DRUG DEVELOPMENT PROCESS [chapter (1)]

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 or 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.

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.

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 lastup 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 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 trails which are called as Post- marketing phase trails are conducted after the drug has been introduced into the market.

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 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 pro missing 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 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 characterization:

It is recognized that drug candidates with drug-like properties are more likely to make into 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 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- Soluability, PKa X-ray, NMR,IR,UV-VIS,MS,PET

Biological Characterization:

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

Goals :

1. To find Efficacy

2. Asses 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

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

Dosage form:

Developability 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
- Excepient 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)

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,Distribution

INVESTIGATIONAL NEW DRUG DEVELOPMENT (IND) :

After pre-clinical trial work with a compound, the FDA becomes involved in a drug development program to determine it is safe to begin human trials. The sponsors file an investigational drug application with the FDA .The compound changes in legal status under the federal food, drug, and cosmetic act. It becomes an investigational drug and is subject to specific regulatory requirements. IND approval is passive-the sponsor may begin clinical trials 30 days after submission of the IND unless the FDA notifies that there is a problem.

The IND contains all known information about the compound. In general IND includes:

 Animal pharmacology and toxicology studies. These are the pre-clinical data that allow the FDA to make an assessment of safety for initial testing in humans.

 Any previous experience with the cmpd in humans from non- US studies.

 Chemistry, manufacturing and control information.

 The protocol and investigator information.

 Assurance that a duly formed IRB will be responsible for initial and continuing review of the trial.

 The responsibilities of the CRO if involved.

 General development plan for the drug.

The IND must be updated on an annual basis. Amendments are filed for any changes in protocols, medicine strength, investigators or other changes in the development program. Investigational New Drug applications are of many types and can be submitted by different stakeholders.

The different types of INDs include the following:

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.

Emergency Use IND This allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of IND. It is also used for patients who do not meet the criteria of an existing study protocol.

Treatment IND This 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 reviewed by the FDA. INDs can also be classified as a Commercial and non-Commercial. A commercial IND permits the sponsor to collect the data on the clinical safety and effectiveness needed for application for marketing in the form of a New Drug Application (NDA). A non-commercial IND permits the sponsor to use the drug in research of early clinical investigations to obtain the advanced scientific knowledge of the new drug, and there is no plan to market the product.

INTRODUCTION TO CLINICAL TRAILS [chapter 2 (a)]

Clinical Trail:

A clinical trial (also clinical research) is a research study in human volunteers to answer specific health questions. Carefully conducted clinical trials are the fastest and safest way to find treatments that work in people and ways to improve health. Interventional trials determine whether experimental treatments or new ways of using known therapies are safe and effective under controlled environments. Observational trials address health issues in large groups of people or populations in natural settings.

Participation:

Participants in clinical trials can play a more active role in their own health care, gain access to new research treatments before they are widely available, and help others by contributing to medical research. All clinical trials have guidelines about who can participate. Using inclusion/exclusion criteria is an important principle of medical research that helps to produce reliable results. The factors that allow someone to participate in a clinical trial are called "inclusion criteria" and those that disallow someone from participating are called "exclusion criteria". These criteria are based on such factors as age, gender, the type and stage of a disease, previous treatment history, and other medical conditions. Before joining a clinical trial, a participant must qualify for the study.

Some research studies seek participants with illnesses or conditions to be studied in the clinical trial, while others need healthy participants. It is important to note that inclusion and exclusion criteria are not used to reject people personally. Instead, the criteria are used to identify appropriate participants and keep them safe. The criteria help ensure that researchers will be able to answer the questions they plan to study.

Process:

The clinical trial process depends on the kind of trial being conducted. The clinical trial team includes doctors and nurses as well as social workers and other health care professionals. They check the health of the participant at the beginning of the trial, give specific instructions for participating in the trial, monitor the participant carefully during the trial, and stay in touch after the trial is completed. Some clinical trials involve more tests and doctor visits than the participant would normally have for an illness or condition. For all types of trials, the participant works with a research team. Clinical trial participation is most successful when the protocol is carefully followed and there is frequent contact with the research staff.

Informed Consent:

Informed consent is the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is also a continuing process throughout the study to provide information for participants. To help someone decide whether or not to participate, the doctors and nurses involved in the trial explain the details of the study. If the participant's native language is not English, translation assistance can be provided. Then the research team provides an informed consent document that includes details about the study, such as its purpose, duration, required procedures, and key contacts. Risks and potential benefits are explained in the informed consent

document. The participant then decides whether or not to sign the document. Informed consent is not a contract, and the participant may withdraw from the trial at any time.

Benefits/Risks:

Benefits:

Clinical trials that are well-designed and well-executed are the best approach for eligible participants to:

 Play an active role in their own health care.

 Gain access to new research treatments before they are widely available.

 Obtain expert medical care at leading health care facilities during the trial.

 Help others by contributing to medical research.

Risks:

There are risks to clinical trials.

 There may be unpleasant, serious or even life-threatening side effects to treatment.

 The treatment may not be effective for the participant.

 The protocol may require more of their time and attention than would a non-protocol treatment, including trips to the study site, more treatments, hospital stays or complex dosage requirements.

Side effects and adverse reactions:

Side effects are any undesired actions or effects of drug or treatment. Negative or adverse effects may include headache, nausea, hair loss, skin irritation, or other physical problems. Experimental treatments must be evaluated for both immediate and long-term side effects.

Safety:

The ethical and legal codes that govern medical practice also apply to clinical trials. In addition, most clinical research is federally regulated with built in safeguards to protect the participants. The trial follows a carefully controlled protocol, a study plan which details what researchers will do in the study. As a clinical trial progresses, researchers report the results of the trial at scientific meetings, to medical journals, and to various government agencies. Individual participants' names will remain secret and will not be mentioned in these reports

Selection:

People should know as much as possible about the clinical trial and feel comfortable asking the members of the health care team questions about it, the care expected while in a trial, and the cost of the trial. The following questions might be helpful for the participant to discuss with the health care team. These questions are found in the informed consent document.

 What is the purpose of the study?

 Who is going to be in the study?

 Why do researchers believe the new treatment being tested may be effective? Has it been tested before?

 What kinds of tests and treatments are involved?

 How do the possible risks, side effects, and benefits in the study compare with my current treatment?

 How might this trial affect my daily life?

 How long will the trial last?

 Will hospitalization be required?

 Who will pay for the treatment?

 Will I be reimbursed for other expenses?

 What type of long-term follow up care is part of this study?

 How will I know that the treatment is working? Will results of the trials be provided to me?

 Who will be in charge of my care?

Ideas for trials;

Ideas for clinical trials usually come from researchers. After researchers test new therapies or procedures in the laboratory and in animal studies, the treatments with the most promising laboratory results are moved into clinical trials. During a trial, more and more information is gained about a new treatment, its risks and how well it may or may not work.

Sponsors:

Clinical trials are sponsored or funded by a variety of organizations or individuals such as physicians, medical institutions, foundations, voluntary groups, and pharmaceutical companies, in addition to federal agencies such as the National Institutes of Health (NIH), the Department of Defense (DOD), and the Department of Veterans Affairs (VA). Trials can take place in a variety of locations, such as hospitals, universities, doctors' offices, or community clinics.

