New Drug Development

Introduction

- Average time to develop new drug is 10 -12 years.
- On an average out of 10,000 – 30,000 potential substances only 1 could make it to the market.
- As per estimates, the cost of bringing a new drug could be upto 2,000 million USD.

Discovery of new drugs:

- **Exercise in prediction of what the new compounds will do in man based on the results of studies in animals**

  Both in vitro & in vivo

- **Two important aspects:**
  - **Selectivity- only the desired effect is obtained**
  - **Dose- quantity that produces desired effect & not the toxic effect**

- **Discovery of new compounds generally proceeds in a logical sequence where the compounds are first tested in animals and if found efficacious and effective they are put to test in man**

STAGES IN NEW DRUG DEVELOPMENT

Synthesis/ isolation of the compound	**1-2 y**
Preclinical studies : screening, evaluation, p/k and short term toxicity testing in animals.	**2-4 y**
Scrutiny and grant of permission for clinical trials	**3-6 M**
Pharmaceutical formulation, standardization of chemical/ biological / immuno assay of compound	**0.5- 1 Y**
Clinical studies : phase I, phase II, phase III trials, long term animal toxicity testing	**3-10 yr**
Review and grant of marketing permission	**0.5-2 Y**
Post marketing surveillance	**Phase IV studies**

The drug development process starts with the synthesis of novel chemical compounds/ similar to existing drugs

OR

Substances with complex structures from various sources

e. g.,

1. **plants (cardiac glycosides)**
2. **animal tissues (heparin),**
3. **microbial cultures (penicillin G)**
4. **cultures of human cells (urokinase)**
5. **by means of gene technology (human insulin).**

As more information about structure–activity relationships obtained, the search for new agents becomes more clearly focused.

Natural Sources

- Plants are the oldest sources of medicine.
- Clues about these have been obtained from traditional systems of medicine prevalent in various parts of the world
- morphine, Ephedra, Cinchona,, belladonna
- Animal parts have been used as cures since early times, e.g. adrenaline, thyroxine, insuiin, liver extract, antisera, etc.

- Few minerals (iron/calcium salts, etc.) are the other natural medicinal substances
- The above natural sources of medicines are by no means exhausted,
- search for new plant, animal and microbial products as drugs is still a productive approach,

Chemical Synthesis

Synthetic chemistry has the largest source of medicines

Randomly synthesized compounds can be tested for a variety of pharmacological activities.

Some useful drugs (barbiturates, chlorpromazine) have been found like this but this approach may not always work

Better to synthesize chemical congeners of natural products/synthetic compounds with known pharmacological activity

- Many families of clinically useful drugs have been fathered by a lead compound but often 'me too' drugs are produced.

- **<u>Structure Activity Relationship</u>: Modification of structures of known drugs to produce more agents having similar basic properties but may show certain improvements**

  e.g. selective Beta agonists (salbutamol) and Beta blockers (propranolol, etc.) have been produced by modifying the structure of isoprenaline

- ✓ **<u>New uses of drugs already in use-</u> Sometimes accidentally or by intelligent observation we might discover a new use of a drug which is already being used for some other indication.**

  e.g. The discovery that aspirin (NSAID) for relief in pain in Rheumatoid Arthritis, also has an anti-platelet action at low doses & can be used for prophylaxis of MI

Chiral compounds

- Pharmacological activity depends on three dimensional interaction of drugs with their target biomolecules
- The enantiomers (R and S forms or d and l isomers) of chiral drugs differ in biological activity, metabolic degradation, etc
- Often only one of the enantiomers is active Single enantiomer drug could be superior to its recemate, because the additional enantiomer may not only be a 'silent passenger' but contribute to side effects, toxicity, etc. or even antagonize the active enantiomer.
- E.g. dextro-dopa is more toxic than levo-dopa

- separate investigation of enantiomers, in case the new drug is a chiral molecule, is required by regulatory authorities

- (S) Atenolol - half dose, better tolerated
- (R) Salbutamol - more active
- Levofloxacin - more active, slower elimination

Newer Techniques of Discovery

Molecular Modeling:

- Advances in protein chemistry and computer aided elucidation of three dimensional structure of key receptors, enzymes, etc. has permitted designing of targeted compounds

  e g. designing of selective COX inhibitors was prompted by the comparative configuration of COX-1 and COX-2 enzyme molecules

- Attempts to produce individualized drugs according to pharmacogenomic suitability.

