

Q. discuss integrated drug development process

DRUG DEVELOPMENT PROCESS

→ Drug discovery is the process of identifying compounds that have potential to become useful new therapies

The following sequence of research activities begins the process that results in discovery of new medicines:

- Target Identification
- Target Validation
- Lead Identification
- Lead Optimization

Drug development phases :- There are three major phases in drug development:

- 1) Pre-clinical research and development
- 2) Clinical research and development
- 3) After the compound is on the market, a possible "post marketing" phase

Approaches of drug discovery

① Pharmacological approach :

→ It's the study of effects of

chemical substances on living system.

Component of pharmacological evaluation:

① Selectivity testing: It involves 2 stages

① Screening for Selectivity:

→ The selectivity of a compound for a chosen molecular target should be assessed because it determines the potency of a drug

② Binding assays:

→ Its aim to determine the dissociation constant of the test compound as a measure of affinity to the receptor

③ Pharmacological Profiling: refers

to determine the pharmacodynamic effect of a new compound

→ It can be either on:

④ in vitro model (study on isolated tissues)

⑤ in vivo models (testing on animals)

→ Testing on animals models of disease can be classified into:

⑥ Acute Physiological and Pharmacological models

⑦ Chronic

⑧ Genetic models

⑨ Safety Pharmacology: is the

evaluation of study of potentially life

threatening pharmacological effects of a potential drug which is

unrelated to the desired therapeutic

effect and therefore may present

a hazard

→ These tests are conducted at doses not too much in excess of the intended

clinical dose

② Toxicological approach:

→ It is very important for the development of new drug.

various toxicological studies

② Acute toxicology: (single dose study)

→ It is the toxicity produced by pharmaceutical when it is administered in one

→ It should be carried out at least on two species usually mice and rats

→ mortality should be checked after 2 hours after parenteral route and upto 7 days after oral administration

③ Subacute studies (Repeated dose study)

→ To determine toxicity after repeated administration of the test material

→ It lasts for 14 to 40 days

→ 2 species are required

→ It is conducted to determine the safety margin and to identify the target organ

④ Chronic toxicity studies (Repeated dose studies)

→ one rodent and one non-rodent species are required.

→ The test compound is administered over more ~~than 90 days~~ ~~test substances~~

→ It provides inference about the long-term effect of a test substance

⑤ Local toxicity studies:

→ They are required when the new drug is proposed to be used in humans

→ species like guinea pigs or rabbits are used. (4)

→ The drug is applied to an appropriate site to determine local effect of that

② Allergenicity / Hypersensitivity + Toxicology Studies

⑧ Genotoxicity studies

⑨ Reproduction studies

⑩ Fertility studies

⑪ Teratogenicity studies

⑫ Prenatal studies

⑬ Carcinogenicity studies

⑭ IND application:

→ IND application is submitted by the company which is responsible for developing the drug to FDA
→ It is submitted after animal studies showed the drug being safe for use in human

→ types:

① Investigator IND: It is submitted by a physician who initiated and conducts an investigation

② Emergency use IND: It allows FDA to authorize use of an experimental drug in emergency situation

③ Treatment IND: Done for the drug who claims to treat serious life threatening disease

→ There are two & IND categories:

④ Commercial

⑤ Non-commercial

④ Drug characterization:

→ When the candidate molecule shows promise as a therapeutic, it must be characterized

→ molecule size, shape, strengths and weakness, preferred conditions for maintaining function, toxicity, bioactivity and bioavailability must be calculated

⑤ Dosage form :

→ one of the initial in the drug development process is to select a desirable product profile and create dosage form that fits well the product and disease

→ This profile is based on the

physicochemical characteristics of the active ingredient, disease-related issues, how the product will be used by providers and patient and market place issues

→ If a product can not be orally absorbed or is entirely metabolised by first pass effect through

Q. explain pre-clinical trials

Pre-clinical trials :

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The pre-clinical phase represents bench (in vitro) and then animal testing, including kinetics, toxicity and carcinogenicity. In the U.S., an investigational new drug application (IND) is submitted to the Food and Drug Administration seeking permission to begin the heavily regulated process of clinical testing in human subjects. The clinical research (IND) phase representing the time from beginning of human trials to the new drug application (NDA) submission that seeks permission to market the drug is by far the longest portion of the drug development cycle and can last from 2 to 10 years. Phase I trials, sometimes called, "first in human" trials, are generally conducted on relatively small groups (typically 10 to 30) of healthy volunteers (except for oncology drugs or other potentially toxic compounds) in specialized units resembling small hospitals with 20 to 50 monitored beds. The "inpatient" portion of Phase I trials usually lasts from a day or two to a week (though follow up can last up to about a month), and are designed to assess the safety of a compound and study its pharmacokinetics and pharmacodynamics.

Assuming a compound is shown to be safe for healthy subjects and survives Phase I, then development proceeds to a series of Phase II trials. These trials typically enroll anywhere from about 20 or 30 patients up to a few hundred at most. These patients usually have relatively "pure" form of the disease for which the drug is intended. In other words, they suffer from as little other intercurrent disease as possible, and the list of concomitant medications they can be taking is usually restricted. For example, patients with newly diagnosed, but untreated, diabetes, with no evidence of end organ damage, would be used to test a new

DRUG DEVELOPMENT PROCESS**INTRODUCTION :**

The entire process of taking a newly discovered compound or drug through regulatory approval to the point of marketing.

During the development, the new drug of the compound should adhere to high standards in the conduct analysis and interpretation of preclinical and clinical studies for its smooth passage through the regulatory approval phase and eventually to marketing. The drug discovery and drug development process is designed to ensure that only those pharmaceutical products that are both safe and effective are brought to market.

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antidiabetic agent. Phase II trials tend to last only a few weeks to, at most, a few months. Initial Phase II trials (sometimes called, IIa) are pilot trials to determine dose range.

They tend to be conducted at specialized centers, like university medical centers, by specialized investigators, such as medical school faculty. For example, patients with newly diagnosed, but untreated, diabetes, with no evidence of end organ damage, would be used to test a new antidiabetic agent. Phase II trials tend to last only a few weeks to, at most, a few months. Initial Phase II trials (sometimes called, IIa) are pilot trials to determine dose range. They tend to be conducted at specialized centers, like university medical centers, by specialized investigators, such as medical school faculty. Phase III trials are conducted on larger group of population. Phase IV trials which are called as Post-marketing phase trials are conducted after the drug has been introduced into the market.

Q. Explain different pharmacological action study in drug development process.

APPROACHES OF DRUG DISCOVERY :**Pharmacological Approach:**

The first step in the process of drug discovery is to identify a molecular target that is associated with a particular disease. The next step is to establish that modulation or intervention of the function of the chosen target is associated with a reversal of the disease process. The research in integrative cell signaling and neuroscience programs in the Department of Pharmacology offers a wealth of novel molecular targets to consider for therapeutic intervention. Once a particular target is selected, a number of

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approaches may be taken to modulate or interfere with the biological function. These approaches might include the use of small molecules or protein biologicals such as monoclonal antibodies that alter biological activity. These efforts are aided by the Yale West Campus screening facilities: High Throughput Cell Biology (HTCB) that offers screening with RNAi and the Small Molecule Discovery Center that provides access to libraries of unique small molecules. We work closely with the Structural Biology program in Pharmacology to obtain the detailed three-dimensional structure of the target along with novel ligands as lead compounds that affect function. Structural biology also assists in lead optimization to obtain candidate compounds that are suitable for further investigation. Possible candidate molecules are further examined in preclinical studies and the most promising compounds would ultimately be examined in clinical trials in humans. Our department offers a number of courses to provide an understanding of how the drug discovery process works from the identification of molecular targets and therapeutic candidates to the design of clinical trials in humans.

As compounds progress through the Athersys tier system, we have obtained information related to compound specificity, selectivity, half-life and disposition in animals, toxicological properties, and efficacy in disease models. Athersys has applied a rigorous pharmacological testing, including testing for effects on liver enzymes, specific cardiac channels, and a large number of unrelated targets where interactions might be problematic. In addition, the company has evaluated the effects of compounds on animal behavioral endpoints, organ pathology and cardiovascular

Q. explain toxicological approach to drug development phase

function to further increase confidence that a compound will be safe and efficacious.

Toxicological Approach:

Although basic toxicology parameters will have been assessed in lead optimization series of in vitro and in vivo studies will be performed in the development phase, usually to registration standards and protocols, in order to fully determine the toxicity profile and therapeutic index, maximum doses for safe administration etc. These will usually be performed in at least two species and should determine both specific (mechanism related) and non-specific (chemical) side effects which could limit the safe dose which can be used in man. If the mechanism is human specific and doesn't occur in man these studies will be limited to non-specific toxicology with ex-vivo human studies etc being implemented to assess the mechanism related effects. The duration and number of dose levels used in these studies will be determined by the drug exposure, length and protocols of the proposed initial (Phase I/II) clinical studies in man.

Studies will also be performed to assess the broader safety effects such as behavioral and physiological effects in vivo.

For the most part, the current approaches to toxicity testing and safety assessment rely on a complex array of traditional studies that evaluate observable outcomes in whole animals, such as clinical signs or pathological changes that are indicative of a disease state. As noted by MacDonald and Robertson, "The approaches that have been taken to assess human risk of

adverse effects from chemical exposure have changed very little over the last several decades." For example, "The global regulatory requirements for registration of new human pharmaceutical chemicals—the data requirements have changed very little since their establishment three and sometimes four decades ago despite the dramatic advances in the sciences that are used for this activity."

1. Most of the toxicology tools used for regulatory assessment rely on high-dose animal studies and default extrapolation procedures, and have remained relatively unchanged for decades, despite the scientific revolutions of the past half-century.
2. Indeed, when the FDA released its strategic plan in August 2011, the need to modernize toxicology to enhance product safety was the first of eight science priority areas identified

Drug Evaluation:

It is recognized that drug candidates with drug-like properties are more likely to make it to market. Thus, drug-like property assessment has been integrated into the current drug discovery and development process.

Research has shown that these physico-chemical properties are closely related to drug's absorption, distribution, metabolism and excretion (ADME). They, together play important roles in the absorption and bioavailability of drug candidates. Early assessments of these properties in drug discovery can help

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(f) Genotoxicity studies

(g) Reproduction studies

(h) Fertility studies

(i) Teratogenicity studies

(j) Prenatal studies

(k) Carcinogenicity studies

Q. Discuss various drug characterization techniques in drug development process

Clinical Research

Drug Discovery and Development

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Drug Discovery and Development

project teams find potential PK issues, optimize chemical series and avoid promoting "problematic" compounds to development

Drug Characterization involves finding of biological and physiochemical properties of potential drug molecules.

❖ Biological Characterization

Interaction of drug molecule with Biological systems

Ex- Receptor binding, Enzyme inhibition

❖ Physiochemical Characterization

Physical and chemical characteristics of potential drug

Ex- Solubility, PKa

X-ray, NMR, IR, UV-VIS, MS, PET

❖ Biological Characterization:

It is needed to assess whether the molecule will likely work in humans.

Goals :

1. To find Efficacy
2. Assess Toxic Effects

Further Divided into

- A. Biochemical Assay
- B. Cellular Assay
- C. System/Whole Animal assay

A. Biochemical Assay

- > Mechanism of action at molecular level
- > Receptor binding assay's (Affinity and selectivity)
- > Metabolic Processing

B. Cellular Assay

- > Cellular Cultures: Cell penetration Receptor activity, Transport
- > Isolated Tissues : Effects on specific tissues, Possible toxicity
- > Liver tissues : Drug metabolism drug interaction

C. System/Whole animal Assay

- > Rat, Mouse : Toxicity, LD50, Organ-Specific efficacy
- > Dog, Rabbit, Guinea pig, Monkey -
- > Pharmacokinetics/Dynamics, BA, Toxicity.
- > Lab Animal Models for disease: Efficacy and toxicity

② > Physiochemical Characterization

Physical and chemical properties of a drug are critical for knowing how it can be formulated/stored/administered

- > Solubility
- > PKa
- > Partition coefficient: Octanol: water
- > Stability

Q. explain the importance of dosage form design in pre-clinical and clinical stages

- > Chemical Structure: Mass Spectroscopy, NMR, X-Ray
- > ~~Crystallography~~
- > Impurities : TLC, HPLC, GC, Mass Spectroscopy
- > Polymorphism

Dosage form:

→ one of the initial in the drug development process is to select a desirable product profile and create dosage form that fits well the product and disease

→ This profile is based on the Physicochemical characteristics of the active ingredient, disease-related issues, how the product will be used by providers and patient and market place issues

→ If a product can not be orally absorbed or is entirely metabolised by first pass effect through liver, then it's not a good candidate for an oral dosage form

Developmental Assessment Supporting Drug Candidate Selection

- Profiling of key Physicochemical Properties
- Biopharmaceutical Assessment

Pre-formulation

- Solubility, Stability, Dissolution Rate and Solid State

Properties

- Salt and Form Screening and Selection
- Excipient Compatibility

Dosage Form Design

- Conventional
- Non-Conventional

- Formulation Development, Evaluation and Scale-up

Dosage form Design: Evolution of Dosage Form Needs

- Preclinical (Toxicology) Dosage Forms
- Biopharmaceutics
- Emphasis is on Exposure, High Drug Concentration
- Suspensions (NaCMC), Drug/Feed Mixtures
- Specialized Forms (Yogurt)
- Absorption, Distribution, Metabolism, Elimination

Phase I Clinical Dosage Forms

- Biopharmaceutics - Simple, Flexible Dosing
- Single/Multiple Dose Tolerability Studies, Healthy Volunteers
- Efficacy Marker - Proof of Concept, Attrition Curve
- Solutions, Powder-in-a-Bottle, Hard Gelatin Capsules

Phase II Clinical Dosage Forms

- Biopharmaceutics, Physico-Chemical, Processing - Larger, Longer Studies
- Patients, Dose Finding and Proof of Concept
- Blinded Capsules or Tablets

Biopharmaceutical

- Mechanism of Action, Target Organ, Dose (Potency) Permeability (Passive, Active, Efflux)
- Pharmacokinetics
- Absorption, Distribution, Metabolism, Elimination

What is IND, different criteria for IND IND (Investigational new drug application)

The US FDA Investigational New Drug (IND) program is the means by which a pharmaceutical company obtains permission to ship an experimental drug across state lines (usually to clinical investigators) before a marketing application for the drug has been approved. The FDA reviews the IND application for safety to assure that research subjects will not be subjected to unreasonable risk. If the application is cleared, the candidate drug usually enters a Phase 1 clinical trial.