Protocol:

A protocol is a study plan on which all clinical trials are based. The plan is carefully designed to safeguard the health of the participants as well as answer specific research questions. A protocol describes what types of people may participate in the trial; the schedule of tests, procedures, medications, and dosages; and the length of the study. While in a clinical trial, participants following a protocol are seen regularly by the research staff to monitor their health and to determine the safety and effectiveness of their treatment.

Placebo:

A placebo is an inactive pill, liquid, or powder that has no treatment value. In clinical trials, experimental treatments are often compared with placebos to assess the treatment's effectiveness. In some studies, the participants in the control group will receive a placebo instead of an active drug or treatment.

Control/Control Group:

A control is the standard by which experimental observations are evaluated. In many clinical trials, one group of patients will be given an experimental drug or treatment, while the control group is given either a standard treatment for the illness or a placebo.

Types of Clinical trails:

 Treatment trials test new treatments, new combinations of drugs, or new approaches to surgery or radiation therapy.

 Prevention trials look for better ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include medicines, vitamins, vaccines, minerals, or lifestyle changes.

 Diagnostic trials are conducted to find better tests or procedures for diagnosing a particular disease or condition.

 Screening trials test the best way to detect certain diseases or health conditions.

 Quality of Life trials (or Supportive Care trials) explore ways to improve comfort and the quality of life for individuals with a chronic illness.

Phases of clinical Trials:

Clinical trials are conducted in phases. The trials at each phase have a different purpose and help scientists answer different questions:

 In Phase I trials, researchers test a new drug or treatment in a small group of people (20-80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.

 In Phase II trials, the study drug or treatment is given to a larger group of people (100-300) to see if it is effective and to further evaluate its safety.

 In Phase III trials, the study drug or treatment is given to large groups of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely.

 In Phase IV trials, post marketing studies delineate additional information including the drug's risks, benefits, and optimal use.

Expanded Access Protocol:

Most human use of investigational new drugs takes place in controlled clinical trials conducted to assess safety and efficacy of new drugs. Data from the trials can serve as the basis for the drug marketing application. Sometimes, patients do not qualify for these carefully-controlled trials because of other health problems, age, or other factors.

For patients who may benefit from the drug use but don't qualify for the trials, FDA regulations enable manufacturers of investigational new drugs to provide for "expanded access" use of the drug. For example, a treatment IND (Investigational New Drug application) or treatment protocol is a relatively unrestricted study. The primary intent of a treatment IND/protocol is to provide for access to the new drug for people with a life-threatening or serious disease for which there is no good alternative treatment. A secondary purpose for a treatment IND/protocol is to generate additional information about the drug, especially its safety. Expanded access protocols can be undertaken only if clinical investigators are actively studying the new treatment in well- controlled studies, or all studies have been completed. There must be evidence that the drug may be an effective treatment in patients like those to be treated under the protocol. The drug cannot expose patients to unreasonable risks given the severity of the disease to be treated.

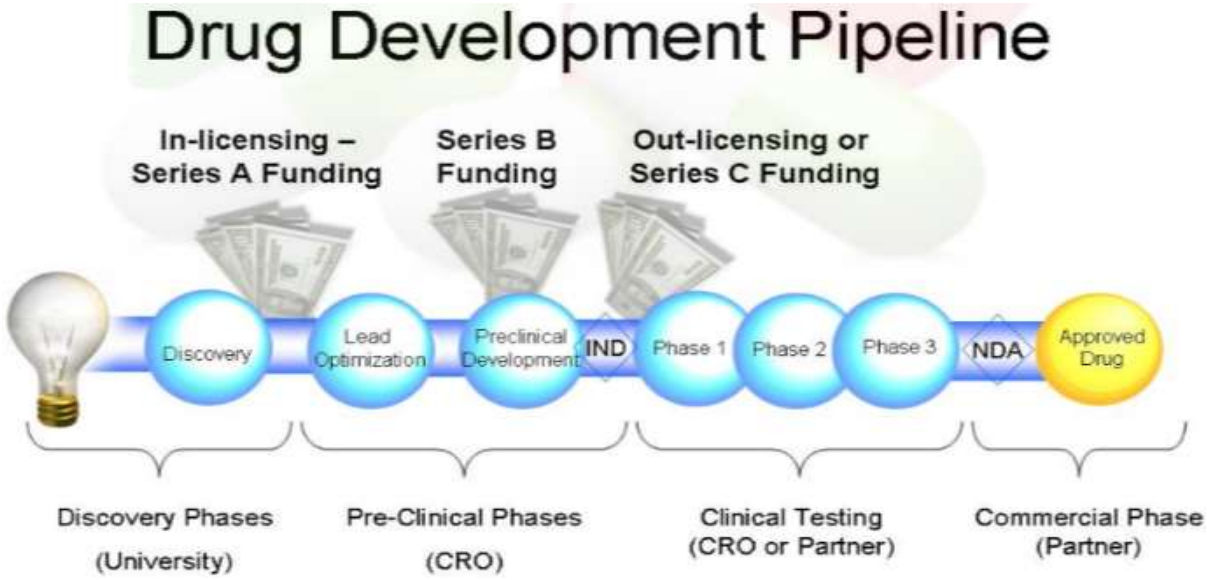
Some investigational drugs are available from pharmaceutical manufacturers through expanded access programs listed in ClinicalTrials.gov. Expanded access protocols are generally managed by the manufacturer, with the investigational treatment administered by researchers or doctors in office-based practice. If you or a loved one are interested in treatment with an investigational drug under an expanded access protocol listed in ClinicalTrials.gov, review the protocol eligibility criteria and location information and inquire at the Contact Information number.

VARIOUS PHASES OF CLINICAL TRIALS _[chapter 2 (b)]

Definition:

"Clinical trial" means a systematic study of new drug(s) in human subject(s) to generate data for discovering and / or verifying the clinical, pharmacological (including pharmacodynamics and pharmacokinetics) and /or adverse effects with the objective of determining safety and / or efficacy of the new drug.

Drug Development Process: The process of drug development can be broadly classified as pre-clinical and clinical. Pre-clinical refers to experimentation that occurs before it is given to human subjects; whereas, clinical refers to experimentation with humans. Within the realm of clinical research, clinical trials are classified into four phases.



Types of Clinical Trails (According to u.s NIH)

- Treatment Trail
- Prevention Trail
- Early Detection/Screening
- Diagnostic Trail
- Quality of life/Supportive Trail

Classification of Various phases of clinical trials: There are five different phases of clinical trials, which include:

- Phase 0 Trials (Micro dosing trials)
- Phase I Trials (Human Pharmacology/ First time in Man Studies)
- Phase II Trials (Pilot Trials/ Therapeutic Exploratory trials)

 Phase III Trials (Expanded clinical trials/Therapeutic Confirmatory trials)

 Phase IV Trials (Post Marketing trials)

1. Phase 0 Trails/Micro dosing Trials:

Micro dosing, or human phase 0 clinical trials, is a technique whereby sub pharmacological doses of prospective drug candidates are administered to human volunteers. A micro dose study provides early pharmacokinetic data in humans and only requires minimal preclinical toxicology safety testing' A micro dose is defined as 100th of the pharmacological dose (or predicted pharmacological dose) or a maximum of 100µg. Micro dosing is a relatively recent innovation and there remains a degree of uncertainty as to whether such a small dose will adequately predict the pharmacokinetics of the therapeutically active dose.