Combinational Chemistry:

- ✓ Involves random mixing and matching of large numbers of chemical building blocks, e.g. amino acids, nucleotides, simple chemicals, to produce libraries of all possible combinations.

- ✓ These are then tested using automated screening devices that can test thousands of compounds a day. If the record shows a positive response the compound is further tested using traditional laboratory methods

Biotechnology

- Several drugs are now being produced by recombinant DNA technology, e.g human growth hormone, human insulin, interferon, etc.
- use of recombinant DNA technology/ genetic engineering also done to clone and express human genes in certain microbes e.g. E. Coli / yeast cells so that they manufacture proteins that medicinal chemists have not been able to synthesize
- Some monoclonal and chimeral antibodies have also been introduced as drugs

- They also produce hormones autacoids in commercial amounts such as insulin, growth hormone, erythropoietin, cell growth factors, interferons, vaccines, immune antibodies

Genetic Medicines:

Synthetic oligonucleotides which target sites on genes, i.e. DNA sequences or mRNA and block the production of disease related proteins without harming healthy tissues

(future prospects in cancer and viral infections

Gene Therapy:

Gene therapy of human genetic disorders is a strategy in which nucleic acid in the form of DNA is administered inside the cells to modify the genetic composition of the cells so that a protein which was not being synthesized earlier is now synthesized

Problems in delivering the genes inside the cells:

viral vectors, DNA encapsulated in a ribosome

Transgenic animals:

Being developed as models of human diseases e.g. spontaneously hypertensive rats

Preclinical testing

To get Information on biological effects of new substances:

- **AFTER synthesizing or identifying a prospective series of compounds, it is tested on animals to expose the whole pharmacological profile.**
- **Initial screening may employ *Biochemical pharmacological investigations* (e. g., receptor binding assays) or experiments on cell cultures, isolated cells, and isolated organs (In vitro)**
- **Experiments are generally performed on a rodent like mouse, rat, guinea pig, hamster rabbit and then on a larger animal (cat, dog, monkey).**
- **These models can't replicate complex biological processes in the intact organism, any potential drug must be tested in the whole animal (In vivo)**
- **so**

Preclinical studies in animals

Animals used -Mouse, rat, hamster, guinea pig, rabbit, cat, dog, monkey

Following tests are undertaken:

- **Pharmacodynamics:** to explore actions relevant to the proposed therapeutic use, and other effects at a range of doses
- **Pharmacokinetics:** to discover how the drug is distributed in and disposed of by, the body

Only animal experiments can reveal whether the desired effects will actually occur at dosages that produce little or no toxicity.

Toxicological investigations- evaluate the potential for:

(1) **toxicity associated with acute or chronic administration;**

(2) genetic damage (genotoxicity, mutagenicity);

(3) production of tumors (oncogenicity or carcinogenicity);

(4) causation of birth defects (teratogenicity).

Even at the level of preclinical testing, only a few new compounds will prove potentially fit for use in humans.

Pharmaceutical technology provides the methods for drug formulation.