Criteria:

- New indication
- Change in the approved route of administration or dosage level
- Change in the approved patient population (e.g. pediatric) or a population at greater or increase of risk (elderly, HIV positive, immunocompromised)
- Significant change in the promotion of an approved drug

Types:

1. Regular IND:
 - An Investigator IND is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction, the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.
2. Emergency IND:
 - Emergency Use IND allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND.
3. Treatment IND:
 - Treatment IND is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place

When to use IND applications:

1. Drug intended to treat or diagnostic serious or life threatening condition
2. No satisfactory alternative available.
3. Controlled clinical trials in progress under IND or when trials completed & FDA review of request to market as pending
4. Sponsor actively pursuing device marketing approval with FDA
5. Need FDA authorization to use experimental drug in an emergency situation that does not allow time for submission of an IND

6. May be used for patients ineligible per existing study protocol (s), or if approved study protocol does not exist

Categories:

- Commercial
- Research (non-commercial)

IND application contents:

1. Cover sheet/ application form
 - Required for initial IND & all subsequent submissions
 - Provides basic info about Sponsor & submission contents
 - Must be signed & dated
 - obligates sponsor to comply with laws and regulations
2. Table of contents
3. Introductory statement
 - drug name, structure, pharmacological class, development history
4. General investigational plan
 - Summary of studies anticipated in first year
 - Study rationale
5. Investigator brochure
 - Package insert
 - Early version contains more clinical data
 - Later version more heavily weighted with clinical area
6. Protocols
 - Must include at least initial protocol (No subjects, Eligibility requirements)
7. Chemistry, manufacturing and control info
8. pharmacology & toxicology info
9. previous human experience with drug
10. Additional information as required by FDA
 - Drug dependency/abuse potential
 - Radioactive drugs
 - Pediatric drugs

Write a note ADME profiling (5 mark)

➤ ADME is an abbreviation in pharmacokinetics and pharmacology for "absorption, distribution, metabolism, and excretion," and describes the disposition of a pharmaceutical compound within an organism.

Absorption:

- For a compound to reach a tissue, it usually must be taken into the bloodstream before being taken up by the target cells.
- Factors such as poor compound solubility, gastric emptying time, intestinal transit time, chemical instability in the stomach, and inability to permeate the intestinal wall can all reduce the extent to which a drug is absorbed after oral administration. Absorption critically determines the compound's bioavailability.

Distribution:

- Distribution is defined as the reversible transfer of a drug between one compartment to another.
- The compound needs to be carried to its effector site, most often via the bloodstream. From there, the compound may distribute into muscle and organs, usually to differing extents. After entry into the systemic circulation, either by intravascular injection or by absorption from any of the various extracellular sites, the drug is subjected to numerous distribution processes that tend to lower its plasma concentration. factors: regional blood flow rates, molecular size, polarity and binding to serum proteins, forming a complex.

Metabolism:

- Compounds begin to break down as soon as they enter the body. The majority of small-molecule drug metabolism is carried out in the liver by redox enzymes, termed cytochrome P450 enzymes. As metabolism occurs, the initial compound is converted to new compounds called metabolites. When metabolites are pharmacologically inert, metabolism deactivates the administered dose of parent drug and this usually reduces the effects on the body. Metabolites may also be pharmacologically active, sometimes more so than the parent drug.

Excretion:

- Compounds and their metabolites need to be removed from the body via excretion, usually through the kidneys (urine) or in the feces. Unless excretion is complete, accumulation of foreign substances can adversely affect normal metabolism.
- The kidney is the most important site and it is where products are excreted through urine.
- Biliary excretion or fecal excretion is the process that initiates in the liver and passes through to the gut until the products are finally excreted along with waste products or feces.
- The last main method of excretion is through the lungs (e.g. anesthetic gases).

Q. Explain inclusion and exclusion in selection of clinical trial subject

Inclusion and exclusion criteria

- In a clinical trial, the investigators must specify inclusion and exclusion criteria for participation in the study
- Inclusion criteria characteristics that the prospective subjects must have if they are to be included in the study, while exclusion criteria are those characteristics that disqualify prospective subjects from inclusion in the study.
- Inclusion and exclusion criteria may include factors such as age, sex, race, ethnicity, type and stage of disease, the subject's previous treatment history, and the presence or absence (as in the case of the "healthy" or "control" subject) of other medical, psychosocial, or emotional conditions.
- Defining inclusion and exclusion criteria increases the likelihood of producing reliable and reproducible results, minimizes the likelihood of harm to the subjects, and guards against exploitation of vulnerable persons.
- Example of inclusion criteria for a study of chemotherapy of breast cancer subjects might be an postmenopausal women between the ages of 45 and 75 who have been diagnosed with Stage II breast cancer. An exclusion criterion for this study might be abnormal renal function tests, if the combination of study drugs includes one or more that is nephrotoxic.
- Inclusion and Exclusion criteria are a very important aspects of clinical research. It helps the researcher to take the precise decisions while including the subjects, thereby eventually impacting the analysis and interpretation of results in clinical research.
- Inclusion criteria provide a set of principles to screen potential candidates that could be included in a clinical research study. The inclusion criteria may differ for diverse studies
- Inclusion of the patients widely depends on factors like:
 - The purpose of the study
 - Trial Design
 - Methodology
 - Subject demography-age, gender, occupation etc.
 - Rationale for involvement of subjects like pregnant women's, fetus, Children's and prisoner who may be considered vulnerable candidate
- The process or the criteria that excludes certain group of people to be included in clinical research.
- Exclusion criteria widely depend on the following factors:
 - The literature on the basis of sex/gender, race, and ethnicity
 - Sample Size
 - Feasibility of study
 - Research Purpose

Q Explain the role of BPOs in conducting clinical research in India?

- Role of business process outsourcing (BPO) market comprises services offered by Contract Manufacturing Organizations (CMOs) and Contract Research Organizations (CROs) to the biotech pharmaceutical companies.
- A rise in demand for low-cost drugs, patent expirations and uncertain economic conditions have compelled the pharmaceutical players to take support of various outsourcing services. This support has facilitated pharmaceutical players to streamline their value chain and focus more on its core strategies. Pharmaceutical companies are now forming long term partnership with the CROs and CMOs to share the costs involved in drug discovery to post marketing approvals. Moreover, they are also leveraging CROs and CMOs expertise such as use of novel technologies, trained staff and previous experiences for effective outcomes.
- The research report on life sciences BPO provides detailed analysis of the global market and helps in understanding the driving forces responsible for the growth of this market. The report discusses the market of life sciences BPO on the basis of different CRO and CMO services. The CRO services comprises clinical data management, monitoring, medical writing, regulatory services, pharmacovigilance, bio-statistics, drug discovery and pre-clinical tests. The CMO services include API manufacturing, Finished Dosage Formulation development and manufacturing and Packaging.

Q. explain phase 1 and phase 2 clinical trial

PHASE I

- Its also called as study of human pharmacology
 - First stage of testing in human subjects.
- Objective:
- Designed to assess the safety, tolerability of the drug over a wide range of doses
 - Study on the drugs PK and PD of properties
 - A sequence of single dose is used, the dose range is determined from animal toxicology test
-
- Method:
- These experiments determines the maximum tolerated dose or non toxic effect level
 - subjects are 20-80 healthy volunteers.
 - The subjects are divided into groups and the experimentation starts with the group assigned to the lowest dose often the dose escalation randomized design is used
 - studies are kept under very close observation repeatedly questioned regarding the onset of undesired signs or symptoms
 - The volunteers undergo repeated sampling of biological fluids, in order to build the p'kinetic profile of the drug under investigation.
 - If the researcher are satisfied with the Safety and tolerability of the first dose, they move to the dose immediately above it, then to the third dose and so on.
 - The study ends when either a dose presenting side effects considered unacceptable or the highest dose is reached.

PHASE II

- It is a Therapeutic Exploratory Trial consists of 20-300 Subjects.
- performed on patients affected by the disease and study.
- Generally the patient selected criteria for phase II are more restrictive compared to phase III, in the sense that subjects with serious or atypical forms of the disease and those with concomitant disease or laboratory abnormalities are generally excluded.
- objectives:**
 - Prove that the drug is active on relevant dynamic endpoint.
 - select the doses and the frequency of administration for the phase III.
 - Objective safety and tolerability data.

Phase II is divided into II A and II B

II A

Aimed to assess drug requirement. How much of the drug should be given.

II B

Aimed to assess drug efficacy. How well drug works at the prescribed dose.

Phase II A

- proof of concept studies II A is useful for dealing with an innovative compound.
- Aims to confirm mechanism of action.
- It is based only in "proofs" in vitro and animal models.
- The sample is rigorously selected in that subjects with a "pure" text book like clinical picture are included.
- The chosen dose is the highest that can be administered based on phase I results.
- The proof of concept studies are generally small and complex.

Advantage:

- the drug does not show a sufficient pharmacodynamic action, it is possible to discontinue.

PHASE II B (SPECIAL STUDIES)

- Dose finding or dose-ranging studies.
- It includes:
 - studies in elderly patients
 - Studies comparing different races
 - Studies in patients with hepatic and renal insufficiency
 - Studies evaluating interactions between the new drug and other drugs of common use in the disease under study.

Disadvantage:

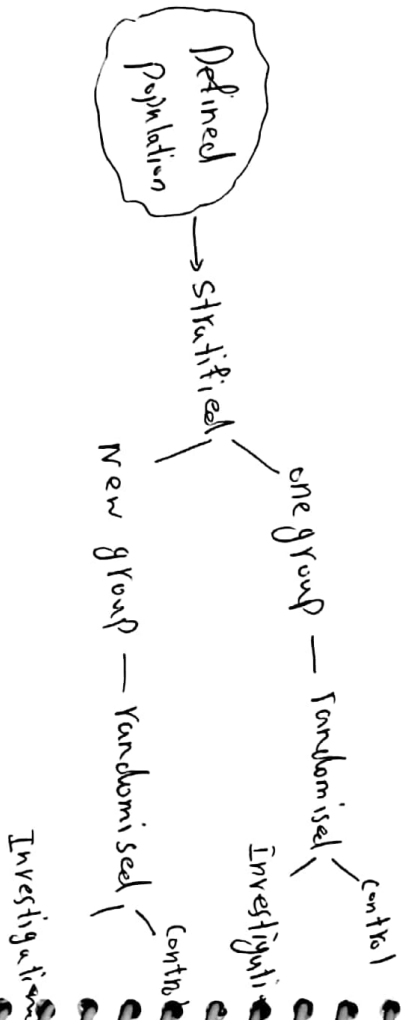
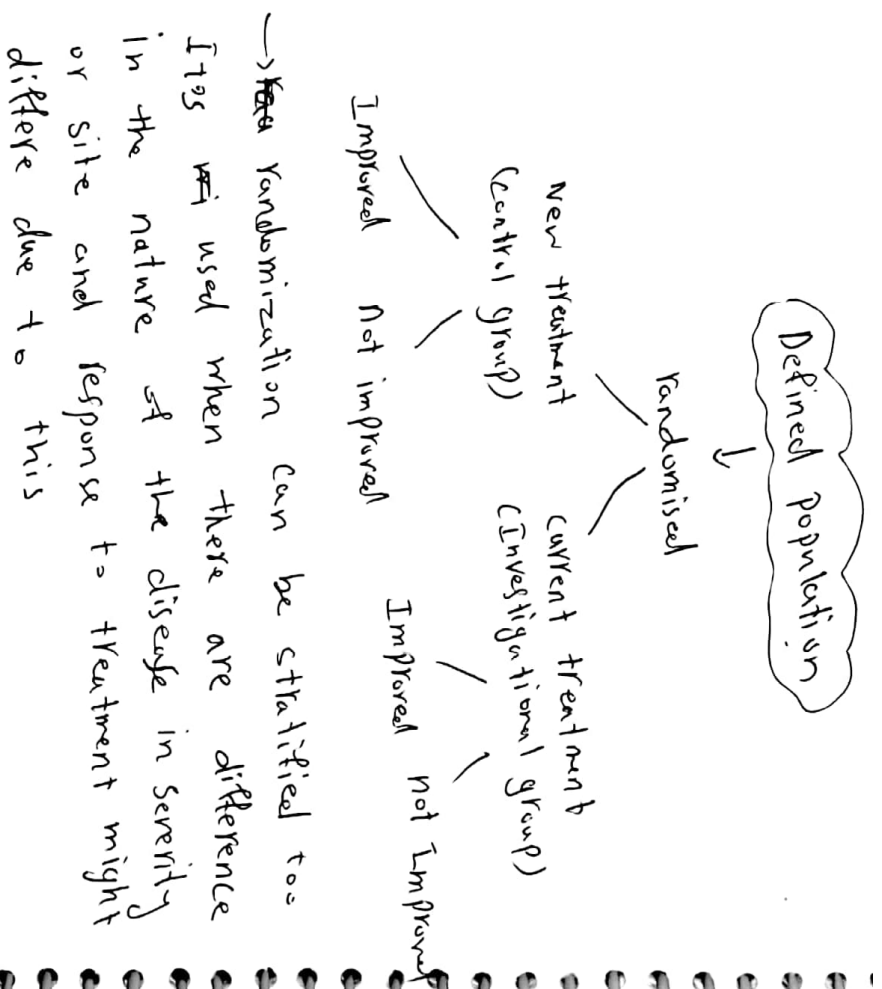
Q. Clinical trial study design (statistical design)