Distinctive future includes;

 the administration of Single Sub therapeutic doses of the study drug to a small number of subjects (10 to 15)

 Purpose is to gather preliminary data on the agents Pharmacokinetics and Pharmacodynamics

 It gives no data on Safety or Efficacy

 It is done to rank drug candidates in order to decide which has the best Pharmacokinetic parameters in humans to take forward for further development

2. Phase I Trials; Phase I trials are intended to demonstrate the safety of a new therapy or combination of therapies. Most phase I studies are performed with successive small groups of patients being treated at increasing doses to define what side effects occur and at what dose level Purpose: to determine the SAFETY of the investigational drug.

Other Objectives include: To determine...

a. Maximum Tolerated dose (MTD)

b. Pharmacokinetics

c. Pharmacodynamics

d. Early Measurement Of Drug Activity

Study Design: Un-blinded, uncontrolled study

Subjects involved:

 Generally, normal volunteers without confounding diseases or concurrent medications are recruited to participate in Phase I trials.

 With anti-neoplastic agents and for certain disease states and to avoid trials in normal subjects, it maybe preferred to begin trials in a patient population.

No. of subjects: 20 – 60

Length of Studies: Several Months

3. Phase II Trials; Phase II studies are esigned to explore the therapeutic efficacy of a treatment or drug in people who have the condition that the drug is intended to treat. They are sometimes called therapeutic exploratory trials and tend to be larger scale than Phase I trials. Many experimental drugs which fail tend to do so during the Phase II trials.

Purpose: To Demonstrate EFFICACY with particular disease;

• An important goal for this Phase is to determine the dose(s) and regimen for Phase III trials.

Additional objectives of Phase II studies can include :

• Evaluation of potential study endpoints

• Evaluation of therapeutic regimens (including concomitant medications)

• Evaluation of target populations (e.g. mild versus severe disease) for further studies in Phase II or III

Study design: Single blinded, placebo controlled

Subjects involved:

• Subjects in Phase II trials are patients with the disease or clinical situation being examined.

• They should be healthy in terms of their disease and free of other serious medical illnesses.

Length of studies: Few months or take up to several years

No. of Subjects: 60 – 200

Phase II trials can be divided into Phase IIA and Phase IIB although sometimes both are combined

Phase IIA is designed to assess dosing requirements i.e. how much of the drug should patients receive and up to what does is considered safe. The safety assessments carried out in Phase I can be repeated on a larger subject group. As more subjects are involved, some may experience side effects which none of the subjects in the Phase I experienced. The researchers aim to find out more about safety, side effects and how to manage them.

Phase IIB studies focus on the efficacy of the drug i.e. how well it works at the prescribed doses. Researchers may also be interested in finding out which types of a specific disease or condition would be most suitable for treatment.

4. Phase III Trials; Phase III trials are the last stage before clinical approval for a new drug or device. By this stage, there will be convincing evidence of the safety of the drug or device and its efficacy in treating people who have the condition for which it was developed. These studies should be intended to provide an adequate basis for marketing approval. Studies in Phase III may also further explore the dose-response relationships (relationships among dose, drug concentration in blood and clinical response), use of the drug in wider populations, in different stages of disease, or the safety and efficacy of the drug in combination with other drug(s).

Purpose:

• Phase IIIa trials are designed to gain safety and efficacy information in a large number of patients.

• 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

Study Design: Randomized controlled, Double blind Cross Over designs

Subjects involved: Phase 3 subjects are patients exhibiting the disease under study and are selected from a larger population of patients .

Length of Studies; Phase llla studies tend to be of longer duration,lasting one to four years.

Phase IIIb (Large-Scale Trials): Purpose: The purpose of Phase lllb trials is to gain experience with the experimental agent in a large number of subjects that reflect the general population at risk. Therefore, the trials are less tightly controlled: All subjects may be receiving experimental drug, and entry criteria are relaxed and larger numbers of patients are enrolled .

Subjects involved: Phase lllb trial subjects come from a larger, heterogeneous patient population. The subject population may focus on specific concurrent illnesses to further delineate the drug's safety.

Length of Studies: Phase lllb studies last one to four years and are used to gather additional data about the investigational agent.

NDA Application;

• New Drug Application (NDA) is done following successful completion of all three phases of human clinical trials, the company analyses all of the data and files an NDA with the FDA if the data successfully demonstrate safety and effectiveness.

• The NDA must contain all of the scientific information that the company has gathered on the compound.

• NDAs can exceed 100,000 pages or more.

• By legislation, the FDA is allowed six months to review an NDA filing.

5. Phase IV Trials; After the three phases of clinical testing and after the treatment has been approved for marketing, there may be a fourth phase to study the long-term effects of drugs or treatment or to study the impact of another factor in combination with the treatment (e.g. whether a particular drug reduces agitation). Usually, such trials are sponsored by pharmaceutical companies and described as Pharmacovigilance.

Purpose:

 Phase IV trials are done for a variety of reasons: to place the drug in the market ("seeding" studies), to make marketing claims, for pharmacoeconomic studies, for quality of life studies, or for surveillance for unexpected or rare adverse events.

 Phase IV trials include additional drug-drug interaction(s), dose-response or safety studies and trials designed to support use under the approved indication(s), e.g. mortality/morbidity studies, epidemiological studies etc.

Study design: Uncontrolled; Observational

Subjects involved: Subjects in Phase IV trials are drawn from the general population with the specific disease. Further conditions are defined by the purpose of the protocol

Length of Studies: The length of Phase IV trials is determined by the purpose of the study and may be indefinite ,such as in post marketing surveillance.

CLINICAL TRAIL PHASES;

Phase	**participants**	**Purpose**	**Special features**
Phase 1	Small number (20- 80) of participants, usually healthy volunteers, in some cases patient with advanced disease(eg, cancer)	To evaluate safety, identity side effects, determine a safe dose range and learn how the agent is absorbed and handled by the body (pharmacokinetics/ dynamics)	Often first time tested in humans
Phase 2	Larger number (hundred) of patient with the condition under study	To further evaluate safety and to determine if the agent has the intended effect in humans .	Sometimes randomized controlled trail
Phase 3	Larger still (thousand) of people with the condition under study	To confirm or further evaluate an agent"s effectiveness , monitor side effects , compare it to commonly used treatment and collect other information that will be to determine whether the agent should be approved and marketed.	Usually randomized, controlled trials.
Phase 4 (postmarketing study)	Various population	To collect additional information after an agent is approved and marketed regarding its risks, benefits and use in various population over a longer period of time.	_

POST MARKETING SURVEILLANCE [chapter 2 (c)]

Introduction:

 To market a drug, the manufacturer must provide evidence of its efficacy and safety to the U.S. Food and Drug Administration (FDA) and specified Regulatory Authorities.

 In premarketing testing, the numbers and types of patients used to demonstrate a drug's efficacy and safety are limited compared with the numbers and types of patients who will eventually be prescribed the drug after it is marketed.

 Although post-marketing surveillance cannot provide knowledge of the safety or efficacy of thugs at the time of their introduction on the market

 Post-marketing surveillance of drug therefore play an important role to discover an undesirable effect that might present at risk

 It provides additional information on the benefits and risk of the drugs

Advantages:

 No fixed Duration / patient population

 Starts immediately after marketing

 Report all ADRs

 Helps to detect :

1. Rare ADR's
2. Drug Interaction's

 Also new uses for drugs {Sometimes called Phase V}

History:

 In the 1960 at least two serious drug reactions were observed in many patients. Thalidomide cause limb deformities (phocomelia)

 Observed in Japan, was the optic nerve damage (sub acute myelo-optic-neuropathy).