Types of tests

1. Screening test
2. Test on isolated organs, bacterial cultures, etc.
3. Tests on animal models of human disease

   Such as

   kindled seizures in rats,

   spontaneously (genetically) hypertensive rats,

   experimental TB in mouse,

   alloxan induced diabetes in rat

4. General observational tests
5. Confirmatory test and analogus activities.

   Antipyeretic and antiinfammatory activity in an analgesic are tested

Types of tests

6. Mechanism of action: attempts are made to find out the mechanism of action e.g. antihypertensive
7. Systemic pharmacology:

   Irrespective of the primary action of the drug, its effects on major organ systems.
8. Quantitative test:

   maximal effect and comparative efficacy
9. Pharamcokinetics:
10. Toxicity test-in at least 2 animal species

Toxicology:

General

- **to see whether and how the drug causes injury (in vitro tests and intact animals) in:**

  — single-dose studies (acute toxicity)- LD 50, Therapeutic index

  — repeated-dose studies (subacute, intermediate)

  ----chronic or long-term toxicology

Toxicity tests

Acute studies-

LD 50- The dose that is lethal to half the population -50% (*median lethal dose)*

ED50- The dose that is effective in half the population -50%(*median effective dose)*

Ehrlich expressed the *therapeutic index* of a drug in terms of the ratio between the average minimum effective dose and the average maximum tolerated dose in a group of subjects, i.e.

Therapeutic index- (Margin of safety)- Maximum non toxic dose/Minimum effective dose

Also TI= Ratio of LD 50 to ED50 - > 1

High TI- safer at wide range of therapeutic doses- e.g. penicillin

Low TI- potentially toxic- e.g. digoxin

Acute toxicity

Single escalating doses are given to small groups of animals that are observed for overt effects and mortality for 1-3 days.

The dose which kills 50% animals (LD50%) is calculated.

Organ toxicity == histopathology

Subacute toxicity:

- Repeated doses are given for 2-12 weeks depending on the duration of intended treatment in man.
- Doses are selected on basis of ED50 and LD50.
- Animals are examined for overt effects, food intake, body weight, hematology etc. and organ toxicity

Chronic toxicity:

- The drug is given for 6 -12 month and effects are studied as in subacute toxicity.

Special long term toxicity :

On drug which cross phase I clinical trials.

Reproduction and teratogenecity:

effect on spermatogenesis, ovulation, fertility and developing foetus are observed

Reproduction studies

Extensive - because of the diversity of physiological processes that may be affected, and because the consequences of error in this field are potentially horrific.

Tests - effects on fertility, reproductive performance, fetal organogenesis, and peri- and postnatal development.

Most studies are in mammals, usually the rat.

Embryo-fetal development studies are conducted in a non rodent, usually the rabbit.

Later development studies include growth, behaviour and intellectual function of progeny, and their fertility (second generation effects).

Special toxicology-

involves evaluating potential for any horrible drug accident/ adverse effect;

all involve interaction with genetic material or its expression in cell division.

Mutagenicity **(genotoxicity) tests are designed to identify compounds that may induce genetic damage. A standard battery of tests is conducted :**

E.g. A test for gene mutation in bacteria, e.g. Ames test

Carcinogenicity (oncogenicity) tests-

- **often not required before the early studies in man unless there is serious reason to be suspicious of the drug, e.g. if the mutagenicity test is unsatisfactory;**
- **the molecular structure, including likely metabolites in man, gives rise to suspicion;**
- **or the histopathology in repeated-dose animal studies raises suspicions.**

When the preclinical testing is completed to the satisfaction of the developer and of the national or international regulatory agency- ***it is time to administer the drug to man***.

Launch the experimental programme that will decide whether the drug is only a drug or whether it is also a medicine –**clinical phase**

Clinical testing

Phase I

First in Human

studies on **healthy subjects** and seeks to determine whether effects observed in animal experiments also occur in humans.

- **Dose–response** relationships are determined
- Subjects- healthy volunteers, sometimes patients -are

exposed to the drug one by one (total 20-40 subjects), starting with the lowest estimated dose increasing stepwise to achieve the effective dose

<u>Emphasis on safety and tolerability</u>

Phase II- First in Patient

Therapeutic exploration and dose ranging

- conducted by physicians who are trained as clinical investigators
- potential drugs are first tested on **selected patients (**100-400) for therapeutic efficacy in those disease states for which they are intended.
- study maybe blinded or open label -2/3centres
- If a beneficial action is evident, and the incidence of adverse effects is acceptably small, goes to next phase