→ clinical trial may fail to achieve its aim without a good design. before a clinical trial may proceed, it will undergo numerous reviews that will include a review of a trial design and applicability of the design to the situation

i) Randomization design

→ It is a process that assigns research participants by chance rather than by choice to either the investigational group or the control group. It prevents selection bias and insures against accidental bias

→ phase III trial are randomised clinical trial and some phase II CT may also be randomised participants have the equal chance of being assigned to either of the group



ii) Blinding design

→ It's important means of reducing risk of bias in study

a) Single blinding

→ It's a study design where the treatment assignment is not known by the study participant

b) double blinding

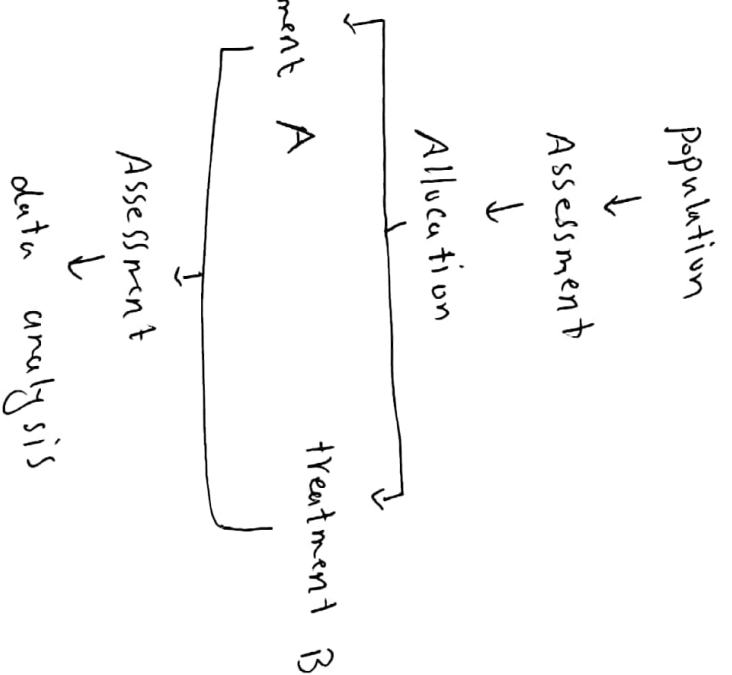
→ when both the investigational and study participant are unaware of the treatment assignment

c) Triple blinding

→ when investigator, study participant and sponsor staff are unaware of the treatment assignment

→ It's imp to maintain blinding throughout the trial to maintain the validity of the trial data

iii) Parallel design



iv) Cross over design

→ It's a study design where each subject will receive a course of each treatment under study

v) Factorial design

→ when patient are being treated with a combination of drug (as in HIV) a new drug may be evaluated by testing it in combination with other drugs rather than by

Itself

Elements to be considered during clinical

trial design

① Types of control:

- control may be an untreated group or a group receiving an active treatment or a placebo. The choice of the comparator is influenced by objective of the study

② volunteer or subject selection

→ It's imp to carefully define the patient population from which the study participant will be drawn, early phase II is restrictive

③ number of subject

→ The size of the trial is influenced by the disease to be investigated, the subjectives of the study, study endpoint

(73)

④ Influence of the disease/indication on trial design

→ The onset and progression of the disease will affect the duration of trial, the timing of each subject treatment and number and timing of assessments

8. objective of phase 1/2/3/4

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PHASE III

- Therapeutic Confirmatory
- phase III are randomized controlled multicenter trials on large patient groups (300-3000) or more depending upon the disease/medical condition studied.
- Phase III has two key goals:
 - 1. To demonstrate the therapeutic efficacy of the drug in representative a sample of the population at which the treatment targeted.
 - 2. To demonstrate the safety and tolerability of the drug in a large sample of the population at which the drug is targeted.

PHASE IV

- Methods of post-marketing surveillance.
 - 1 > descriptive study:
 - Case report
 - Case series
 - 2 > analytical studies:
 - Case-control
 - Case-cohort
 - Cross-sectional
- Also called as safety surveillance.
- Purpose:
 - Detect any rare or long-term ADR in large population are large period of time that in not possible in phase 1-3.
 - Harmful effects discussed by phase IV may result in drug being no longer sold or restricted to certain use.
 - Continue CT initiated in phase III.

Methods of Randomization

- Randomization methods are used to randomly assigned participants to either a treatment group or a control group.
- Randomization means that participants have an equal chance of being allocated to different treatment groups. This method increases statistical power and meets the assumption of equipoise in the randomly allocated groups.

Methods:

1. Simple randomization:

- Study participants are randomly assigned to equally sized treatment groups.
- In experimental research designs, simple randomization means randomly assigning study participants to treatment groups so that each group has the same number of participants. Equally allocating study participants to treatment groups maximizes statistical power.
- If there are 50 (N) number of subjects, the treatment plans are divided equally ie, 25(n1) and 25 (n2). Such that $n1+n2 = N$. The envelopes with the treatment plans are labelled and shuffled. The order of the envelopes give the order of treatment of subjects.

2. BLOCK RANDOMIZATION:

- Randomly assign study participants to treatment groups in small blocks of four or six.
- Block randomization is commonly used in the two treatment situation where sample sizes for the two treatments are to be equal or approximately equal. The process involves recruiting participants in short blocks and ensuring that half of the participants within each block are allocated to treatment "A" and the other half to "B".

of. Difference between phase 2a and 2b

PHASE II

- It is a Therapeutic Exploratory Trial consists of 20-300 Subjects.
 - performed on patients affected by the disease and study.
 - Generally the patient selected criteria for phase II are more restrictive compared to phase III, in the sense that subjects with serious or atypical forms of the disease and those with concomitant disease or laboratory abnormalities are generally excluded.
- objectives:
- Prove that the drug is active on relevant dynamic endpoint.
 - select the doses and the frequency of administration for the phase III.
 - Objective safety and tolerability data.

Phase II Study/ Clinical trial

Phase II Types:

- Phase II A: Designed to assess dosing requirements
- Phases IIB: Designed to study efficacy

Phase IA	Phase IB
EARLY PHASE	LATE PHASE
Pilot clinical trials	Pivotal clinical trials
20-200 PATIENTS	50-300 PATIENTS
Not multicentric	Multicentric
SINGLE BLIND comparison with a standard drug	DOUBLE BLIND compared with a placebo or standard drug

3. STRATIFICATION:

- Randomly assign study participants across strata to represent prognostic characteristics.
- A stratification factor is a categorical covariate which divides the patient population according to its levels e.g.
 - sex, 2 levels: Male, Female
 - age, 3 levels: <40, 40-59, ≥ 60 years
- The most important part of using stratified randomization is choosing the correct variable(s) by which to stratify study participants and randomly assign them. Stratified randomization is a strong deterrent of confounding in applied research.

4. Unequal allocation randomization:

- Randomly assign study participants to unequally sized treatment groups.
- is a method of randomly assigning study participants to treatment groups in a disproportionate fashion. Unequal allocation randomization is used when the intervention, itself, is the focus of the experiment. Essentially, you want more people to receive the treatment so that treatment effects will be more precise and accurate. Ratios of allocation of 2:1, 3:1, and 4:1 to the treatment group are acceptable. The effect of unequal allocation "plateaus" at the 4:1 level. When used with experimental research designs, unequal allocation randomization is used to study more serious disease states that require stronger treatments. The side effects of promising treatments can also be studied using unequal allocation.

Case-Control Study

→ A study that compares patient who have a disease or outcome of interest (cases) with patient who don't have the disease or outcome (control) and look back retrospectively to compare how frequently the exposure to a risk factor is present in each group is determine the relationship between risk factor and the disease.

→ Case and control must be comparable with respect to known confounding factors such as age, sex, occupation.

→ The case control studies are widely used to assess the safety of medicine.

→ Data from case control studies are used to calculate an odds ratio which is the ratio of the odds of

Developing the disease for exposed patient to the odds of developing the disease for unexposed patients

suspected or risk factor	Cases (disease present)	Control (disease absent)
present	a	b
absent	c	d

→ if it's our intention to test the hypothesis that cigarette smoking cause lung cancer using the case control method, a group of lung cancer cases (a+c) and a group of suitably matched control (b+d)

→ if $\frac{a}{(a+c)} > \frac{b}{(b+d)}$ an association

is said to exist between smoking and lung cancer

Advantages

- easy to conduct
- inexpensive
- no risk to subject
- Require comparatively few subjects
- ethical problems minimal
- Allow the study of several different etiological factors

Disadvantages

- selection of an appropriate control group may be difficult
- we cannot measure incident records
- bias may occur during obtaining past records
- Not suited to the evaluation of therapy or prophylaxis of diseases

g. Difference between Retrospective and Prospective study

① Prospective Study

- A prospective cohort study or current cohort study is one in which the outcome (eg disease) has not yet occurred at the time the investigation begins
- , most prospective studies begin in the present and continue into future

eg: uranium mine employee and
chance of lung cancer

② Retrospective study:

→ A retrospective cohort study of
historical cohort study is one in
which the outcomes have all occurred
before the start of the investigation

→ The investigator goes back in time
sometime 10 to 30 years to select
his study group from existing records
of past employment medical or
other records and traces them forward
through time from a past date fixed
on the records usually up to present

Q. Observational Studies

→ It's a study in which a
researcher simply observes behaviour
in a systematic manner without
influencing or interfering with the
behaviour

Different observational studies:

- ① Case control
- ② Cohort study
- ③ cross sectional study

Case Control Study

→ A study that compares patient who have a disease or outcome of interest (case) with patient who don't have the disease or outcome (control) and look back retrospectively to compare how frequently the exposure to a risk factor is present in each group is determine the relationship between risk factor and the disease

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	a+c	b+d

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Cohort Study

- Cohort study ~~the~~ are studies that identify subsets of define population and follow them over time, looking for difference in their outcome
- Cohort study generally used to compare exposed patient to unexposed patient although they can also be used to compare one exposure to another.

- The term cohort is define as the group of people who share a common characteristics or experience within the defined time period eg: Age, occupation, exposure to drugs, vaccine, pregnancy

Indication:

- when there is good evidence of an association between an exposure and disease confirmed by case control studies (11)

→ when exposure is rare but the incidence of disease high among exposed

cohort	yes	no	total
exposed to putative etiologic factor	a	b	a+b
not exposed to putative etiologic factor	c	d	c+d

Types:

① prospective study

→ A prospective cohort study or

current cohort study is one in which the outcome (eg disease) has not yet occurred at the time the investigation begins

→, most prospective studies begin in the present and continue into future

eg: uranium mine employee and chance of lung cancer

② Retrospective study:

→ A retrospective cohort study or historical cohort study is one in which the outcomes have all occurred before the start of the investigation

→ The investigator goes back in time sometime 10 to 30 years to select his study group from existing records of past employment medical or other records and traces them forward through time from a past date fixed on the records usually up to & present

③ Combined:

→ in this type of study the retrospective and prospective elements are combined ⑬

→ The cohort is identified from the past records and is assessed of date for the outcome, the same cohort is followed up prospectively in to future assessment of outcome

Advantages:

- incidence can be calculated
- It provides direct estimate of relative risk
- Odds response ratio can also be calculated

Disadvantages:

- studies involve a large no of people
- It takes long time to complete the study
- expensive

→ may cause harm / risk to the patient
→ certain administrative problem such as loss of experienced staff, loss of finding

Cross section studies

- It also known as instantaneous studies, simultaneous study or prevalence study
 - These are studies of use of drugs at the specific point of time and are conducted through surveys, data base analysis or medication chart review
 - They help the collection of data on a cross section of population which may comprise the whole population
 - This types of studies provides information about the situation that exist at a single time
- Population
- disorder < exposed
not disorder < not exposed

Advantage:

- Study can be short term
- Relatively inexpensive to conduct
- It can only measure disease prevalence rather than incidence
- They can provide a wealth of data that is much used in health system research

Disadvantage:

- No direct estimate of risk and the scope for bias
- It's not possible to establish temporality

Q. Write note on meta analysis

Meta analysis

➤ Meta-analysis is the statistical procedure for combining data from multiple studies. When the treatment effect (or effect size) is consistent from one study to the next, meta-analysis can be used to identify this common effect. When the effect varies from one study to the next, meta-analysis may be used to identify the reason for the variation.