 The PMA, Senator Edward Kennedy (D-Mass) suggested that a better system was needed for monitoring the use and effects of prescription chugs after they were marketed.

 As a result, the Joint Commission on Prescription Drug Use was established in 1976, funded largely by the drug industry, with the mandate to design a. post-marketing surveillance system to detect, quantify, and describe the anticipated and unanticipated effects of marketed drugs

 The delayed discovery of practolol's adverse effects spurred efforts to improve post-marketing surveillance

SOURCES OF PMS INFORMATION:

The following maybe considered as sources of information, Some sources are proactive and some are reactive.

 Expert users groups ("focus groups').

 Customer surveys.

 Customer complaints and warranty claims.

 Post CE-market clinical trials.

 Literature reviews.

 Device tracking/implant registries.

 User reactions during training programmers.

 The media.

NEED OF POST-MARKETING SURVEILLANCE:

The primary objective of post-marketing studies is to develop information about drug effects under customary conditions of chug use. Rare adverse events may not be detected in pre-licensure studies because even very large clinical trials have limitations.

Access to more patients and better data.

 Given diversity of data sources, innovative approaches to retrieval of key data may have great potential vs. single unified system.

 Better background rates, comparable "control" populations.

 Increase in "non-medical' data sources e.g., pharmacy, supermarket, employer vaccination.

 All patients vaccinations and health outcomes are immediately and continuously accessible in automated database allowing optimal detection and analysis are applicable to safety initiatives for other medical products.

Methods of Post Marketing Surveillance (PMS):

The primary objective of post marketing studies is to develop information about drug effects under customary conditions of drug use. Initial clues about a drug's potential effects come from the experimental studies carried out with both animals and humans in the premarketing period. Spontaneous or voluntary reporting (e. g., in letters to the editors of medical journals) is the oldest, and to-date, the most productive source of new in- formation about a drug's possible effects once a drug is marketed. Other types of studies are used to examine in more detail the possible effects of a drug. In general, these other types of studies use either cohort or case-control methods Thus, four types of studies are generally used to identify drug effects:

1. Controlled clinical trials,

2. Spontaneous or voluntary reporting

3. Cohort studies, and

4. Case-control studies

1. Controlled clinical trials: PMS studies conducted after the launch of a product is part of Phase IV development of the drug. Some of these studies may be retrospective case-control evaluations. These are done to evaluate rare suspected side effects. For example, when there was a suspicion that use of oral contraceptives may be associated with an increased incidence of thrombophlebitis (clotting of blood in the deep veins) and thromboembolism (blockage of smaller arteries due to detached blood clots) case- control studies were carried out. A group of cases of thromboembolism were compared with age matched controls that were as similar to the cases as possible, but without the disease.

- To minimize bias through such methods as randomization and " double-blinding"
- Directly monitor patients for the duration of the study.
- For evaluating a. thug's efficacy and safety.
- They are often costly.

2. Spontaneous or voluntary reporting: Spontaneous reports are, by definition, submitted voluntarily although under certain circumstances these reports may be encouraged, or "stimulated", by media reports or articles published in medical or scientific publications, or by product lawsuits. In many parts of the world adverse event reports are submitted electronically using a defined message standard by physicians and other health providers & hospitals which may act to alert FDA and pharmaceutical firms to possible adverse effects of drugs.

3. Cohort studies: Studies follow a. defined group of patients (the cohort) for a. period of time. Patient's are not randomly assigned, & there is no blinding. If adverse reactions occur. A second group of patients the controls) with the same medical condition, who are not taking the chug and who may be receiving alternative treatment. In this method, patients can be directly monitored to ensure they take the drug appropriately, and to observe the drug’s effects or monitoring can be less controlled. With less control, a larger cohort can be followed, but bias is thus increased

4. Case-control studies: Case-control studies identify patients with the adverse effects to be studied (the cases), and compare them with a. sample (the controls), drawn from the same cohort that gave rise to the cases. Controls are matched as closely as possible with the cases, except with regard to the drug’s suspected adverse effect, to examine whether exposure to the drug is the cause. Patients with conditions suspected of being associated with a certain drug would have their medical records reviewed or be interviewed concerning the use of that drug. The histories of the controls would also be studied for information about drug use in the general population. By comparing the proportion of drug users among the cases with the proportion of drug users in the general population, it is possible to infer the relative frequency with which adverse reactions occur in users of certain drugs as compared with nonusers.

ABBREVIATED NEW DRUG APPLICATION (ANDA) [chapter 2 (d)]

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. 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 applicants 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.

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 annoted 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:

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.

CDSCO GUIDELINES [chapter 2 (e)- CDSCO)]

GOOD CLNICAL PRACTICES FOR CLINICAL RESEARCH IN INDIA;

Good Clinical Practice is a set of guidelines for biomedical studies which encompasses the design, conduct, termination, audit, analysis, reporting and documentation of the studies involving human subjects. The fundamental tenet of GCP is that in research on man, the interest of science and society should never take precedence over considerations related to the well being of the study subject. It aims to ensure that the studies are scientifically and ethically sound and that the clinical properties of the pharmaceutical substances under investigation are properly documented. The guidelines seek to establish two cardinal Principles; Protection of the rights of human subjects and authenticity of biomedical data generated.

These guidelines have been evolved with consideration of WHO, ICH, USFDA and European GCP guidelines as well as the Ethical Guidelines for Biomedical research on Human Subjects issued by the Indian Council of Medical Research. They should be followed for carrying out all biomedical research in India at all stages of drug development, whether prior or subsequent to product registration in India.

Prerequisites for the study;

- 2.1 Investigational Pharmaceutical Product
- 2.2 Pre-clinical supporting data
- 2.3. Protocol
- 2.3.1. Relevant components of Protocol
- 2.3.1.2. Objectives and Justification
- 2.3.1.3. Ethical Considerations
- 2.3.1.4. Study design
- 2.3.1.5. Inclusion, Exclusion and Withdrawal of Subjects
- 2.3.1.6. Handling of the Product(s)
- 2.3.1.7. Assessment of Efficacy
- 2.3.1.8. Assessment of Safety
- 2.3.1.9. Statistics
- 2.3.1.10. Data handling and management
- 2.3.1.11. Quality control and quality assurance
- 2.3.1.12. Finance and insurance
- 2.3.1.13. Publication policy

- 2.3.1.14. Evaluation
- 2.3.2. Supplementaries and appendices
- 2.4. Ethical & Safety Considerations
- 2.4.1. Ethical Principles
- a. Principles of essentiality
- b.Principles of voluntariness, informed consent and community agreement
- c. Principles of non-exploitation
- d. Principles of privacy and confidentiality
- e. Principles of precaution and risk minimisation
- f. Principles of professional competence
- g. Principles of accountability and transparency
- h. Principles of the maximisation of the public interest and of distributive justice
- i. Principles of institutional arrangements
- j. Principles of public domain
- k. Principles of totality of responsibility. Principles of compliance
- 2.4.2. Ethics Committee:
- 2.4.2.1 Basic Responsibilities
- 2.4.2.2. Composition
- 2.4.2.3. Terms of Reference
- 2.4.2.4. Review Procedures
- 2.4.2.5. Submission of Application
- 2.4.2.6. Decision Making Process
- 2.4.2.7. interim Review
- 2.4.2.8. Record Keeping
- 2.4.2.9. Special Considerations
- 2.4.3. Informed Consent Process
- 2.4.3.1. Informed Consent of Subject :

