preclinical data

➢ **Determines:**

- Safety and dose initially identified
- Pharmacokinetic and pharmacodynamic effects.
- Determine maximum tolerated dose(MTD) and adverse effects of this dose

Phase II (Phase IIa, Phase IIb)

- Therapeutic Exploratory trial
- 50-500
- First time in patient with target disease
- Randomized and controlled (can be placebo controlled) , may be blinded
- Done by clinician
- multicenter studies
- 1 – 2 years study duration

➢ **Prerequisites :**

- Review of phase I data

➢ **Determines:**

- Therapeutic efficacy
- Dose- response relationships
- Safety and Tolerability
- Dose and regimen for next phase

- **Phase IIa**: Decides the drug dosage, includes 20-30 patients, and takes up to weeks/months.(Pilot clinical trials)
- Mainly focus to evaluate safety and efficacy in selected population of patients.
- **Phase IIb** : Studies dose response relationship, drug-drug interactions.(Well- controlled trials)

Phase III (Phase IIIa, Phase IIIb)

- Therapeutic confirmatory trial
- 1000-5000
- Large scale controlled trials
- Double-blind randomized trials
- Cross over study design
- Multicentric trials
- 3- 5 years study duration

❑**Phase IIIa** : Conducted after efficacy of medicine demonstrated but prior to regulatory submission of new drug application (NDA)

- Conducted in special group of patient
- Provide information needed for the package insert and labeling of the drug

❑**Phase IIIb** : After NDA submission but prior to the drug's approval and launch.

➢Then drug will be submitted to the relevant regulatory authorities for licensing. NDAs (New Drug Application ,in India) and MAAs (Marketing Authorization Application ,in UK) FDA (in ,USA).

➢**Determines :**

- Comparison of the test drug with the placebo/standard drug. Adverse drug reactions/adverse events are noted.
- Confirm efficacy
- Safety and tolerability
- Adverse drug reactions/adverse events

Phase IV (post-marketing surveillance)

- Post-approval study
- Open label
- No fixed duration

- After approval/post-licensure and post-marketing studies/surveillance studies. Following up on the patients for an exceptionally long time for potential adverse reactions(Pharmacovigilance) and drug-drug interactions, Pharmacoeconomics, Drug utilization studies.

- Periodic safety update report(PSUR) submitted every six month for first 2 year → then annually for next 2 yr.

➢Need for PMS :

1.Unreliability of preclinical safety data

- Well-controlled conditions
- Small and specific sample size

2.Changing pharmaceutical marketing strategies

- Aggressive marketing
- Launch in many countries at a time

3.Changing physician and patient preferences

- Increasing use of newer drugs

4.Easy accessibility

- Easy access by internet
- Increasing conversion of prescription drugs to OTC drugs

- **Schedule Y specifies requirements and guidelines on clinical trials, import and manufacture of new drugs.**

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Thank you