Purposes

- To establish statistical significance with studies that have conflicting results
- To develop a more correct estimate of effect magnitude
- To provide a more complex analysis of harms, safety data, and benefits
- To examine subgroups with individual numbers that are not statistically significant

Advantages

- Greater statistical power
- Confirmatory data analysis
- Greater ability to extrapolate to general population affected
- Considered an evidence-based resource

Disadvantages

- Difficult and time consuming to identify appropriate studies
- Not all studies provide adequate data for inclusion and analysis
- Requires advanced statistical techniques
- Heterogeneity of study populations

meta analysis models:

① Fixed effect model: It provides a weighted average of a series of study estimates. ~~the estimated variation is commonly used as study weight~~

② Random effects model: It is used to synthesize heterogeneous research is the random effects model of meta analysis

~~ADVERSE DRUG REACTIONS~~

Q. write a note on ANDA

Clinical Research

ANDA

ABBREVIATED NEW DRUG APPLICATION (ANDA)

Introduction:

"ANDA" is the abbreviation for "Abbreviated New Drug Application". It contains data which when submitted to FDA's Center for Drug Evaluation & Research, Office of Generic Drug, provides for the review & ultimate approval of a generic drug product.

Once approved an applicant may manufacture & market the generic drug product provided all issues related to patent protection, safe, effectiveness, low cost alternative to the public. Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical (animal) & clinical (human) data to establish safety & effectiveness. A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics & intended use.

All approved products, both innovator & generic, are listed in FDA's Approved Drug Products with Therapeutic Equivalence Evaluations.

Generic applicants must scientifically demonstrate that their product is bioequivalent (i.e. performs in the same manner as the innovator drug). The rate of absorption or bioavailability of the generic drug, is compared to that of the innovator drug.

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The generic version must deliver the same amount of active ingredients into a patient's bloodstream in the same amount as that in the innovator drug. Using bioequivalence as the basis for approving generic copies of the drug products was established by the "Drug Price Competition & Patent Term Restoration Act of 1984", also known as the Waxman-Hatch Act.

At the same time, the branded name companies can apply for up to five additional years longer patent protection for the new medicines they developed to make up for time lost while their products were going through FDA's approval process. Generic drug application reviewers focus on bioequivalence data, chemistry & microbiology data, request for plant inspection, & drug labeling information.

ANDA Requirement:

1. **Signed FDA form 356h.** Provides information regarding the applicant's name & address, name of the drug product, the product strength & route of administration, indication of drug master files cited, proposed indications, a statement regarding whether the product is for prescription or over the counter.
2. An index should specify volume & page number for each complete & detailed item.
3. **Information on the basis for which the ANDA is being submitted.**

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- a) Name of the reference drug, its dosage form & strength.
 - b) Information on exclusively for the listed drug.
 - c) If a suitability petition is approved a reference to the FDA number that was assigned to that suitability petition.
4. **Condition for use, including,**
- a) A statement regarding the condition for which the drug will be used.
 - b) A reference to the annotated labeling for the product & the currently approved labeling for the listed drug product.
5. A statement that active ingredient is the same as for that of the reference drug. For the combination product this must be shown for both active ingredients.
6. **Route of administration, dosage form & strength.** This should include a statement that the route of administration, dosage form & strength are same as the reference drug.
- Bioequivalence:** This should include information to demonstrate that the proposed drug is bioequivalent to the listed drug product.
7. **Labeling:** Include a copy of currently approved labeling for the listed drug as well as the proposed labeling for the drug being provided for in the ANDA. A side by side comparison of two sets of labeling is also necessary.
8. **Chemistry, Manufacturing & Controls:** Describe the composition, manufacture, specifications & analytical procedures for the drug substance & drug product.
9. **Human Pharmacokinetics & Bioavailability:**

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This include information concerning

- The Design
- The Dosing procedure
- The number & frequency of blood & urine collection & Methodology for the assay

10. Samples: The sample of the Drug substance & finished product should be provided four individuals units with sufficient quantities in each unit to permit the FDA to perform all the tests included in the specifications at least three times

11. Analytical method for drug substance & drug product. This section should consists of the specifications, analytical method, certificates of analysis, method of analysis, method validation & stability indicating data as contained in the chemistry, manufacturing & control part of the application.

12. Labeling. 12 specimen of the final printed label & all labeling for the drug product are to be included.

13. Case report forms & tabulations. The need for these should be discussed with appropriate personnel of the division of bioequivalence prior to submission of the ANDA.



We got more than just Notes..

- ➡ Educational Videos
- ➡ Power Point Presentations
- ➡ Case Studies
- ➡ Quiz and Assignments
- ➡ Question Banks
- ➡ Infographs and Pictograms

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Q. write note on ICH-GCP guideline

ICH-GCP guidelines (International Conference on Harmonization)

- ICH-GCP is an international Conference on Harmonization Good Clinical Practice
- the guideline was developed with consideration of the current good clinical practices of the European Union Japan, and the United States as well as those of Australia, Canada, the Nordic countries and the world health organization.
- The ICH was developed in April 1990, hosted by the European Federation of Pharmaceuticals Industries and Association (EFPIA) in Brussels

SPONSORS AND REGIONS of ICH-GCP: Members

- EMEA: The European medicines agency.
- EFPIA: European Federation of Pharmaceutical Industries Association.
- PhRMA: Pharmaceutical Research and Manufacturers of America.
- JMHW: Japanese Ministry of Health Welfare
- JPhMA: Japanese Pharmaceutical Manufacturers Association

OBJECTIVE:

- To provide a unified standard for the European Union (EU), Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.
- To identify and then to reduce differences in technical requirements for drug development among regulatory agencies

AIMS:

- Unify registration requirements for new products
- reduce medicinal product development cost more economic use of animal, human and material resources.
- Accelerate medicinal product licensing times: avoid repeat testing in different regions.
- increase patent protection times through reducing delay in licensing times.

Principles:

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if anticipated benefits justify the risks.
3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
4. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
5. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB) / independent ethics committee (IEC) approval / favourable opinion.
6. The medical care given to, and medical decisions made on behalf of subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
7. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
8. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
9. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

10. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
11. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
12. Systems with procedures that assure the quality of every aspect of the trial should be implemented

Q. essential documents in conducting clinical trial

ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL

- > Essential Documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements.
- > Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor and monitor. These documents are also the ones which are usually audited by the sponsor's independent audit function and inspected by the regulatory authority as part of the process to confirm the validity of the trial conduct and the integrity of data collected.
- > The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated: 1) before the clinical phase of the trial commences, 2) during the clinical conduct of the trial, and 3) after completion or termination of the trial. A description is given of the purpose of each document, and whether it should be filed in either the investigator/institution or sponsor files, or both. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable.
- > Trial master files should be established at the beginning of the trial, both at the investigator/institution's site and at the sponsor's office. A final close-out of a trial can only be done when the monitor has reviewed both investigator/institution and sponsor files and confirmed that all necessary documents are in the appropriate files.
- > Any or all of the documents addressed in this guideline may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority.

DRUG INTERACTION MONITORING				
1 NO. & NO.	2	3	4	5
1782	Acetaminophen	Methotrexate	moderate	increase the risk of liver injury
1781	ticlopidine	clopidogrel	ANTAGONISM	reduce the effects of clopidogrel in helping to prevent heart attacks or strokes

CDSO Guideline (central drug standard control organization)

➤ The Central Drugs Standard Control Organization (CDSCO) is the national regulatory body for Indian pharmaceuticals and medical devices, and serves parallel function to the European Medicines Agency of the European Union, the PMDA of Japan and the Food and Drug Administration of the United States.

Steps:

I. Application for permission:

form	items	appendix
Pharmaceutical and chemical info	2	1
Animal pharmacology data	3	1,4
Human clinical pharmacology	5,6,7	1
Regulatory status in other country	9,2	1
Animal toxicology data	4	1,3
Full prescribing info (dose, dosage form, composition, ADR)	10	1

II. Clinical trials:

- a. **Approval Clinical Trial**
 - Clinical trial on a new drug shall be initiated only after the under permission has been granted by the licensing authority under rule 21 (b) and the approval obtained from the respective ethics committee)
 - All trial investigator(s) should possess appropriate qualification training and experience and should have access to such investigational and treatment facilities as are relevant to the proposed trial protocol
 - protocol amendments if become necessary before initiation or during the course of a clinical trials, all such amendments should be notified to the licensing authority
- b. **responsibilities of sponsor**
 - The clinical trial Sponsor is responsible for implementing and maintaining quality assurance systems to ensure that the clinical trial is conducted and data generated, documented and reported in compliance with the protocol and Good Clinical Practice (GCP) Guidelines)
 - Sponsors are required to submit a status report on the clinical trial to the Licensing Authority at the prescribed periodicity.
- c. **responsibilities of investigator**
 - The Investigator(s) shall be responsible for the conduct of the trial according to the protocol and the GCP Guidelines)
 - Standard operating procedures are required to be documented by the investigators for the tasks performed by them.
- d. **informed consent**
 - In all trials, a freely given, informed, written consent is required to be obtained from each study subject. The Investigator must provide information about the study verbally as well as using a patient information sheet, in a language that is non-technical and understandable by the study subject)
 - Where a subject is not able to give informed consent the same may be obtained from a legally acceptable representative
- e. **responsibilities of the ethics committee**
 - It is the responsibility of the ethics committee that reviews and accords its approval to a trial protocol to safeguard the rights, safety and well being of all trial subjects.)
- f. **human pharmacology (phase I)**
 - The objective of studies in this Phase is the estimation of safety and tolerability with the initial administration of an investigational new drug into human(s). Studies in this Phase of development

usually have nontherapeutic objectives and may be conducted in healthy volunteers subjects or certain types of patients.)

g. therapeutics exploratory trials (phase II)

- The primary objective of Phase II trials is to evaluate the effectiveness of a drug for a particular indication or indications in patients with the condition under study and to determine the common short-term side-effects and risks associated with the drug)
- An important goal for this Phase is to determine the dose(s) and regimen for Phase III trials.

h. therapeutics confirmatory trials (phase III)

- Phase III studies have primary objective of demonstration or confirmation of therapeutic benefit(s). Studies in Phase III are designed to confirm the preliminary evidence accumulated in Phase II that a drug is safe and effective for use in the intended indication and recipient population.

i. post marketing trials (phase IV)

- Post Marketing trials are studies performed after drug approval and related to the approved indication(s).
- These trials may not be considered necessary at the time of new drug approval but may be required by the Licensing Authority for optimizing the drug's use.

III. Study in special population:

- Pediatrics
- Geriatric
- Pregnant or lactating women
- People with specific diseases

Q. What are medical devices? classify with example

Medical Devices

➤ As per USFDA An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them, intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.

Classification:

Classification by USFDA:

- **Class-I (Low Risk):**
 - Class I medical devices have the least amount of regulatory control. Class I devices present minimal potential harm to the user. devices are typically simple in design, manufacture and have a history of safe use.
 - Eg: Elastic bandages . Examination Glove, Adult Incontinence Pad, tongue depressors, arm slings, and hand-held surgical instruments.
- **Class -II (Medium Risk):**
 - Class II medical devices are devices where General Controls are not sufficient to assure safety and effectiveness and existing methods/standards/guidance documents are available to provide assurances of safety and effectiveness.
 - Eg: Catheter Cannula, Dialyzer . Piston syringe , Needle, Infusion Pumps, Bone fixation screw, Blood pressure Kit

- **Class-III (High risk):**

- Class III medical devices have the most stringent regulatory controls. For Class III medical devices, sufficient information is not available to assure safety and effectiveness through the application of General Controls and Special Controls. Class III devices usually support or sustain human life, are of substantial importance in preventing impairment of human health, or present a potential unreasonable risk of illness or injury to the patient. Typically a Pre-Market Approval (PMA) submission to the FDA is required to allow marketing of a Class III medical device.
- Eg: Pacemakers, Dental Lasers, Heart Valves

Classification by CDSO:

- **Class A (Class-I)**– Devices involving low risk levels (Thermometer)
- **Class B (Class-II a)**– devices involving low to medium risk (Hypodermic Needle)
- **Class C (Class-II b)**– Devices involving moderate to high risk (Lung ventilator)
- **Class D (Class-III)**– Devices involving high risk. (Heart valve, implantable device)

Q. Write note on Clinical Study Report

Clinical Study Report

- It is a full length detailed document containing the new drug therapeutic efficacy, safety data for an individual study with a therapeutic or diagnostic agent

Structure of a full Clinical Study Report according to the International Conference on Harmonization of Technical Requirements:

1. Title Page

- Study Title
- Name of test drug/investigational product
- Studied indication, study design
- Sponsor name and address
- Protocol identifier
- Dates of initiation, early termination, termination, completion of the study

2. Synopsis

- Synopsis summarizes the study in brief.

3. Table of Contents

- for the individual clinical study report This section contains the table include summary tables, figures and graphs.

