CLINICAL TRIALS

Important (SHORT NOTE)

→ It is a prospective ethically designed investigation on human subjects to objectively discover / verify / compare the results of two or more therapeutic measures (drugs)

Drug development has 3 phase.

Drug discovery phase.
↓
Pre-clinical phase.
↓
Clinical trial phase.

Drug discovery Phase.

- Target centered approach.
- Compound centered approach.

Target centered approach

→ A potential target (receptor / enzyme / protein) involved in a disease process is identified.

Search for compounds that interact with these targets as agonists, antagonists or modulators.

Eg: ACEI for anti-hypertensives, SSRIs for anti depressant action.

Compound centered approach

(1) Natural products as lead compounds
- derived mainly from fungal & plant sources.
eg: penicillin, streptomycin, vinca alkaloids.
- can be used as a starting point for semisynthetic products.

(2) Molecular modifications of known compounds.
Eg: Each generation of cephalosporins is developed from the original molecule.

(3) Analogs of natural ligands:
- Natural ligand of a receptor can be used as starting point for drug development.
Eg: Levodopa precursor of dopamine used in Parkinson's disease.

↓

The LEAD COMPOUND obtained will undergo LEAD OPTIMISATION before introducing it into the pre-clinical phase.

Lead Optimization (modification)

→ It is a stage of drug discovery which aims to increase the potency of the compounds on its target & to optimize selectivity and stability.

more desirable pharmacokinetic or pharmacodynamic effect. properties & less adverse effect.

→ After lead optimization, the obtained lead compound is then subjected to pre clinical evaluation.

Pre-clinical Phase

It is a stage of research that begins before clinical trials (testing in humans) during which important safety data is collected by studying on animals

Importance

→ To determine the safety index, maximum tolerated dose, toxic dose, human equivalent dose.

→ To assess the stability of compound under various route like oral, rectal parenteral.

→ To evaluate the pharmacokinetics & pharmacodynamic effect

Pre clinical studies

Initially done on rodents then on larger animals.

Toxicological studies:

Acute toxicity

Sub-acute toxicity

Chronic toxicity

Special toxicity

↳ effect on reproduction performance.

- Teratogenicity
- Mutagenicity
- carcinogenicity

All pre-clinical studies done under GLP guidelines

Good laboratory practice

All human studies → ICH-GCP guidelines

Good Clinical P

IND (Investigational New Drug).

DCGI → Drug controller General, Govt. of India (New-Delhi)

FDA → USA (food & drug administration)

MHRA → UK.

DCGI → India.

CDSCO & CDA.

Clinical Trial Phase (Questions)

Phase I (Human pharmacology)

Blinding → to reduce bias in participant / researcher/assessment details.

Hiding info from participant/researcher.

3 types:

Single blinding — participant doesn't know

Double blinding — participant and researcher

Triple-blinding -

Phase I - Human pharmacology studies.
Phase II - Therapeutic exploratory phase.
Phase III - Therapeutic confirmatory phase
Phase IV - post - Marketing surveillance.

Phase I

performed in 20-100 healthy human subjects

Phase in which drug is administered 1st time in humans → FIH (First - in human)

→ If drug is expected to have significant toxicity (as in case of anti cancer / AIDS therapy) volunteers with particular disease used rather than healthy

Non-blind or open label type.

Objectives.
1. Estimation of safety & tolerability
2. Determination of PK
3. Assessment of PD.
4. Determine safe clinical dosage range
5. Detect any predictable toxicity

Phase II

100 - 200 people
Studied first time in patients with target disease to determine the efficacy.

Here end point is decided.
Definitive end point → pain relief
Surrogate end point
↳ red^n of tumor size by anticancer drugs.

Phase II A (Early phase)

200 patients.
assess dosing range
single blind study.

Phase II B : (late phase.

200 - 400 patients
to study efficacy
Double blind study design

~~Phase~~ objectives.
→ To explore therapeutic efficacy in patients
→ To define optimum therapeutic dosage.
→ To determine doses & regimen for phase 3 trial.

Phase III

Performed on large scale multicentred (heterogenous) population around 1000 - 5000 + people.
→ To establish safety & efficacy.
→ To minimise errors in info gathered in phase I and II
→ Double blind cross over design.

Objectives.
confirm efficacy
confirm safety profile.

To establish dose - response relationship.

assess benefit/risk relationship to support licensing.

New Drug Application NDA.

NDA applied.
Drug control authorities.
New drug data → enter market

rare side effects
↳ post marketing trial.

every 6 months for first 2 years & then annualy for next 2 years → report.