- 2.4.3.2. Essential information for prospective research on subjects
- 2.4.3.3. Informed Consent in Non-Therapeutic Study :
- 2.4.4. Essential Information on Confidentiality for Prospective Research Subjects Safeguarding confidentiality
- 2.4.5. Compensation for Participation
- 2.4.6. Selection of Special Groups As Research Subject
- 2.4.6.1. Pregnant or nursing women
- 2.4.6.2. Children
- 2.4.6.3. Vulnerable groups
- 2.4.7 Compensation for Accidental Injury
- 2.4.7.1. Obligation of the sponsor to pay

GCP GUIDELINES [chapter 2 (e)- GCP)

Good clinical practice (GCP) is an international quality standard that is provided by ICH, an international body that defines standards, which governments can transpose into regulations for clinical trials involving human subjects. These standards for clinical trials are referred to as ICH-GCP which is a recommendation in clinical guidelines.

Good Clinical Practice is defined as a standard for the Design, Conduct, Performance monitoring, Auditing, Recording, analysis and Reporting of clinical trails that provides assurance that the data and the reported results are credible and accurate and that the rights integrity and confidentiality of the trail subjects are protected .

GCP enforces tight guidelines on ethical aspects of a clinical study. GCP aims to ensure that the studies are scientifically authentic and that the clinical properties of the investigational product are properly documented. Ongoing research shows that whether conducting research involving a new drug, a behavioural intervention, or an interview or survey, GCP provides investigators and their study teams with the tools to protect human subjects and collect quality data

Principles of ICH-GCP;

2.1 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).

2.2 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 the anticipated benefits justify the risks.

2.3 The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

2.4 The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

2.5 Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

2.6 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.

2.7 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.

2.8 Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

2.9 Freely given informed consent should be obtained from every subject prior to clinical trial participation.

2.10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

2.11 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).

2.12 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.

2.13 Systems with procedures that assure the quality of every aspect of the trial should be implemented.

ICH GUIDELINES [chapter 2 (e)- ICH]

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of pharmaceutical product registration. The purpose of ICH is to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines by recommending ways to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration. Harmonisation would lead to a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines while maintaining safeguards on quality, safety, and efficacy, and regulatory obligations to protect public health. ICH guidelines have been adopted as law in several countries, but are only used as guidance for the U.S. Food and Drug Administration. In the 1980s, what is today the European Union began harmonising regulatory requirements. In 1989, Europe, Japan, and the United States began creating plans for harmonisation; ICH was created in April 1990 at a meeting in Brussels.

There are 4 categories of ICH Guidelines;

1) Quality (Q)

2) Safety (S)

3) Efficacy (E)

4) Multidisciplinary (M)

QUALITY GUIDELINES (Q) :

Q1A - Q1F Stability;

Q1A(R2) - Stability Testing of New Drug Substances and Products

Q1B Stability Testing - Photostability Testing of New Drug Substances and Products

Q1C Stability Testing for New Dosage Forms

Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products

Q1E Evaluation of Stability Data

Q1F Stability Data Package for Registration Applications in Climatic Zones III and IV

Q2 Analytical Validation;

Q2(R1) Validation of Analytical Procedures: Text and Methodology

Q3A - Q3D Impurities;

Q3A(R2) Impurities in New Drug Substances

Q3B(R2) Impurities in New Drug Products

Q3C(R5) Impurities: Guideline for Residual Solvents

Q3D Guideline for Elemental Impurities - NEW

Q3D Implementation of Guideline for Elemental Impurities

Q4 - Q4B Pharmacopoeias;

Q4 Pharmacopoeias

Q4A Pharmacopoeial Harmonisation

Q4B Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions

Q5A - Q5E Quality of Biotechnological Products;

Q5A(R1) Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin Q5A

Q5B Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products

Q5C Stability Testing of Biotechnological/Biological Products

Q5D Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products

Q5E Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process

Q6A- Q6B Specifications;

Q6A Specifications : Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances

Q6B Specifications : Test Procedures and Acceptance Criteria for Biotechnological/Biological Products

Q7 Good Manufacturing Practice;

Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients Q7A

Q7 Q&As Questions and Answers: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients

Q8 Pharmaceutical Development;

Q8(R2) Pharmaceutical Development

Q9 Quality Risk Management;

Q9 Quality Risk Management

Q10 Pharmaceutical Quality System;

Q10 Pharmaceutical Quality System

Q11 Development and Manufacture of Drug Substances;

Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)

Q12 Lifecycle Management;

Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

SAFETY GUIDELINES (S) :

S1A - S1C Carcinogenicity Studies;

S1 Rodent Carcinogenicity Studies for Human Pharmaceuticals

S1A Need for Carcinogenicity Studies of Pharmaceuticals

S1B Testing for Carcinogenicity of Pharmaceuticals

S1C(R2) Dose Selection for Carcinogenicity Studies of Pharmaceuticals

S2 Genotoxicity Studies;

S2(R1) Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Us

S3A - S3B Toxicokinetics and Pharmacokinetics;

S3A Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies

S3A Q&As Questions and Answers: Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure - Focus on Microsampling

S3B Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies

S4 Toxicity Testing;

S4 Duration of Chronic Toxicity Testing in Animals (Rodent and Non Rodent Toxicity Testing)

S5 Reproductive Toxicology;

S5(R2) Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility

S6 Biotechnological Products;

S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals

S7A - S7B Pharmacology Studies;

S7A Safety Pharmacology Studies for Human Pharmaceuticals

S7B The Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals

S8 Immunotoxicology Studies;

S8 Immunotoxicity Studies for Human Pharmaceuticals

S9 Nonclinical Evaluation for Anticancer Pharmaceuticals;

S9 Nonclinical Evaluation for Anticancer Pharmaceuticals

S10 Photosafety Evaluation;

S10 Photosafety Evaluation of Pharmaceuticals

S11 Nonclinical Safety Testing;

S11 Nonclinical Safety Testing in Support of Development of Paediatric Medicines

EFFICACY GUIDELINES (E) :

E1 Clinical Safety for Drugs used in Long-Term Treatment;

E1 The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life Threatening Conditions

E2A - E2F Pharmacovigilance;

E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting

E2B(R3) Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports

E2B(R3) IWG Implementation: Electronic Transmission of Individual Case Safety Reports

E2C(R2) Periodic Benefit-Risk Evaluation Report

E2C, E2CA

E2C(R2) Q&As Questions & Answers: Periodic Benefit-Risk Evaluation Report

E2D Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting

E2E Pharmacovigilance Planning

E2F Development Safety Update Report

E3 Clinical Study Reports;

E3 Structure and Content of Clinical Study Reports

E4 Dose-Response Studies;

E4 Dose-Response Information to Support Drug Registration

E5 Ethnic Factor ;

E5(R1) Ethnic Factors in the Acceptability of Foreign Clinical Data

E6 Good Clinical Practice;