4. List of Abbreviations and Definitions of Terms

5. Ethics

- Independent Ethics Committee,
- Patient information and consent

6. Investigators and Study Administrative Structure

- Contains:
 - The administrative structure of the study,
 - Principal investigator,
 - Coordinating investigator,
 - Steering committee,
 - Administration,
 - Monitoring and evaluation committees

7. Introduction

> Contains:

- Context of the development of the test drug/investigational product.
- Relating the critical features of the study to that development.

8. Study Objectives

- A statement describing the overall purposes of the study should be provided.

9. Investigational Plan

- Overall study design and plan – Description
- Discussion on study design and choice of control groups
- Selection of Study Population
- Treatments
- Efficacy and Safety Variables
- Data Quality Assurance

10. Study Patients

- Disposition of Patients
- Protocol Deviations

11. Efficacy Evaluation

- Data Sets Analyzed
- Demographic and other baseline characteristics
- Measurements of treatment compliance
- Efficacy results and tabulations of individual patient data
- Adjustments for Covariates

12. Safety Evaluation

- Extent of exposure (dose, duration, number of patients)
- Most common adverse events, laboratory test changes etc.
- Serious adverse events and other significant adverse events

13. Discussion and Overall Conclusions

- The efficacy and safety results of the study and the relationship of risks and benefit

14. Tables, Figure and Graphs Referred to But Not Included in the Text

15. Reference List

- A list of articles from the literature pertinent to the evaluation of the study

16. Appendices

- This section should be prefaced by a full list of all appendices available for the study report.

17. PREMATURE TERMINATION OR SUSPENSION OF A STUDY

- > If the trial is terminated prematurely or suspended for any reason and the termination or suspension presents an immediate threat to the health or welfare of participants, the researcher will promptly inform the participants and the IRB. If the termination or suspension does not present an immediate threat to the health or welfare of participants, the researcher should notify the IRB to get approval of any information to be given to participants. The research must provide appropriate therapy and follow-up to participants, and, where required should inform the sponsor.
- > If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the IRB. The IRB and the Office of Sponsored Programs should be provided a detailed written explanation for the termination or suspension. If the suspension is lifted the investigator should notify the IRB in writing.
- > If the sponsor terminates or suspends a trial, the investigator should promptly inform the Office of Sponsored Programs and the IRB and provide the IRB a detailed written explanation of the termination or suspension. If subjects were enrolled locally in the study, a final progress report must also be submitted to the IRB. If the suspension is lifted the investigator should notify the IRB in writing.
- > If the IRB terminates or suspends a study, the investigator should notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension. Any action taken to suspend or terminate a study must be reported to OHRP and the sponsor within thirty (30) days of the action. If the study involved a regulated drug, device or biologic, a report will be sent to FDA. When the PI has adequately addressed the concerns of the IRB the IRB may lift the suspension on the research. If the concerns are not addressed, the IRB may terminate the research or take other action in order to protect the health and welfare of the participants.

Selection and recruitment of Study Subjects (5 mark)

- The investigator is responsible for ensuring the unbiased selection of an adequate number of suitable subjects according to the protocol. It may be necessary to secure the co-operation of other physicians in order to obtain a sufficient number of subjects. In order to assess the probability of an adequate recruitment rate for subjects for the study it may be useful to determine prospectively or review retrospectively the availability of the subjects. Investigator should check whether the subject(s) so identified could be included in the study according to the protocol. The investigator should keep a confidential list of names of all Study Subjects allocated to each study. This list facilitates the investigator / institution to reveal identity of the subject(s) in case of need and also serve as a proof of Subject's existence. The investigator / institution shall also maintain a Subjects' screening log to document identification of Subjects who enter pre-study screening. A Subject's enrolment log shall also be maintained to document chronological enrolment of Subjects in a particular Study.
- The investigator is responsible for giving adequate information to subjects about the trial in accordance with the GCP. The nature of the investigational product and the stage of development and the complexity of the study should be considered in determining the nature and extent of the information that should be provided.

Challenges in the implementation of guidelines

Challenges are of two types:

1. TECHNICAL BARRIERS FOR IMPLEMENTATION OF ICH GCP REGULATIONS.
2. POLITICAL BARRIERS FOR IMPLEMENTATION OF ICH GCP, REGULATION.

1. Technical challenges:

Four major categories of players can be identified in the ICH GCP arena:

1. The health authorities,
2. The academic institution,
3. The clinical investigators,
4. and the pharmaceutical industry.

Patients & the public as the ultimate recipients of the benefits (or failures) of the ICH GCP process, constitute an important 5th party although not directly participating in the implementation or control of the process.

Some of these common barriers are personnel's knowledge, facility, equipment and finances.

The most common and consistent barrier to different degree across countries is the lack of sufficient personnel in all player categories. Health authorities usually complain about the shortage of competent medical & paramedical professionals to evaluate protocols & related documentation, the shortage of quality compliance inspectors, and the scarcity of auxiliary personnel.

Lack of insufficient knowledge/know-how and training at academic & clinical investigators levels (ethic committee, institutional review board), cumbersome bureaucratic implementation process in starting/conducting clinical studies, and lack of GCP training program.

2. Political challenges:

- 1) Lack of or insufficient legislative/regulatory frame work.
- 2) The most frequent areas of noncompliance include: ethics committee, institutional review board (IRBS), composition and practices, informed consent, issued content, process, signature and dating, investigator dedication of authority, unreliable, excessive dedication, clinical monitoring, non existing adequate reporting of ADR, infrequent, and/or inefficient).

2. Clinical trials for vaccines

➤ A vaccine trial is a clinical trial that aims at establishing the safety and efficacy of a vaccine prior to it being licensed.

Development of vaccines can be simplified into two broad stages:

1. **Pre-clinical development** is research carried out in lab assays and on animals. It includes:
 - Identification of relevant antigens (e.g. screening)
 - Creation of the vaccine concept
 - Evaluation of vaccine efficacy in test tubes and animals
 - Manufacture of the vaccine to Good Manufacturing Practice standards
2. **Clinical development** is when the vaccine is first tested in humans. It covers four stages over several years, from initial clinical trials in humans (phase I) right through to introduction and beyond (phase IV). Clinical development is built on rigorous ethical principles of informed consent from volunteers, with an emphasis on vaccine safety as well as efficacy.
 - a) Phase I clinical trials are small-scale trials to assess whether the vaccine is safe in humans and what immune response it evokes. For diseases of poverty this covers trials in European volunteers (phase Ia) and then in populations in Developing Countries (phase Ib).
 - b) Phase II clinical trials are larger and look mainly to assess the efficacy of the vaccine against artificial infection and clinical disease. Vaccine safety, side-effects and the immune response are also studied.

c) Vaccines that progress to phase III clinical trials are studied on a large scale of many hundreds of subjects across several sites to evaluate efficacy under natural disease conditions. If the vaccine retains safety and efficacy over a defined period, the manufacturer is able to apply to the regulatory authorities for a licence to market the product for human use.

d) The final phase IV happens after the vaccine has been licensed and introduced into use. Also called post-marketing surveillance, this stage aims to detect rare adverse effects, as well as to assess long term efficacy.

Design and statistical consideration:

- Safety studies:** the studies should be randomized and controlled. Follow up safety should be actively monitored and planned.
- Immunogenicity:** The main objective of comparative immunogenicity study is to rule out the difference between response to study vaccine and a control.
- Efficacy:** Endpoint used to evaluate efficacy could range from disease incidence to well established marker with activity.
- Statistical Considerations:** Stratified – Randomization may be recommended. For sample size, the FDA requires that sample size calculation for each study endpoint should be performed

Pregnant women as research participant

Research involving pregnant women, fetuses and human in vitro fertilization are subject to special federal regulations that guide IRB deliberations on such studies.

Research studies involving **pregnant women or fetuses** can be approved by the IRB if the following requirements of federal regulations are satisfied:

- Preclinical studies have been conducted, including studies on pregnant animals; clinical studies, that include non pregnant women and provide data for assessing potential risks to pregnant women and fetuses
- Risk to fetus is caused solely by interventions or procedures that hold prospect of direct benefit for the woman or the fetus or,
- If no benefit, risk to the fetus is not greater than minimal and the research develops important biomedical knowledge not obtainable by any other means.
- Any risk is the least possible for achieving the objectives of the research.
- Individuals engaged in the research will have no part in: 1) any decisions as to the timing, method, or procedures used to terminate a pregnancy, and 2) determining the viability of the fetus at the termination of the pregnancy; and
- No inducements, monetary or otherwise, will be offered to terminate the pregnancy.

Drug research using pregnant women as subjects is governed by federal regulations. Stanford University considers it prudent to apply these requirements to clinical research involving pregnant women, as follows:

"No pregnant woman may be involved as a subject in a human clinical research project unless (1) the purpose of the research is to meet the health needs of the mother and the fetus will be placed at risk only to the minimum extent necessary to meet such needs, or (2) the risk to the fetus is minimal."

{Research involving the use of pregnant women as subjects} may be conducted only if the mother and father are legally competent and have given their informed consent after having been fully informed regarding possible impact on the fetus, except that the father's informed consent need not be secured if (1) the purpose of the research is to meet the health needs of the mother; (2) his identity or whereabouts cannot reasonably be ascertained; (3) he is not reasonably available; or (4) the pregnancy resulted from rape."

q. explain ethical guideline for clinical research

General Ethical Principles

→ All research involving human subject should be conducted in ~~accordance~~ accordance with three basic ethical principles;

① Respect for the persons incorporated at least two fundamental:

a) Respect for autonomy
b) protection of persons with impaired autonomy

② Beneficence refers to the ethical obligation to maximize benefits and minimize harms

③ Justice refers to the ethical obligation to treat each person in accordance with morally right and proper to give each person what is due to him or her

The Guidelines (Ethical guidelines)

Guideline 1 (Ethical justification and scientific validity of biomedical research)

→ Research is said to be ethically justified if it protects rights and safety is fair to

all the subjects and is mutually acceptable in the community in which it's carried out
→ research is said to be scientifically valid if it present with the aim of providing benefits to the individual, locality and medical profession

Guideline 2 (Ethical Review committee) (ERC)

- investigator should present the detailed protocol to ERC
- ERC members and research team must be un-related
- CR shall be initiated only if ERC permits to do so
- any financial help or what so ever should not change ERC's decision

Guideline 3 (Ethical review of externally sponsored research)

- externally sponsoring organization and investigator should submit the detailed protocol for ethical review in sponsoring country
- ethics/laws in the sponsoring country must be as strict as that of investigators

Guideline 4 (Individual informed consent)

- It's a voluntarily obtained approval from the individual/subject to get enrolled in the proposed CR

- investigator should obtain IC
- waiver may be applied

Guideline 5 (obtaining informed consent)

- Approach subject
- explain the purpose/Aim of study, foreseeable risk and benefits
- compensation for the loss
- in a language that is understood by subject
- obtain IC form legally authorised relation if subject is impaired

Guideline 6 (obtaining informed consent: obligation to sponsor and investigator)

- They should refrain from intimidation false influence or using the subject
- Re-consent

Guideline 7 (Inducement to participate)

- Normally all the subject and indirectly related persons will be compensated for their loss, loss of time energy in case of worsen health
- they will be reimbursed for their financial loss
- Reimbursement/health facilities must not be so good/high induced subject

- ERC

Guideline 8 (Benefit and risk of the study participants follows the beneficence principle)

- before conducting research investigator must ensure

that potential benefits and risk are reasonably balanced

→ Risk are minimised

→ any interventions made should benefit at least subjects

Guideline 9 (Research in population or community with limited resources)

→ Investigator / sponsor must make sure that the limited available resources are enough to conduct the research according to its proposed protocol

→ if any new knowledge invented new tools introduced during the notice of subject ethically / morally accepted!

Guideline 10 (Choice of Control in CR)

→ Sponsor / investigator should selectively choose the control group who are going to receive (EET)

→ therapeutic / preventive intervention made must be according to EET intervention

→ placebo / no treatment

→ when to give: (i) when EET is not readily available

(ii) withdrawal from EET ~~preclude~~ produced temporary damage, when relief from the side effect of EET is slow

Guideline 11 (Study in children)

→ The treatment procedures / interventions can't be made as like with adults

→ only enrolled if the purpose of research is to obtain info. regarding the children health by drug - therapy for child?