Phase III – Multicentric

- involves a **larger group of patients** in whom the new drug will be **compared with conventional** treatments in terms of therapeutic outcome.
- As a form of human experimentation, these clinical trials are subject to review and approval by institutional ethics committees according to international codes of conduct (Declarations of Helsinki, Tokyo, and Venice).
- Safety, tolerability and possible drug interactions are assessed on a wider scale, while additional pharmacokinetic data may be obtained.
- During clinical testing, **many** drugs are revealed to be **unusable.**
- Ultimately, **only one new drug** typically remains from some **10000** newly synthesized substances.
- NDA submitted

Approval for marketing

- The decision to **approve a new drug** made by a **national regulatory body** (Food and Drug Administration in the United States.; **Drug Controller General of India**) to which manufacturers are required to submit their applications.
- Applicants must document by means of appropriate test data (from preclinical and clinical trials) that the **criteria of efficacy and safety have been met** and that product forms (tablet, capsule, etc.) satisfy general standards of **quality control.**

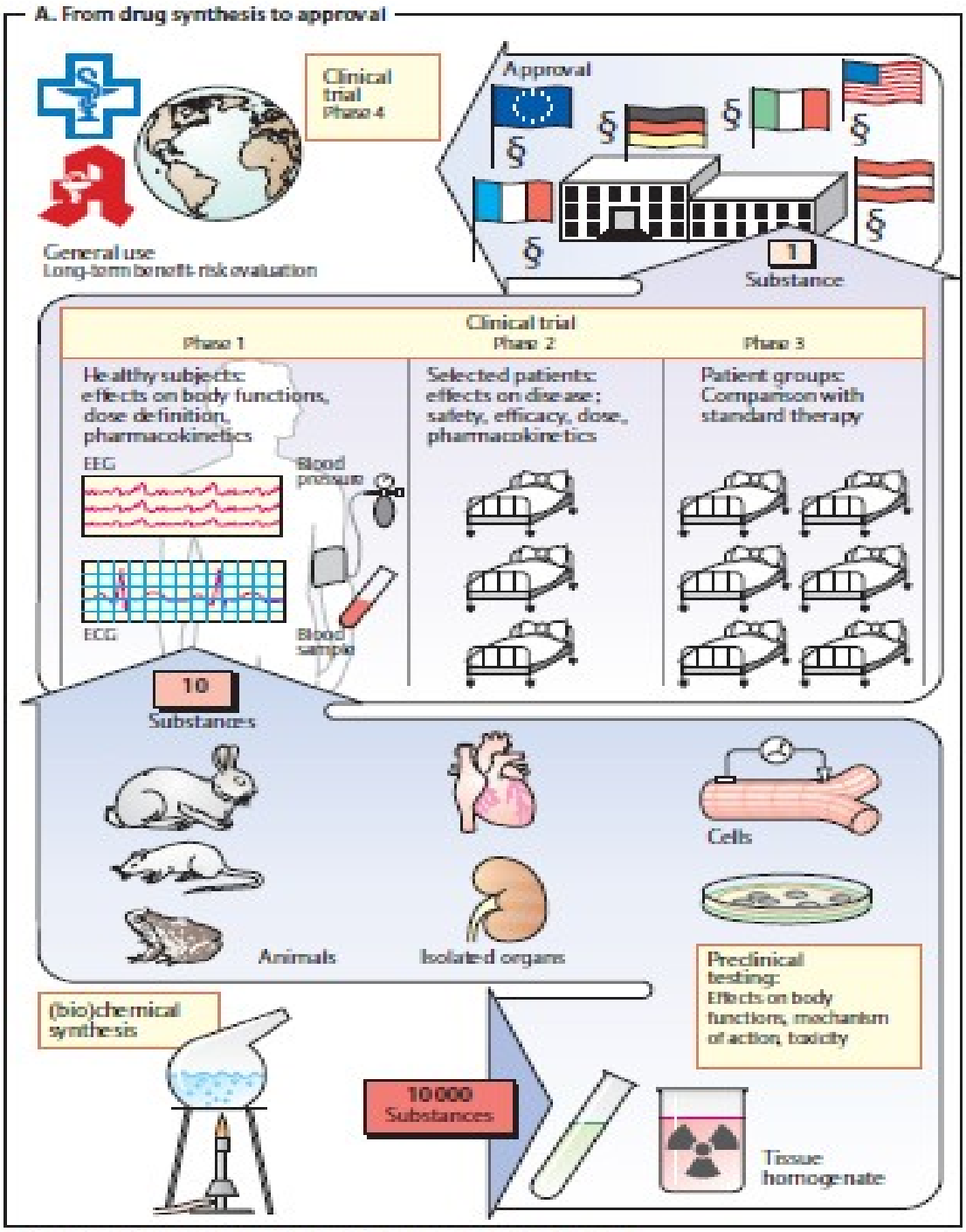
Postmarketing

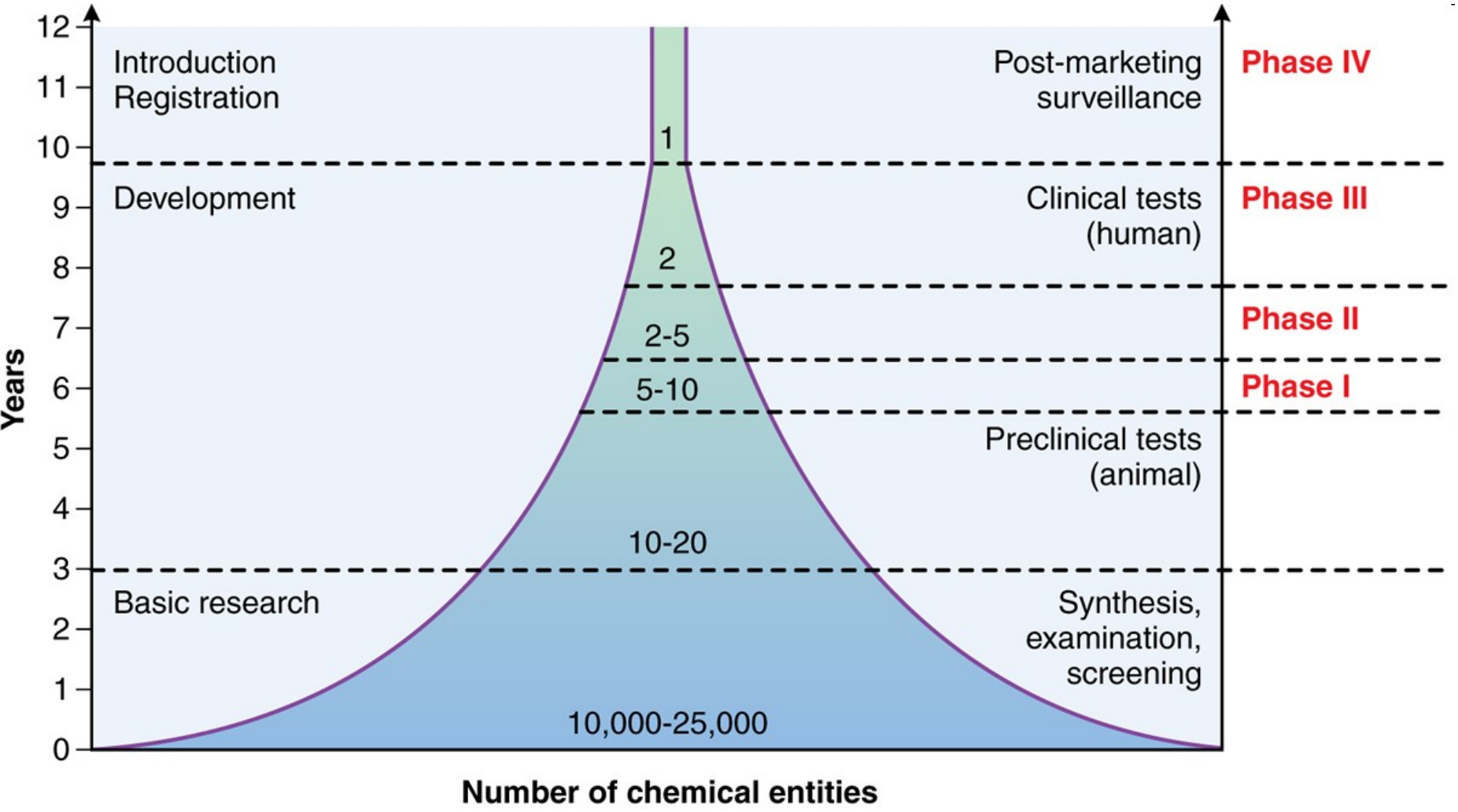
- Following approval, the new drug may be marketed under a **trade name** and thus become available for prescription by physicians and dispensing by pharmacists.
- **Phase IV clinical trials** -As the drug gains more widespread use, regulatory surveillance continues in the form of post licensing studies.