E6(R1) Good Clinical Practice

E6(R2) Addendum: Good Clinical Practice

E7 Clinical Trials in Geriatric Population;

E7 Studies in Support of Special Populations:Geriatrics

E8 General Considerations for Clinical Trials;

E8 General Considerations for Clinical Trials

E9 Statistical Principles for Clinical Trials;

E9 Statistical Principles for Clinical Trials

E10 Choice of Control Group in Clinical Trials;

E10 Choice of Control Group and Related Issues in Clinical Trials

E11 Clinical Trials in Pediatric Population;

E11 Clinical Investigation of Medicinal Products in the Pediatric Population

E12 Clinical Evaluation by Therapeutic Category;

E12 Principles for Clinical Evaluation of New Antihypertensive Drugs

E14 Clinical Evaluation;

E14 The Clinical Evaluation of QT/QTc Interval Prolongation and Pro-arrhythmic Potential for Non-Anti-arrhythmic Drug

E15 Definitions in Pharmacogenetics / Pharmacogenomics;

E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories

E16 Qualification of Genomic Biomarkers;

E16 Biomarkers Related to Drug or Biotechnology Product Development: Context, Structure and Format of Qualification Submissions

E17 Multi-Regional Clinical Trials;

E17 General principle on planning/designing Multi- Regional Clinical Trials

E18 Genomic Sampling Methodologies;

E18 Genomic Sampling Methodologies for Future Use

MULTIDISCIPLINARY GUIDELINES (M):

M1 MedDRA Terminology;

MedDRA Medical Dictionary for Regulatory Activities

M2 Electronic Standards;

ESTRI Electronic Standards for the Transfer of Regulatory Information

M3 Nonclinical Safety Studies;

M3(R2) Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

M4 Common Technical Document;

CTD The Common Technical Document

M5 Data Elements and Standards for Drug Dictionaries;

M5 Data Elements and Standards for Drug Dictionaries

M6 Gene Therapy;

M6 Virus and Gene Therapy Vector Shedding and Transmission

M7 Genotoxic Impurities;

M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic

M8 Electronic Common Technical Document (eCTD);

Electronic Common Technical Document (eCTD)

CHALLENGES IN THE IMPLEMENTATION OF GCP GUIDELINES [chapter 2 (f)]

Some of the challenges in the implementation of GCP guidelines:

1. Professional Training on GCP
2. Infrastructure
3. Regulatory Environment
4. ERB/ IRB/ IEC
5. ICD Administration
6. Safety Reporting
7. Investigational Product
8. Record Keeping/ Source Document(s)
9. Grants & Payments
10. Trial Report / Publication

1.Professional Training on GCP;

- The scarcity of GCP trained competent professionals.
- Lack of professional training on GCP across various stakeholders (sponsor, investigator, ERB, patient, regulators etc).
- No Indian university offers a curriculum in this
- Discipline.

2.Infrastructure;

- Most of the hospitals in India do not meet the infrastructure requirements as per GCP guidelines.
- Lack of supportive infrastructure like labs and diagnostics up to the standards of international accreditation.

3. Regulatory Environment;

- Biggest challenge is their implementation and adherence.
- Do not have a regulatory inspection system in place to monitor and adherence and compliance to these guidelines.
- Mostly the adherence to GCP guidelines is a matter of self- discipline at the part of sponsor(s), investigator(s) and ERB(s).

4.ERB/IRB/IEC;

 GCP requires written standard operating procedures (SOP) for ERB/IRB/IEC.

 No standard guidelines on what should be the content of an ideal SOP.

 Many of the hospitals either do not have the written SOP for ERB or have improper guidelines not about all the critical elements

 of GCP.

 No provision to check whether the SOP is being followed during each meeting or not.

5.ICD Administration;

 In India, the patient/legal representatives has an immense faith on treating doctor that they insist on signing the documents without even reading or after reading it superficially.

 A layman can not understand the wording and contents of the majority of documents.

 Situation becomes even grim when translations are used, which leads to varied interpretations due to lack of authentic validation.

 Lack of patients advocacy group who can be a guardian to the patient?s rights and safety, makes poor uneducated masses susceptible to abuse in clinical trials in the name of treatment

6. Safety Reporting;

 Investigator and sponsor have joint responsibility to report all the serious and un-expected adverse events to ERB/IRB and regulatory authority(ies).

 The regulatory pharmacovigilance presently is not optimally implemented for adverse event handling and review.

 In majority of cases sponsor does not even comply with the expedited safety reporting to local regulatory authority and regulators often remain unaware of this fact.

7.Investigational Product;

 Investigational product storage, handling and access control is a major challenge.

 It is difficult to produce an evidence of temperature chain being maintained during shipment of investigational product(s) from sponsor’s facility to investigator site(s)

 Eg: courier, custom clearance etc.

 There is no validation and regular standardization of thermometers provided by the sponsor.

 No standardized solutions are available for storing investigational product(s) requiring

8. Record Keeping/Source Document(s);

 Record retention and retrieval is always a major challenge in majority of hospitals.

 The documentation of patient disease, treatment and progress notes is not adequate to meet the standards of good documentation practices that ensure data completeness and correctness.

 Hospitals using electronic records as source data/ document compliance to CFR part 11 is a major hurdle.

 Archival of trial documents for the stipulated time frame and under proper environmental

9.Grants & Payments;

 Trials agreements are based on the institutional practices where the research grants goes to a centralized research account, which in majority of the cases remains un-utilized.

 No incentive to the investigator(s) for investing extra-time, efforts and intellectual capital.

10. Trial Report/Publication;

 Negative trials or trials that get terminated prematurely are rarely published.

 This is a major threat towards validity of Evidence Based Medicine as one gets to know the positive results only.

 India, no doubt has a talented pool of clinical research professional(s) but the above mentioned challenges needs to be addressed in order to perform the world-class clinical trials in compliance with GCP guidelines.

Ethical Guidelines In Clinical Research [chapter 2 (g)]

STATEMENT OF GENERAL PRINCIPLES IN BIOMEDICAL RESEARCH INVOLVING HUMAN PARTICIPANTS;

This statement of Ethical Guidelines for Biomedical Research on Human Participants shall be known as the ICMR Code and shall consist of the following:-

(a) Statement of General Principles on Research using Human Participants in Biomedical Research

(b) Statement of Specific Principles on Research using Human Participants in specific areas of Biomedical Research

These Statements of General and Specific Principles may be varied, amended, substituted and added from time to time.

GENERAL STATEMENT;

Medical and related research using human beings as research participants must necessarily ensure that -

(i) The PURPOSE, of such research is that it should be directed towards the increase of knowledge about the human condition in relation to its social and natural environment, mindful that the human species is one of the many species in a planet in which the well being of all species is under threat, no less from the human species as any other, and that such research is for the betterment of all, especially the least advantaged.

(ii) Such research is CONDUCTED under conditions that no person or persons become a mere means for the betterment of others and that human beings who are subject to any medical research or scientific experimentation are dealt with in a manner conducive to and consistent with their dignity and well being, under conditions of professional fair treatment and transparency; and after ensuring that the participant is placed at no greater risk other than such risk commensurate with the well being of the participant in question in the light of the object to the achieved.