→ permission granted by parents / child's legal representative

→ consent given by child free will

→ children has right to continue / leave study process when desired

Guideline 12 (Study in population with mental disorder)

→ only enrolled if the proposed / aim of study is to see how drug actions or to gain info about mental health

→ consent given by parent / legal representative Justice

Guideline 13 (Research involving vulnerable population)

vulnerable: prone to get affected / harmed

→ consent seeking should explain about the risk that are certain to occur

→ They should be treated / handled in a special way so that risk may be decreased

→ compensation / reimbursement

Guideline 14 (Research involving children)

• investigator should ensure that:

→ The purpose of the research is to obtain the knowledge and info about health - care needs of children

→ The research might not equally will be carried out with ~~adults~~ Adults

→ consent has been obtained from parents / legal

- representation
- child decision to refuse or withdraw from study shall be respected

Guideline 13 (Research involving individual who due to mental/behaviour disorder can't give adequate consent)

- The purpose of the research is to obtain the knowledge and info about health-care needs of individual with ^{disorder} behaviour
- the research might not equally will be carried out with ~~people~~ other normal people
- consent has been obtained from parents/legal representation
- subject decision to refuse or withdraws from study shall be respected

Guideline 14 (Research involving women)

- The sponsor investigator and ethical review committee shall not limit women of child bearing age from participating in the research
- The change of fertile women of getting pregnant during the course of study shall not limit them
- The sponsor investigator before enrolling the fertile women in the study make sure that pregnancy test is done and access to the appropriate contraceptive method is introduced to women

Guideline 15 (Research involving pregnant women)

- The investigator should ensure that:
 - The purpose of study is to obtain knowledge/insight regarding health care needs of pregnant women

/ fetus • Risk benefit to fetus pregnant women; Subsequent offspring & their fertility

Guideline 16 (Safe guarding confided entiality)

- The name, details about - research process investigation, drug used result obtained during research shall be mentioned confidentially

Guideline 17 (Rights of the injured subjects to treatment and compensation)

- The research subject where injured during the process are entitled to free medical treatment till they become normal
- if physically impaired handicapped, paralysed or other irreversible physical damages has occurred they are entitled to compensation
- If dead their dependants are entitled to compensation

Guideline 18 (Strengthening the capacity for scientific and ethical review of biomedical research)

- ethically accepted: it means the research doesn't harm the belief system & the area/individual doesn't disturb the other people of the locality and does not harm their daily routine

Guideline 19 (ethical obligation of external
sponsor to provide health



Q Discuss about institutional review board.

INSTITUTIONAL REVIEW BOARDS (IRB)

→ An institutional review board (IRB), also known as an independent ethics committee (IEC), is a type of committee that applies research ethics by reviewing the methods proposed for research to ensure that they are ethical.

Responsibilities:

- An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects
- The IRB/IEC should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the IRB/IEC requests
- The IRB/IEC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year
- The IRB/IEC may request more information than be given to subjects when, in the judgment of the IRB/IEC, the additional information would add meaningfully to the protection of the rights, safety and/or well-being of the subjects
- When a non-therapeutic trial is to be carried out with the consent of the subject is legally acceptable representative, the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials.
- Where the protocol indicates that prior consent of the trial subject or the subject is legally acceptable representative is not possible, the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials (i.e., in emergency situations).
- The IRB/IEC should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject.

Composition:

- ❖ The IRB/IEC should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. It is recommended that the IRB/IEC should include:
 - ✓ At least five members.
 - ✓ At least one member whose primary area of interest is in a non-scientific area.
 - ✓ At least one member who is independent of the institution/trial site

Q. explain different regulation in USA, Europe, India
Regulatory Authority in India : CDSCO

→ clinical trials in India are regulated by schedule Y of the drug and cosmetic rules, The rules are enforced by the office of the DCGI under CDSCO has prime responsibility for monitoring all clinical trials in India

List of regulatory bodies in India are:

① DCGI (Drug Controller General of India) :-

→ It's a regulatory apex body under government of India which over-see all clinical trials undergoing in India. This agency reviews the clinical study protocol and associated relevant documents. It's governed by rules in amended schedule Y in addition to the experts at DCGI's office

② ICMR (Indian Council of Medical Research) :-

→ The ICMR, New Delhi, the apex body in India for the formulation co-ordination and promotion of biomedical research is one of the oldest ~~medicin~~ medical research bodies in the world

③ GEAC (Genetic Engineering Approval Committee) :-

→ clinical trials involving use of ~~genetic~~ genetic engineered products would be referred by DCGI to ~~GEAC~~ GEAC for recommendation. Based on recommendations received, DCGI provides for conduct of clinical trials involving genetically engineered products

④ DBT (Department of Biotechnology) :-

→ DBT ~~plays~~ an important role in the conduct of clinical trials by supporting the DCGI in reviewing the studies which are related to the field of modern biology and biotechnology in India. Stem cells research and trials are governed by DBT. All clinical trials in the area of stem cells have to be cleared by DBT

⑤ Atomic Energy Review Board (AERB) :-

→ The mission of the board is to ensure that use of ionizing radiation and nuclear energy in India does not cause undue risk to health and environment

⑥ DTAB (Drug Technical Advisory Board) :-

→ The DTAB is a highest technical body under the drug and Cosmetic Act, has endorsed the adoption of GCP guidelines for clinical trial in India

⑦ DCGT (Director General of Foreign Trade) :-

→ it oversees import and export of all biological samples from/to overseas countries, this is responsible for issuance of import and export licenses

Clinical Research regulation in USA - FDA

→ The US FDA (US Food and Drug Administration) is an agency of the United States Department of Health and Human Services and responsible for regulating and supervising the safety of foods, dietary supplements, drug, vaccine, biological medical ~~and~~ product, blood products

→ FDA monitors the manufacture, import, transport, storage and ~~is~~ safe of about 1 ~~trillion~~ trillion worth of products annually

→ There are several sets of regulations and laws that govern clinical trials;

- The first GCP Regulations (GCP) is a general term for GCP good quality guidelines and regulations / GCP encompasses good manufacturing practice (GMP), Good laboratory practice (GLP) and good clinical practice (GCP)

→ GCP specifies how a clinical trial is performed

→ The purpose of GCP is to:

- protect patient safety and rights
- ensure data integrity
- prevent careless errors

→ The FDA agency is organized into the following major sub divisions, each focused on a major area of regulatory responsibility

- The office of the Commissioner (OC)
- The center for drug evaluation and research (CDER)
- The center for biologic evaluation and research (CBER)
- The center for Veterinary medicine (CVM)

European Union Clinical Trial Directive

→ The EU directive was ~~the~~ first published by the EMA (European medicines agency) in 2001
→ Regulatory in Europe is EMA, it relies on the results of clinical trials carried out by pharmaceutical companies to reach its opinion on the authorisation of medicines,
EMA is a decentralised body at the European Union with headquarters in London

→ medicine can be authorized in the European Union by using either the centralized authorization procedure or national authorization procedure

→ The purpose of EMA was to harmonize the initiation and conduct of clinical trials in European Union, it was also designed to:

- protect patients, especially in incapacitated and minor patients
- standardize applications for starting trials
- standardize ethical committee process

→ The EMA is a European agency for the evaluation of medicinal products

→ Committee:

- Committee for medicinal product for human use (CHMP)
- Committee for medicinal products for veterinary use (CVMP)
- Committee for orphan medicinal products (COMP)
- Committee on herbal medicinal products (HMPs)

→ The EU directive applies to all medicinal trials that are interventional, it applies to both commercial and non-commercial trials

→ The directive does not automatically become effective across European Union each country must implement it by passing law enacting them

Q. Give an overview of regulatory environment in India

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Full forms (5m)

MHRA → Medicine and Health Product Regulatory Agency

CRO → Contract Research Organization

CRF → Case Report Form

MAH → Marketing Authorisation Holder

EMA → European Medicines Evaluation Agency

CTA → Clinical Trial Agreement

GLP → Good Laboratory Practices

CFR → Code of Federal Regulations

(2m)

IND → Investigational New Drug Application

DCGI → Drug Controller General of India

PVPI → Pharmacovigilance Programme of India

BPO → Business Process Outsourcing

Q. Accelerated Approval

> Speeding the availability of drugs that treat serious diseases are in everyone's interest, especially when the drugs are the first available treatment or if the drug has advantages over existing treatments. The Food and Drug Administration has developed four distinct and successful approaches to making such drugs available as rapidly as possible:

- Priority Review
- Breakthrough Therapy
- Accelerated Approval
- Fast Track

Accelerated Approval Designation:

- The United States Food and Drug Administration (FDA) initiated the FDA Accelerated Approval Program in 1992 to allow faster approval of drugs for serious conditions that fill an unmet medical need. The faster approval relies on use of surrogate endpoints.
- A surrogate endpoint used for accelerated approval is a marker - a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit.
- Using surrogate or intermediate clinical endpoints can save valuable time in the drug approval process. For example, instead of having to wait to learn if a drug actually extends survival for cancer patients, the FDA may approve a drug based on evidence that the drug shrinks tumors, because tumor shrinkage is considered *reasonably likely to predict* a real clinical benefit.
- Drug must treat a serious condition
- Provide significant improvement in safety or effectiveness when compared to drugs currently on the market
- May use surrogate endpoints to demonstrate clinical benefit
- Approval is granted on conditional basis — post-approval trials are necessary
- Earlier and more frequent communication with the FDA during development
- Application is submitted in one package
- Drug is subjected to expedited withdrawal

Q Priority Review, Fast Track

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- Priority Review
- Breakthrough Therapy
- Accelerated Approval
- Fast Track

Fast Track Designation:

- The purpose is to get important new drugs to the patient earlier
- Drug must be intended to treat a serious condition
- May address an unmet medical need, Filling an unmet medical need is defined as providing a therapy where none exists or providing a therapy which may be potentially better than available therapy.
- Fast Track designation request can be submitted at any time during drug development process
- Supporting data can be clinical or nonclinical
- Earlier and more frequent communication with the FDA during development
- Rolling review of application, Rolling Review, which means that a drug company can submit completed sections of its Biologic License Application (BLA) or New Drug Application (NDA) for review by FDA, rather than waiting until every section of the NDA is completed before the entire application can be reviewed.

• Fast Track designation may be withdrawn if drug no longer meets qualifying criteria

- Fast Track designation must be requested by the drug company. The request can be initiated at any time during the drug development process. FDA will review the request and make a decision within sixty days based on whether the drug fills an unmet medical need in a serious condition

Priority Review:

- Drug must treat a serious condition
- Provide significant improvement in safety or effectiveness when compared to drugs currently on the market
- Drug review process is shortened to 6 months
- A Priority Review designation will direct overall attention and resources to the evaluation of applications for drugs that, if approved, would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications.

Q. write note on CRA

Clinical Research Associate (CRA)

- The Clinical Research Associate (CRA) is the primary representative of the sponsor and arguably has the most direct impact on the proper and accurate reporting of adverse events in clinical trials. This impact is encompassed within the following responsibilities
- The CRA is the first line of communication between the sponsor and investigator throughout the study. One of the most critical functions of the CRA is to assure that investigators are fully aware of, and comply with, their responsibilities for adverse event reporting. To achieve this, the CRA must often teach the adverse event reporting requirements to investigators

RESPONSIBILITIES:

- Identify and recruit investigators.
- Conduct on-site clinical monitoring which includes: document review, ensuring accurate data recording, verifying patient data, adherence to the protocol of a clinical trial in accordance with GCP/ICH guidelines, and Excel's/sponsor's SOPs.
- Perform on-site visits, including site qualification, initiation, monitoring and closeout visits.
- Assist investigator meeting including preparation, liaison, presentations, problem resolutions, and follow up.
- Ensure timely submission of protocol / consent documents for EC/IRB approval.
- Maintain all files and documentation pertaining to studies.
- Motivate investigators in order to achieve recruitment targets.
- Maintaining regular contact with study sites to ensure protocol/GCP compliance.
- Communicate progress of study and relevant information to Project Manager/Sr CRA and other project team members.
- Complete accurate study status reports in time.
- Ensure the correct storage of drugs and the diligent account of all drugs in accordance with SOPs.
- Deal with CRF queries in a timely manner.
- Participate, if requested, in the preparation of and review of study documentation, e.g. draft protocols, draft CRFs, monitoring guidelines and elements of final report.
- Ensure correct archiving of files on completion of a study.

❖ There are five major areas of responsibility through which the CRA can impart knowledge of adverse event reporting to investigators:

- Providing initial training on adverse event reporting requirements for investigators
- Reviewing data to assure accuracy and completeness of reported events
- Providing new information to the investigator
- Monitoring the clinical trial to detect potentially unreported adverse events
- Assuring follow-up data is reported for adverse events when require

Q. what is an investigator brochure , explain content.

INVESTIGATOR'S BROCHURE

- The Investigator's Brochure is a compilation of the clinical and nonclinical data on the investigational product that are relevant to the study of the product in human subjects

Contents:

- The Investigator Brochure should include:

1. Table of contents

2. Summary – not exceeding 2 pages.

- ✓ Highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available of investigational product (IP).

3. Introduction:

- ✓ Chemical name, active ingredients, pharmacological class, anticipated – therapeutic/ diagnostic indication(s).
- ✓ General approach to be followed in evaluating the IP

4. Description of I.P.

- ✓ Physical, Chemical and pharmaceutical properties of I.P.
- ✓ Storage and handling of I.P.
- ✓ Any structural similarity with the other known compound given.

5. Non clinical studies

- ✓ The results of all relevant non clinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form.
- The information provided may include:
 - Species tested,
 - Number of sex in each group
 - Unit dose (mg/kg)
 - Dose interval,
 - Route of administration and
 - Duration of dosing.

INVESTIGATOR

a) NON CLINICAL PHARMACOLOGY:

- ✓ A summary of the pharmacological aspects of the investigational product studied in animals, should be included.

b) PHARMACOKINETICS AND PRODUCT METABOLISM IN ANIMALS

- ✓ A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given.

c) TOXICOLOGY

(The study of the adverse effects of chemicals on animals)

- A summary of the toxicological effects found in relevant studies conducted in different animal species.
- Single dose
- Repeated dose
- Carcinogenicity
- Special studies
- Reproductive toxicity
- Genotoxicity

6. EFFECTS IN HUMANS

- A thorough discussion of the known effects of the investigational product in humans, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities.