- Only on the basis of long term experience will the **risk–benefit ratio** be properly assessed and, thus, the **therapeutic value** of the new drug be determined.

✘ **Some drugs withdrawn after marketing- e.g. rofecoxib, gatifloxacin**

- If the new drug offers hardly any advantage over existing ones, the cost–benefit relationship needs to be kept in mind


A. From drug synthesis to approval
Clinical trial Phase 4
General use
Long-term benefit-risk evaluation
Approval
1
Substance
Clinical trial
Phase 1
Phase 2
Phase 3
Healthy subjects: effects on body functions, dose definition, pharmacokinetics
Selected patients: effects on disease; safety, efficacy, dose, pharmacokinetics
Patient groups: Comparison with standard therapy
EEG
ECG
Blood pressure
Blood sample
10
Substances
Animals
Isolated organs
Cells
Preclinical testing: Effects on body functions, mechanism of action, toxicity
(bio)chemical synthesis
10000
Substances
Tissue homogenate



The phases, time lines, and attrition that characterize the invention of new drugs.

Characteristics of Phases of the Clinical Trials of new drugs

PHASE I	PHASE II	PHASE III	PHASE IV
First in Human	First in Patient	Multi-Site Trial	Post-Marketing Surveillance
10-100 participants	50-500 participants	A few hundred to a few thousand participants	Many thousands of participants
Usually healthy subjects volunteers; occasionally patients with advanced or rare disease	Patient-receiving experimental drug	Patient/subject-receiving experimental drug	Patients in treatment with approved drug

PHASE I	PHASE II	PHASE III	PHASE IV
Open label may be blinded (can be placebo-controlled);	Randomized & controlled (can be placebo-controlled)	Randomized & controlled or uncontrolled	Open label may be blinded
Efficacy & tolerability	Efficacy & dose ranging	Confirm efficacy in larger population	Adverse events compliance, drug-drug interactions
Months to 1 year duration	1-2 years	3-5 years	No fixed
Success rate: 50%	Success rate: 30%	Success rate: 25-50%	----

A Therapeutic trial (Clinical Trial)

- A carefully and ethically designed experiment with the aim of answering some precisely framed questions.
- It requires:
  - **Equivalent groups of people that means that the two groups which are selected should be very similar to each other in number, age, sex, severity of disease and it's complications**
  - **Treated at the same time and under the same conditions**
  - **Groups should be constructed by random allocation of patients**
- In principle this method is applicable to any disease and any treatment and may be applied on any scale

- This is what is known as a randomized controlled trial. Randomization tries to control biases of various kinds when assessing the effects of treatment

- Random allocation means that the investigator will randomly divide the patients into two groups without being conscious of the fact that he is dividing the patients based on any characteristic

Fundamental requirements of any trial are:

1. An hypothesis- statement/question that the given trial is going to test or analyse
2. Definition of the primary end point- defines the result which the investigator is looking for. This may not be achieved in all patients
3. Method of analysis – defines the statistical test which will tell us if the result obtained is statistically significant or not
4. A Protocol – The written document which will give the details as to how the clinical trial is to be carried out. Includes all details of all type of subjects to be enrolled, method of study, statistical tests and analysis of results

The aims of a therapeutic trial, not all of which can be attempted in a single trial are:

- Whether a treatment is of value
- Magnitude of that value (compared to other treatments)
- The types of patients in whom it is of value
- The best method of applying the treatment (how often and in what dose, if it is a drug)
- The disadvantage and dangers of the treatment

Design of trials

Techniques to avoid bias:

1. Randomization: Randomization introduces a deliberate element of chance into the assignment of treatments to the subjects in a clinical trial. It tends to produce treatment groups that have a balanced distribution of prognostic factors both known and unknown. Together with blinding it helps to avoid possible bias in the selection and allocation of subjects

2. Blinding: The fact that both doctors and patients are subject to bias due to their feelings and beliefs has led to this phenomenon called blinding

Double Blind Technique:

- This is a control device to prevent bias from influencing Results.
- It rules out the effect of hope anxiety of the patient by giving both, the drug under investigation and a placebo of identical appearance in such a way that the subject does not know what he is receiving
- On the other hand it also rules out the influence of preconceived hopes of and unconscious communication by the investigator or observer by keeping him the second blind man ignorant of whether he is prescribing a placebo or an active drug

Non-blind trial: - is an open trial

- Single Blind trial: where subject is blinded but the investigator is aware – sometimes used in research when the double blind procedure is impractical or unethical

Trial Design:

- Prospective trial: begins from the present and continues into the future
- Retrospective trial: study is done of events that have occurred in the past
- Combination: When study starts somewhere in the past and will continue in the future
- Single Patient group design: Only one group of patients which are treated with the same drug throughout the study

- **Cross sectional trials**: short term trials (10 weeks) Patients are usually placed into one/two groups and data obtained from each group is analysed.

  Used for assessment for safety & efficacy

- **Longitudinal trials**: long term (several months or longer) Placebo/active drug controls are seldom used.

  The patient's data is generally compared with their own baseline values to identify changes. Many epidemiological population studies conducted during Phase IV are longitudinal trials

- **Parallel group designs**: Patients randomized into one of the two treatment groups and usually receive the assigned treatment throughout the trial period. It may be either the trial drug or placebo. This is a robust design especially useful in conditions that fluctuate over a short term, e.g. migraine. Disadvantage is usually larger no. of subjects required compared to crossover design

- **Cross over design**:

  Here, each patient receives both treatments and are compared in the clinical trial.

  The advantage of this design is that subject to subject variation is eliminated from treatment comparison so that number of subjects is reduced.

- **In a basic cross over design each subject receives each of the two treatments in a randomized order**
- **The main disadvantage of the crossover design is carry over effects i.e. the residual influence of treatments on subsequent treatment periods.**
- **This can be avoided to some extent by separating treatments with a washout period and lengths based on the knowledge of the disease and the new medication. The crossover design is best suited for chronic stable diseases e.g. Hypertension, chronic stable angina,**

End Point/outcome of Therapeutic investigations:

- Therapeutic effect itself - e.g. sleep, eradication of infection,
- Surrogate effect

  - short term effect that can be correlated with long term therapeutic benefit. E.g. blood lipids, blood glucose, blood pressure, etc.