(iii) Such research must be subjected to a regime of EVALUATION at all stages of the proposal i.e., research design and experimentation, declaration of results and use of the results thereof, and that each such evaluation shall bear in mind the objects to be achieved, the means by which they are sought to be achieved, the anticipated benefits and dangers, the potential uses and abuses of the experiment and its results, and above all, the premium that civilised society places on saving and ensuring the safety of each human life as an end in itself.

STATEMENT OF GENERAL PRINCIPLES;

Any research using the human beings as participants shall follow the principles given below –
I. Principles of essentiality whereby the research entailing the use of human participants is considered to be absolutely essential after a due consideration of all alternatives in the light of the existing knowledge in the proposed area of research and after the proposed research has been duly vetted and considered by an appropriate and responsible body of persons who are external to the particular research and who, after careful consideration, come to the conclusion that the said

research is necessary for the advancement of knowledge and for the benefit of all members of the human species and for the ecological and environmental well being of the planet.

II. Principles of voluntariness, informed consent and community agreement whereby research participants are fully apprised of the research and the impact and risk of such research on the research participant and others; and whereby the research participants retain the right to abstain from further participation in the research irrespective of any legal or other obligation that may have been entered into by such human participants or someone on their behalf, subject to only minimal restitutive obligations of any advance consideration received and outstanding. Where any such research entails treating any community or group of persons as a research participant, these principles of voluntariness and informed consent shall apply, mutatis mutandis, to the community as a whole and to each individual member who is the participant of the research or experiment. Where the human participant is incapable of giving consent and it is considered essential that research or experimentation be conducted on suchna person incompetent to give consent, the principle of voluntariness and informed consent shall continue to apply and such consent and voluntariness shall be obtained and exercised on behalf of such research participants by someone who is empowered and under a duty to act on their behalf. The principles of informed consent and voluntariness are cardinal principles to be observed throughout the research and experiment, including its aftermath and applied use so that research participants are continually kept informed of any and all developments in so far as they affect them and others. However, without in any way undermining the cardinal importance of obtaining informed consent from any human participant involved in any research, the nature and form of the consent and the evidentiary requirements to prove that such consent was taken, shall depend upon the degree and seriousness of the invasiveness into the concerned human participant's person and privacy, health and life generally, and, the overall purpose and the importance of the research. Ethics committee shall decide on the form of consent to be taken or its waiver based on the degree of risk that may be involved.

III. Principles of non-exploitation whereby as a general rule, research participants are remunerated for their involvement in the research or experiment; and, irrespective of the social and economic condition or status, or literacy or educational levels attained by the research participants kept fully apprised of all the dangers arising in and out of the research so that they can appreciate all the physical and psychological risks as well as moral implications of the research whether to themselves or others, including those yet to be born. Such human participants should be selected so that the burdens and benefits of the research are distributed without arbitrariness, discrimination or caprice. Each research shall include an in-built mechanism for compensation for the human participants either through insurance cover or any other appropriate means to cover all foreseeable and unforeseeable risks by providing for remedial action and comprehensive aftercare, including treatment during and after the research or experiment, in respect of any effect that the conduct of research or experimentation may have on the human participant and to ensure that immediate recompense and rehabilitative measures are taken in respect of all affected, if and when necessary.

IV. Principles of privacy and confidentiality whereby the identity and records of the human participants of the research or experiment are as far as possible kept confidential; and that no details about identity of said human participants, which would result in the disclosure of their identity, are disclosed without valid scientific and legal reasons which may be essential for the purposes of therapeutics or other interventions, without the specific consent in writing of the

human participant concerned, or someone authorised on their behalf; and after ensuring that the said human participant does not suffer from any form of hardship, discrimination or stigmatisation as a consequence of having participated in the research or experiment.

V. Principles of precaution and risk minimisation whereby due care and caution is taken at all stages of the research and experiment (from its inception as a research idea, its subsequent research design, the conduct of the research or experiment and its applicative use) to ensure that the research participant and those affected by it including community are put to the minimum risk, suffer from no known irreversible adverse effects, and generally, benefit from and by the research or experiment; and that requisite steps are taken to ensure that both professional and ethical reviews of the research are undertaken at appropriate stages so that further and specific guidelines are laid down, and necessary directions given, in respect of the conduct of the research or experiment.

VI. Principles of professional competence whereby the research is conducted at all times by competent and qualified persons who act with total integrity and impartiality and who have been made aware of, and are mindful of, preferably through training, the ethical considerations to be borne in mind in respect of such research or experiment.

VII. Principles of accountability and transparency whereby the research or experiment will be conducted in a fair, honest, impartial and transparent manner after full disclosure is made by those associated with the research or experiment of each aspect of their interest in the research, and any conflict of interest that may exist; and whereby, subject to the principles of privacy and confidentiality and the rights of the researcher, full and complete records of the research inclusive of data and notes are retained for such reasonable period as may be prescribed or considered necessary for the purposes of post-research monitoring, evaluation of the research, conducting further research (whether by the initial researcher or otherwise) and in order to make such records available for scrutiny by the appropriate legal and administrative authority, if necessary.

VIII. Principles of the maximisation of the public interest and of distributive justice whereby the research or experiment and its subsequent applicative use are conducted and used to benefit all human kind and not just those who are socially better off but also the least advantaged; and in particular, the research participants themselves and or the community from which they are drawn.

IX. Principles of institutional arrangements whereby there shall be a duty on all persons connected with the research to ensure that all the procedures required to be complied with and all institutional arrangements required to be made in respect of the research and its subsequent use or application are duly made in a bonafide and transparent manner; and to take all appropriate steps to ensure that research reports, materials and data connected with the research are duly preserved and archived.

X. Principles of public domain whereby the research and any further research, experimentation or evaluation in response to, and emanating from such research is brought into the public domain so that its results are generally made known through scientific and other publications subject to such rights as are available to the researcher and those associated with the research under the law in force at that time.

XI. Principles of totality of responsibility whereby the professional and moral responsibility, for the due observance of all the principles, guidelines or prescriptions laid down generally or in respect of the research or experiment in question, devolves on all those directly or indirectly connected with the research or experiment including the researchers, those responsible for funding or contributing to the funding of the research, the institution or institutions where the research is conducted and the various persons, groups or undertakings who sponsor, use or derive benefit from the research, market the product (if any) or prescribe its use so that, inter alia, the effect of the research or experiment is duly monitored and constantly subject to review and remedial action at all stages of the research and experiment and its future use.

XII. Principles of compliance whereby, there is a general and positive duty on all persons, conducting, associated or connected with any research entailing the use of a human participant to ensure that both the letter and the spirit of these guidelines, as well as any other norms, directionsand guidelines which have been specifically laid down or prescribed and which are applicable for that area of research or experimentation, are scrupulously observed and duly complied with. These 12 principles laid down under Statement on General Principles are common to all areas of biomedical research. The specific issues are mentioned under relevant topics.

INSTITUTIONAL REVIEW BOARDS/INDEPENDENT ETHICS COMMITTEE [chapter 2 (h)]

IRB/IEC Responsibilities:

1) 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.

2) The IRB/IEC should obtain the following documents:

 Trial protocol(s)/amendment(s),

 Written informed consent form(s) and consent form updates that the investigator proposes for use in the trial,

 Subject recruitment procedures (e.g. advertisements),

 Written information to be provided to subjects,

 Investigator's Brochure (IB),

 Information about payments and compensation available to subjects,

 Available safety information, The investigators current curriculum vitae and/or other documentation evidencing qualifications, &

 Any other documents that the IRB/IEC may need to fulfill its responsibilities.