7. Summary of Data and Guidance for the Investigator

- This section should contain non clinical and clinical data of IP.
- IB – provide the investigator a clear understanding of
 - The possible risks
 - Adverse reactions
 - Observations & precautions needed for the clinical trial.

- A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

Responsibilities:

1. Investigator's Qualifications and Agreements:

- The investigator should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement, and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority.

2. Adequate Resources:

- The investigator should be able to demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

3. Medical Care of Trial Subjects:

- A qualified physician, should be responsible for all trial-related medical decisions.
- The investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial.

4. Communication with IRB/IEC:

- Before initiating a trial, the investigator should have written and dated approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures, and any other written information to be provided to subjects.

5. Compliance with Protocol:

- The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority and which was given approval/favorable opinion by the IRB/IEC.

6. **Investigational Product:**
 - The investigator and/or a pharmacist or other appropriate individual, who is designated by the investigator, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product.
7. **Randomization Procedures and Un-blinding:**
 - The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature un-blinding.
8. **Informed Consent of Trial Subjects:**
 - Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other written information to be provided to subjects.
9. **Records and Reports:**
 - The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
10. **Progress Reports:**
 - The investigator should submit written summaries of the trial status to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.
11. **Safety Reporting:**
 - All serious adverse events should be reported immediately to the sponsor except for those SAEs that the protocol or other document identifies as not needing immediate reporting. The
12. **Premature Termination or Suspension of a Trial**
 - If the trial is prematurely terminated or suspended for any reason, the investigator should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement, should inform the regulatory authority
13. **Final Report(s)**
 - Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator should provide the IRB/IEC with a summary of the trials outcome, and the regulatory authority with any reports required.

Q. Role and Responsibility of auditors

AUDIT

- A Systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted and the data were recorded, analyzed and accurately reported according to the Protocol, Sponsor's SOP, Good Clinical Practice and Applicable Regulatory requirement

Responsibilities:

- 1) **Planning of audit:**
 - a. **Establishing the Goals of Audits:**
 - One or more objectives should be established for a trial audit based on the importance of the trial with regard to submissions to regulatory authorities
 - The most important part of audit planning is to specify the goal(s) of the audit.
 - By establishing the goal(s) of an audit, the subjects and methods of the audit will be determined and the consistent conduct of the audit will be ensured.
 - b. **Designing and Updating the Audit Plan**
 - Planning is essential to systematically, effectively, and efficiently conduct an audit with consideration of resource management in the auditing department.
 - Audit plans, such as an annual plan, a monthly plan, and a plan specific to each trial or audit, should be established based on:
 - Consideration of the goal.
 - Contents
 - The progress of the targeted trial & other relevant factors.
 - c. **Determining the Subject(s), Timing, and Method(s) of an Audit**
 - The subject(s) (e.g., a medical institution, CRO system, clinical trial/study report, computerized system validation, and database),
 - Timing (e.g., before the start of the trial, during the trial, after the completion of the trial, or periodically)
 - Method(s) (e.g., sampling, interview, or tour) of an audit should be determined based on the goal(s) established for the audit.
 - e. **Information in the Audit Plan (irrespective of the type of audit- annual / monthly)**
 - I. The goal of the audit.
 - II. The subject of the audit.
 - III. The scope of the audit.
 - IV. The timing of the audit.
 - V. The name, title and address of the auditor
 - VI. The reference documents required.
 - VII. The person to whom the audit report will be submitted.

2) Conduct of an Audit

- Done by Auditor-according to written plan & procedures
 - Involves the examination & evaluation of information obtained through investigation of the Audit trial (SOPs etc) & trial site (facilities & equipment's) as well as interviews with auditee.
 - a. Explaining the Auditing Procedures
 - Auditor should explain auditee in detail about goals & methods of audit- for effective collect of data
 - b. Conducting an Audit and Collecting Information
 - Two types of sponsor's audit
 - Auditing of internal trial-related department(s)
 - Auditing of external establishment(s) involved in the trial concerned, e.g., a medical institution, laboratory, and/or CRO.
 - Based upon audit observations collected –auditor will say whether it is in compliance with GCP or not.
 - c. Confirmation and Evaluation of Audit Observations
 - Auditor should discuss the observation made with auditee, so that errors can be confirmed / avoided & can collect if any other information required.
 - Auditor should examine whether any violation of protocol / deviation form GCP guidelines.
- ## 3) Report the results of an Audit
- a. Auditor – reports to Sponsor – to make recognize findings & improve.
 - To preserve the independence of auditing, the auditor must not be directly involved in the corrective and preventive action (CAPA) process.
 - a. Preparation of an Audit Report
 - Reports will be prepared based upon results of evaluation.
 - The contents of an audit report will be as follows:
 - Information that identifies the trial, such as the chemical name or identification code of the investigational drug, the trial title, and the protocol number.
 - The date of issuing the audit report.
 - The subject of the audit.
 - b. Persons to whom Audit Reports are submitted
 - Auditor should submit report to the sponsor.
 - A copy of audit report to the Sponsor's auditee
 - Auditor should keep in mind about the confidentiality of the reports while handling the data.
- ## 4) Corrective and Preventive Actions
- Implementation of CAPA is necessary after audits, to eliminate errors.
 - Once audit complete, auditor will should provide CAPA plan to auditee, that will be utilized to remediate issues of non-compliance.

5) Completion of an Audit

- Upon receipt of the preliminary responses to the CAPA from the auditee, the audit is completed.
- CAPA follow-up and subsequent effectiveness verification should be ensured by continued interaction between the auditor and auditee until mutual agreement has been met that the CAPA have been addressed.

6) Audit Certificate:

- The sponsor should attach the audit certificate to a clinical trial/study report of the targeted trial.
- It should contain the following information:
 - Information that identifies the trial, such as the chemical name or identification code of the investigational drug, the trial title, and the protocol number.
 - The date of issuing the audit certificate.
 - The contents of the audit
 - The name, title and address of the auditor
 - The name and workplace address of the auditee.

7) Keeping Audit Record:

- Audit records should be kept according to sponsor's SOPs for record keeping.
- The SOPs should specify the procedures for keeping or destroying audit-related records, as well as the place, subject, and duration of record keeping.

> Participate, if requested, in the preparation of and review of study documentation, e.g. draft protocols, draft CRFs, monitoring guidelines and elements of final report.

> Ensure correct archiving of files on completion of a study.

There are five major areas of responsibility through which the CRA can impart knowledge of adverse event reporting to investigators:

1. Providing initial training on adverse event reporting requirements for investigators;
2. Reviewing data to assure accuracy and completeness of reported events;
3. Providing new information to the investigator;
4. Monitoring the clinical trial to detect potentially unreported adverse events; and
5. Assuring follow-up data is reported for adverse events when required

Q. Role and responsibilities of Sponsor in clinical trials

Sponsor

The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The sponsor is responsible for securing agreement from all involved parties to ensure direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

Agreements, made by the sponsor with the investigator/institution and any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

The sponsor should utilize qualified individuals (e.g. biostatisticians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and CRFs and planning the analyses to analyzing and preparing interim and final clinical trial reports.

Responsibilities:

1. The sponsor should utilize appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports.
2. To assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. The IDMC should have written operating procedures and maintain written records of all its meetings.
3. Maintains SOPs

4. Maintain a security system that prevents unauthorized access to the data.
5. Maintain a list of the individuals who are authorized to make data changes.
6. Maintain adequate backup of the data.
7. The sponsor is responsible for selecting the investigator(s)/institution(s). Each investigator should be qualified by training and experience and should have adequate resources to properly conduct the trial for which the investigator is selected.
8. The sponsor should update the investigator's Brochure as significant new information becomes available.
9. The sponsor is responsible for supplying the investigator(s)/institution(s) with the investigational product.
10. The sponsor should not supply an investigator/institution with the investigational product(s) until the sponsor obtains all required documentation (e.g. approval/favourable opinion from IRB/IEC and regulatory authorities).
11. Ensure timely delivery of investigational products to the investigators.
12. Maintain records that document shipment, receipt, disposition, return, and destruction of the investigational products.
13. Maintain a system for retrieving investigational products and documenting this retrieval (e.g. for deficient product recall, reclaim after trial completion, expired product reclaim).
14. Maintain a system for the disposition of unused investigational product(s) and for the documentation of this disposition.

Contract research coordinators:

RESPONSIBILITIES OF CRCs

CRCs work in a team under the direct supervision of the PIs. CRCs usually have to handle multiple responsibilities.

The responsibilities of a CRC can be broadly categorized as:

- a. General responsibilities
- b. Trial specific responsibilities

General Responsibilities

- Capacity Building

The work of the CRC begins the day he/she joins employment, whether or not the sponsor has selected an investigative site for any particular trial. The CRC ensures that the potential pool of potential Investigators and Sites keep increasing. The CRC is always on the look out for new trial sites with Investigators who are research naïve.

a. explain designing of CRF with example
Case Report Form (CRF)

Clinical Research

Designing of Clinical Documents

INTRODUCTION

(CRF is a trial document for collecting and recording, patient-related information in a standardized and uniform manner. This is important for the clinical trial team because the analysis and reporting of trial outcome is largely based on the completeness and accuracy of data recorded from each patient recruited in the trial.)

(The CRF can be paper-based or in the electronic format allowing direct data entry into the database) CRF must be distinguished from protocol which provides detailed methodology of all aspects of trials whereas, CRF enables to collect subjects' information enrolled in the study as per the protocol

A good CRF should have the following characteristics:

- I. It should be clear, systematic and unambiguous.
- II. It should provide comprehensive instructions to be followed by investigator to obtain complete information as per approved protocol and regulatory requirements.
- III. It should provide guidance on eligibility criteria for the patient to continue in the trial.
- IV. The design should minimize uncertainties and facilitate entry verification (e.g., cross-check between related data) by monitor.
- V. It should facilitate in designing and creating clean database requiring minimum query resolution between the investigator, monitor and data manager.

Ideally, the CRF should be critically reviewed by designer, quality assurance department, monitor, investigator, data manager and statistician meeting the objectives of a trial

CRF DESIGN AND DEVELOPMENT

→ A good CRF design invites significant contribution and repeated reviewing by expert team member to meet the objectives. The team consists of:-

1. CRF designer
2. Medical advisor
3. Clinical monitor
4. Data entry leader
5. Data manager
6. Statistician

→ The CRF designer prepares a frame work based on protocol. The initial version shows the visits and various assessments on each visit, which are reviewed in the backdrop-of the latest copy of protocol (ideally final approved version). Any change in protocol must be informed immediately for necessary amendments in the CRF.

→ The design should be in accordance with GCP standards and SOP requirements follow standard format to maintain uniformity. The protocol requirements have to be translated into simple and clear questions with appropriate space for recording patient responses using design pointers. At the same time, 'instructions'

are generated to guide and remind the investigator regarding various assessments and actions required at each visit

→ As a part of quality control process, the first CRF version thus prepared is checked against the protocol and for internal consistency by an independent reviewer. The first version is subsequently circulated to all team members for review and suggestion invited for appropriate amendments circulating same copy avoids duplication of suggested changes. Thereafter, all team members meet to discuss the implications of the suggested changes and guide the designer to incorporate the essential changes in the CRF.

→ The CRF designer will subsequently generate the second version which is again reviewed by the team for fine tuning. No meeting is required unless the protocol has changed demanding major amendments in CRF. In the meantime, the designer will select and brief the printers regarding design characteristics, type and size of paper and card required, font size, number of CRFs required and deadlines for distribution.

→ The comments on second version are considered for final version which for quality assurance review and later sent to project manager for approval. Once approved, the printer should provide a finished proof copy of the CRF. The Project manager finally reviews the finished proof copy of the CRP (material, binding, format, etc) and orders for printing multiple copies. As per GCP guidelines, copies of each version, annotations, review meeting decisions, quality control/quality assurance checks and all approval documents must be retained and archived as they represent raw data for the trial.

Q. INFORMED CONSENT PROCESS

INFORMED CONSENT OF PARTICIPANTS

- All biomedical research involving human participants, the investigator must obtain the informed consent of the prospective participant.
- Informed consent protects the individual's freedom of choice and respect for individual's autonomy and is given voluntarily to participate in research or not.

Informed consent form/patient information sheet

- Adequate information about research is given in a simple and easily understandable unambiguous language in a document.
- Informed consent form : components
 - Nature and purpose of study starting it as research
 - Duration of participation with number of participants
 - Procedure to be followed
 - Investigation, if any, to be performed
 - Foreseeable risk and discomfort adequately describe and whether project involves more than minimal risk
 - Benefits to participant community or medical profession as may be applicable
 - Policy on compensation
 - Availability of medical treatment for such injuries or risk management
 - Alternative treatments if available
 - Steps taken for ensuring confidentiality
 - No loss of benefits on withdrawal
 - Benefit sharing in the event of commercialization
 - Contact details of PI / local PI / co-PI in multi centric studies for asking more information related to the research or in case of injury.

Q. Discuss data management and it's component

Clinical Data Management (CDM)

- **Data management** includes all aspects of data planning, handling, analysis, documentation and storage, and takes place during all stages of a study. The objective is to create a reliable data base containing high quality data

Steps:

1. Planning the data needs of the study
2. Data collection
3. Data entry
4. Data validation and checking
5. Data manipulation
6. Data files backup
7. Data documentation

- Each of these processes requires thought and time; each requires painstaking attention to detail.
- The main element of data management are database files. **Database files** contain text, numerical, images, and other data in machine readable form. Such files should be viewed as part of a **database management systems (DBMS)** which allows for a broad range of data functions, including data entry, checking, updating, documentation, and analysis.