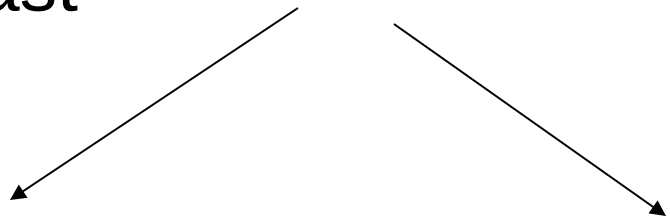
  - This is especially done where it is difficult to measure the therapeutic outcome which may be a good quality life free from disease/disease complications

  - Sometimes a pharmacokinetic parameter may be a surrogate effect e.g. plasma conc. Of a drug

Size of Trials:

- Before the start of any controlled trial it is necessary to decide the number of patients that will be needed to deliver an answer
- For ethical as well as practical reasons- this depends on the magnitude of differences which is desired to be known
- Smaller the difference in the effect to be measured between two treatment groups, larger the sample size required
- This calculation is done by a statistician

- Clinical trial completed
- Data processed
- Analysed
- Interpreted
- Comparison with data obtained from similar trial in the past



- Data extrapolated to a new population New trial planned To evaluate new groups

hypothesis formulated- new trial planned to evaluate hypothesis

Limitations of clinical trials:

Results obtained in clinical trials may not occur in actual practice due to-

- Misdiagnosis
- Poor compliance
- Poor choice of dose interval
- Coincidental development of an undiagnosed/separate illness that may influence results
- Undetected genetic/environmental variables that may modify disease/pharmacological actions of the drug/ or unknown therapy by another physician

Pharmacoepidemiology:

- It is the study of the use & effects of drugs in large number of
- These are part of the Phase IV studies
- They are observational studies that are done when the drug is available for use in the general population
- The groups to be compared are assembled from subjects who are and who are not (the control group) taking the treatment in the ordinary way of medical care
- There are generally two approaches:
    - Observational cohort
    - Case control

Observational Cohort studies:

- ✓ Patients receiving a drug are followed up to determine the outcome.
- ✓ This is a prospective study
- ✓ This type of study is scientifically inferior to a randomised controlled trial
- ✓ This is cumbersome for research on drugs

Case Control Studies:

- ✓ In contrast to Observational cohort studies which are forward looking, case control studies are retrospective or backward looking.
- ✓ The investigator assembles a group of people/patients who have a condition desired to investigate e.g. a group of women suffering from thromboembolism
- ✓ Then a control group of women of similar age group and parity not suffering from this condition is assembled
- ✓ A complete drug history is taken for each group
- ✓ The two groups are followed up backwards to determine the proportion of women in each group that has taken the suspected agent (in this case-OC Pills)

Controlled clinical trial

The classic randomised controlled trial (RCT) is The most secure method for drawing a causal inference about the effects of treatments.

Randomisation attempts to control biases of various kinds when assessing the effects of treatments.

RCTs are employed at all phases of drug development and in the various types and designs of trials

Placebo

- Most patients respond in a positive way to any therapeutic intervention by interested, caring, and enthusiastic doctor.

- The manifestation of this phenomenon in the subject is the **placebo response (Latin, "I shall please")** and may involve objective physiologic and biochemical changes as well as changes in subjective complaints associated with the disease.

- **Placebo**-a tablet or capsule containing inert ingredients that is identical in appearance to the active agent. This inert replica of the drug is designated as a *placebo*

- The magnitude of the response varies considerably from patient to patient and may also be influenced by the duration of the study.
- Placebo adverse effects and "toxicity" also occur but usually involve subjective effects: stomach upset, insomnia, sedation, etc.

- Nocebo- negative response

pharmacovigilance

Refers to the process of identifying and responding to issues of drug safety through the detection of adverse drug effects, in the community

- ✓ Spontaneous reporting by doctors, paramedics, patients
- ✓ Active surveillance

Orphan drugs and diseases

A free market economy is liable to leave rare diseases untreated, e.g.
Some cancers (in all countries) and some common diseases, e.g. parasitic infections (in poor countries).

Where a drug is not developed into a usable medicine because the developer will not recover the costs then it is known as an orphan drug,
and the disease is an orphan disease; the sufferer is a health orphan.

Drugs for rare diseases inevitably must often be licensed on less than ideal amounts of clinical evidence.

The remedy –

- government can undertake drug development
- government offers incentives, e.g. tax relief, subsidies, exclusive marketing rights, to pharmaceutical companies
- in case of poor countries, international aid programmes