1. Data collection:

- Before analyzing data must collected reviewed coded, computerized, verified, checked, and converted to forms suited or the analyses to be conducted.
- The process must be adequately documented to provide the foundation for analyses interpretation.
- Data collection import baseline data from:
 - Existing systems
 - Import lab results
 - Scan results
 - Other digital data

2. Data management software (data analysis):

- Many DBMS are Available for personal computer. Options include:
 - 1) **Spreadsheet** Are to be available for all but the smallest data system, since they are unreliable and easily corrupted.
E.g. excel, SPSS datasheet (statistical package for the social science)
 - 2) **Commercially database program** Are expensive, Tend to be large and slow and often **Lack control data entry** facilities.
E.g. oracle, access.

- **Contact detail of chairman of the IEC for appeal against violation of rights**
 - **Voluntary participation**
 - **If test for genetics and HIV is to be done, counseling for consent for testing must be given as for national guidelines**
 - **Storage period of biological sample and related data with choice offered to participant regarding future use of sample, refusal for storage and receipts of its result**
 - a) **A copy of participant/patient information sheet should be given to the participant for her/his records.**
 - b) **The inform consent should be brief in content highlighting that it is given of free will or voluntarily after understanding the implications of risks and benefits and she/he could withdraw without loss of routine care benefits.**
 - c) **Assurance is given that confidentiality would be maintained and all the investigations/interventions could be carried out only after consent is obtained**
- Fresher or re-consent is taken in following conditions:**
- Availability of new information's which would necessitate deviation of protocol.
 - When a research participant regains consciousness from unconscious state or is mentally competent to understand the study. If such an event is expected then procedure to address it should be spelt out in the informed consent form.
 - When long term follow of or study extension is planned later.
 - When there is change in treatment modality, procedures, site visits.
 - Before publication if there is possibility of disclosure of identity through data presentation or photographs.

3) Especially data entry programs are ideal for data entry and storage.

E.g. SPSS data entry builder, Epi Data.

➤ Epi data Reports to a group of applications used in combination for Creating documented data structures and analyses of quantitative data.

3. Data entry and validation:

➤ Data processing errors are errors that occur after data have been collected.

This is distinct from measurement errors which are differences between the true state of affairs and what appears on the data connection form.

➤ Errors that are actors during data entry are:

- Transposition (e.g. 19 becomes 91 during data entry)
- Copying errors (e.g. 0 (zero) becomes O during data entry)
- Coding errors (e.g. a racial group gets improperly coded because of changes in the coding scheme.)
- Routing errors (e.g. the interviewer ask the wrong question or asks questions in the wrong order.)
- Consistency errors (contradictory responses, such as the reporting of a hysterectomy after the respondent has identified himself as male.)
- Range errors (responses outside of the range of plausible answers, such as a reported age of 290)

Methods to prevent data entry errors include:

- i. Manual checks during data collection (e.g. checks for completeness handwriting legibility)
- ii. Range and consistency checking during data entry (e.g. preventing impossible results, such as age greater than 110)
- iii. Double entry and validation following data entry.

4. Data backup and storage:

➤ There are two kinds of computer users.

- i. Those that have lost a major chunk of data.
 - ii. Those who are going to lose a major chunk of data.
- Data loss can be due to natural disorders human error and computer failure.
 - You have worked too hard to collect data and you must not take care of it.
 - The most common loss of data among studies is due to loss of data somewhere on the computer.
 - The best way to prevent such loss is to know the physical location of your data (Local drive, removable media, network) And to use logical file names. All too often students save files to unknown location (usually the default set up by the program).
 - But never find saved files or have the saved files deleted by the local area network as a part of routine data cleanup.
 - Always be aware of the location and path folder to which files are being written.

5. Documentation:

➤ Documentation is a special challenge.

➤ Documentation should include:

1. The objectives and methods of study.
2. Details of events and activities.
3. For each data collection activity a record of the detailed procedures used and accounting of the number of subjects in scope the number selected for data collection and the disposition for all subjects (by category, e.g. Could not count, refusal). This material should have cross references to original sources. (E.g. computer runs) (enable Verification when necessary).
4. List and descriptions of all interventions applied and materials used (e.g. intervention materials, Training materials).
5. Documentation on all computerized data and final analyses (Information on databases, variables, computer runs).

- It is essential to back-up all data (e.g. data files, code books, software settings, computer programs, word processing documents.)
- Backup system sent all manual or automated copying of files to Removable media (e.g. Floppy disk, zip disks, tape) or to network storage.
- Backup procedures should be truly tested to ensure Archived files remain uncorrupted and can be restored.
- Procedures should be written up so that personnel unfamiliar with backup and restore methods could follow them from scratch.
- Health researchers must be aware of confidentiality and ethical requirements when working with research files.
- This is especially important when data contain personal identifiers and medical information.
- It is it researchers study to make him or herself of local national and international laws Governing us of health data.

Q. write the application of computers in clinical data management (5 mark)

- The use of computers for data processing and statistical analysis requires careful planning and execution by experienced personnel. Errors are liable to happen in the recording of data in the CRFs, as well as in the transfer of data to the computer using a database management software.
- In a typical trial the sequence of data collection might be registration and randomisation, a record of the patient's name or code, trial number, date of birth, date of randomisation and allocated treatment (if the trial is not blind) will be entered into the database.
- Quality data management via computers entails careful planning and execution by well-trained data managers. As the processes of data transcription and entry into computers are highly susceptible to producing errors, a series of checks for validity and completeness should be carried out immediately upon the return of CRFs. Items that are commonly verified include range checks for clinical parameters such as serum levels. These may be excessively high or extremely low (due to out-of-range or wrong units recorded), or in the case of qualitative variables, a nonpermitted code.

Q. write note on QA and QC

QA and QC

Quality Assurance

- It is known as QA and focuses on preventing defect.
- Quality Assurance ensures that the approaches, techniques, methods and processes are designed for the projects are implemented correctly. Quality assurance activities monitor and verify that the processes used to manage and create the deliverables have been followed and are operative.
- Quality Assurance is a proactive process and is prevention in nature. It recognizes flaws in the process. Quality Assurance has to complete before Quality Control.
- QA is the technique of managing the quality.
- Eg : Verification
- QA means Planning for doing a process.

Quality Control

- It is known as QC and focuses on identifying defect. QC ensures that the approaches, techniques, methods and processes are designed in the project are following correctly. QC activities monitor and verify that the project deliverables meet the defined quality standards.
- Quality Control is a reactive process and is detection in nature. It recognizes the defects. Quality Control has to complete after Quality Assurance.
- QC is method to verify the quality.
- Eg : Validation.
- QC Means Action for executing the planned process.

Different between QA & QC

- QA, processes are planned to evade the defects.
- QC agreements with discovery the defects and modifying them while making the product.
- QA detects weakness.
- QC detects defects.
- QA is process oriented
- QC is product oriented.
- QA is failure prevention system.
- QC is failure detection system

2. Electronic Data Processing

- Electronic Data Processing (EDP) refers to the use of automated measures using simple, repetitive actions and computer technology to organise and store documents and sometimes to transfer them from paper to a digital format
- The term Electronic Data Processing is one that is infrequently used in modern computing. Originally coined in an era in which the idea of storing and processing data on computers could be entertained by only the largest of businesses, EDP is now a reality of daily life for the vast majority of businesses around the globe. In fact, the term has since been updated variously to the better known terms 'IT' (Information Technology) and 'IS' (Information Systems).

Advantage:

- **Speed.** Information stored and managed via EDP can be retrieved almost instantly on a well-maintained internal network or even the Internet.
- **Efficient.** Summary documents and related materials such as invoices, reports, and statements can be automatically and quickly generated via EDP.
- **Economic.** Once an Electronic Data Processing system is created and implemented, over time it reduced the costs of managing data by a significant margin.
- **Reduced Labor.** Duplication of effort and repeated entries due to mistakes in manual data entry are reduced or eliminated by EDP.

Elements:

- **Hardware:** The servers and desktops or terminals used to enter and store data.
- **Software:** Spreadsheets, custom applications, databases, and other pieces of code used to manage and collect the data.
- **Procedure:** A coherent and agreed-upon system for entering and manipulating data, designed to eliminate duplication of entry and data corruption.
- **Personnel:** The staff trained to work with the EDP, ranging from the entire work force to a select group.

SAFETY MONITORING IN CLINICAL TRIALS

> Clinical trials are a cornerstone in search for medical advances. There has been progress in the design and conduct of a clinical trial. This led to an increased awareness of ethical issues and safety monitoring. It is the Policy of National Institutes of Health (NIH) that a system should be there to ensure the safety of participants. The establishment of Data safety monitoring boards is required for multi site clinical trials involving potential risks to the patient.

❖ Safety monitoring is done by :

1. Investigator
2. IRB/IECs
3. Sponsor
4. Monitor

1. IRB — Responsibility:

- An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. ~~IRB/IEC should~~
- The IRB/IEC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year.

2. INVESTIGATOR — Responsibility:

- During and following subject participation in a trial, the investigator should ensure that the adequate medical care is provided to the subject for any adverse events, including clinically significant laboratory values, related to the trial. ~~Investigator should~~

3. SPONSOR — Responsibility:

- The sponsor may consider establishing an independent data-monitoring committee (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. ~~Sponsor should~~

4. MONITOR - Responsibility:

- Determining whether all adverse events (AEs) are appropriately reported within the time periods required by GCP, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirements. ~~Monitor should~~

SAFETY MONITORING IN DIFFERENT PHASES OF CLINICAL

TRIAL:

- Phase I: Experimental drug given in a small group of people (20-80) to evaluate its safety, determine a safe dose range, identify side effects.
- Phase II: Experimental study drug is given to a larger group of people (100-300) to see if it is effective and to further evaluate its safety.
- Phase III: Experimental study drug is given to a larger group of people (1000-3000) to confirm its effectiveness, monitor side effects, collect information for safety.
- Phase IV: Post marketing studies gives additional information including drug risks, benefits and optimal use.

DATA AND SAFETY MONITORING BOARD: (DSMB)

- This is used mainly for randomized controlled clinical trial. For phase III trials DSMB is required to provide an ongoing critical and unbiased evaluation of the progress of study.

FUNCTIONS OF DSMB:

- To ensure safety of the patient
- To ensure that the protocol is designed in a ethical manner
- To review interim toxicity data

COMPOSITION OF DSMB:

1. Multidisciplinary representation, including physicians from relevant medical specialties and biostatisticians. This may include other experts such as bioethicists, epidemiologists and basic scientists.
2. Members who are free of significant conflicts of interest

Active Surveillance in ADR reporting (5 mark)

- Active surveillance, in contrast to passive surveillance, seeks to ascertain completely the number of adverse events via a continuous preorganized process.
- An example of active surveillance is the follow-up of patients treated with a particular drug through a risk management program. Patients who fill a prescription for this drug may be asked to complete a brief survey form and give permission for later contact. In general, it is more feasible to get comprehensive data on individual adverse event reports through an active surveillance system than through a passive reporting system.
- Active surveillance can be achieved by reviewing medical records or interviewing patients and/or physicians in a sample of sentinel sites to ensure complete and accurate data on reported adverse events from these sites.
- The selected sites can provide information, such as data from specific patient subgroups, that would not be available in a passive spontaneous reporting system.
- Moreover, active surveillance can capture ADRs across the entire population of patients exposed to drugs in a variety of clinical settings, and is thus able to inform health authorities on true drug risks in everyday clinical practice.
- At the same time, an active surveillance system allows targeted recruitment and follow-up of patients focused on a specific ADR, a specific drug, or a specific patient subpopulation (e.g. age groups, ethnic groups, gender). With such targeted investigations, relevant information on a specific drug safety question can be obtained very efficiently and within a relatively short time.
- Most importantly, active surveillance provides a means to evaluate drug safety particularly in "orphan populations", often excluded from clinical trials, such as children, or women during pregnancy.

Q. Role of Eudravigilance in safety monitoring (5 mark)

- Eudravigilance is a system for monitoring the safety of medicines.
- Its components facilitate electronic reporting of suspected adverse reactions related to medicines and the effective analysis of data.
- This enables the early detection of potential safety issues. It is the European data processing network and management system for reporting and evaluation of suspected adverse reactions during the development of new drugs and for following the marketing authorisation of medicinal products in the European Economic Area (EEA).
- The system contains different components that perform specific tasks in the process of electronic reporting of suspected adverse drug reactions.

Role:

- Electronic exchange of Individual Case Safety Reports (ICSR, based on the ICH E2 BM specifications):
 - EudraVigilance Clinical Trial Module (EVCTM) for reporting Suspected Unexpected Serious Adverse Reactions (SUSARs).
 - EudraVigilance Post-Authorisation Module (EVPAM) for post-authorisation ICSRs.
- Early detection of possible safety signals from marketed drugs for human use.
- Continuous monitoring and evaluation of potential safety issues in relation to reported adverse reactions.
- Decision-making process, based on a broader knowledge of the adverse reaction profile of drugs.