 The IRB/IEC should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed and the dates for the following:

 approval/favorable opinion;

 modifications required prior to its approval/favorable opinion;

 disapproval / negative opinion; and

 Termination/suspension of any prior approval/favourable opinion.

3) 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.

4) 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.

5) 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.

6) 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.

7) 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).

8) 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.

9) The IRB/IEC should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment will be prorated should be specified.

Composition, Functions and Operations:

1) 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:

a) At least five members.

b) At least one member whose primary area of interest is in a nonscientific area.

c) At least one member who is independent of the institution/trial site.

 Only those IRB/IEC members who are independent of the investigator and the sponsor of the trial should vote/provide opinion on a trial-related matter.

 A list of IRB/IEC members and their qualifications should be maintained.

2) The IRB/IEC should perform its functions according to written operating procedures, should maintain written records of its activities and minutes of its meetings, and should comply with GCP and with the applicable regulatory requirement(s).

3) An IRB/IEC should make its decisions at announced meetings at which at least a quorum, as stipulated in its written operating procedures, is present

4) Only members who participate in the IRB/IEC review and discussion should vote/provide their opinion and/or advise.

5) The investigator may provide information on any aspect of the trial, but should not participate in the deliberations of the IRB/IEC or in the vote/opinion of the IRB/IEC.

6) An IRB/IEC may invite nonmembers with expertise in special areas for assistance.

Procedures;

The IRB/IEC should establish, document in writing, and follow its procedures, which should include:

1) Determining its composition (names and qualifications of the members) and the authority under which it is established

2) Scheduling, notifying its members of, and conducting its meetings.

3) Conducting initial and continuing review of trials.

4) Determining the frequency of continuing review, as appropriate.

5) Providing, according to the applicable regulatory requirements, expedited review and approval/favourable opinion of minor change(s) in ongoing trials that have the approval/favourable opinion of the IRB/IEC.

6) Specifying that no subject should be admitted to a trial before the IRB/IEC issues its written approval/favourable opinion of the trial.

7) Specifying that no deviations from, or changes of, the protocol should be initiated without prior written IRB/IEC approval/favorable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), telephone number(s))

8) Specifying that the investigator should promptly report to the IRB/IEC:

a) Deviations from, or changes of, the protocol to eliminate immediate hazards to the trial subjects

b) Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial

c) All adverse drug reactions (ADRs) that are both serious and unexpected.

d) New information that may affect adversely the safety of the subjects or the conduct of the trial

9) Ensuring that the IRB/IEC promptly notify in writing the investigator/institution concerning:

a) Its trial-related decisions/opinions

b) The reasons for its decisions/opinions.

c) Procedures for appeal of its decisions/opinions.

Records;

 The IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3 years after completion of the trial and make them available upon request from the regulatory authority (ies).

 The IRB/IEC may be asked by investigators, sponsors or regulatory authorities to provide its written procedures and membership lists.

REGULATORY ENVIRONMENT IN EUROPE [chapter 2 (i)-Europe]

Regulatory Authority: EUROPE – EMEA; Regulatory Authority in Europe is European Medicines Agency (EMEA). The European Medicines Agency relies on the results of clinical trials carried out by pharmaceutical companies to reach its opinions on the authorisation of medicines. Although the authorisation of clinical trials occurs at Member State level, the Agency plays a key role in ensuring that the standards of good clinical practice (GCP) are applied across the European Economic Area (EEA) in cooperation with the Member States. It also manages a database of clinical trials carried out in the European Union.

EMEA;

 The European Medicines Agency (EMEA) is a decentralized body of the European Union with headquarters in London

 Medicines can be authorized in the European Union by using either the centralized authorization procedure or national authorization procedures

 The centralized procedure (also known as the 'Community authorization procedure'). This procedure results in a single marketing authorization (called a 'Community marketing authorization') that is valid across the European Union, as well as in the states Iceland, Liechtenstein and Norway

 The centralized procedure is compulsory for human medicines that are:

* Derived from biotechnology processes, such as genetic engineering

* Intended for the treatment of HIV/Aids, cancer, diabetes, neurodegenerative disorders or autoimmune diseases and other immune dysfunctions

* Officially designated 'orphan medicines' (medicines used for rare diseases)

 For medicines that do not fall within these categories (the 'mandatory scope'), companies have the option of submitting an application for a centralized marketing authorization to the EMEA, as long as the medicine concerned is a significant therapeutic, scientific or technical innovation, or if its authorization would be in the interest of public health

 Applications through the centralized procedure are submitted directly to the EMEA. Evaluation by the Agency's relevant scientific committee takes up to 210 days, at the end of which the committee adopts an opinion on whether the medicine should be marketed or not. This opinion is then transmitted to the European Commission, which has the ultimate authority for making decisions on marketing authorizations in the EU

 Once a Community marketing authorization has been granted, the marketing-authorization holder can begin to make the medicine available to patients and healthcare professionals in all EU countries.

National authorization procedures:

 Each EU Member State has its own procedures for the authorization, within their own territory, of medicinal products that fall outside the scope of the centralized procedure

 Information about these national procedures can normally be found on the website of the national competent authority in the country concerned.

 The Heads of Agencies website is a useful entry point for such information

 However, there are also two possible routes available to companies for the authorization of such medicinal products in several countries simultaneously:

a. Decentralized procedure:

 Using the decentralized procedure, companies may apply for simultaneous authorization in more than one EU country of medicinal products that have not yet been authorized in any EU country and that do not fall within the mandatory scope of the centralized procedure

b. Mutual-recognition procedure:

 In the mutual-recognition procedure, a medicine is first authorized in one EU Member State, in accordance with the national procedures of that country. Following this, further marketing authorizations can be sought from other EU countries in a procedure whereby the countries concerned agree to recognize the validity of the original, national marketing authorization.

Good Clinical Practice - Human Medicinal Products;

 Requirements for the conduct of clinical trials in the EU, including GCP and GMP and inspections of these, have been implemented in the Clinical Trial Directive (Directive 2001/20/EC) and the GCP Directive (2005/28/EC)

 Clinical trials included in marketing authorization applications in the European Economic Area (EEA)are required to be conducted in accordance with GCP (Directive 2001/83/EC Annex I, as amended by Directive 2003/63/EC)

 Volume 10, Clinical Trials, of the Rules Governing Medicinal Products in the European Union, brings together information on clinical trial authorization, safety monitoring, GCP inspections and GCP and GMP requirements for clinical trials in the EEA

 Europe has adopted the ICH-GCP in July 1996 and this is published also on the EMEA website (ICH has developed unified standards for Europe, US and Japan).

GCP Inspectors Working Group:

 The Sector draws on the expertise of member states' inspectorates for the fulfilment of many of its GCP related tasks. This is primarily achieved through the GCP Inspectors Working Group

 The GCP Inspectors Working Group meets on a regular basis four times a year, at EMEA with representatives of the GCP inspectorates of the European Economic Area Member States, observers from candidate countries and Switzerland

 The GCP Inspectors Working Group has developed procedures for the coordination, preparation, conduct and reporting of GCP inspections carried out in the context of the Centralized Procedure.

REGULATORY ENVIRONMENT IN INDIA [chapter 2 (i)- india]

Regulatory Authority : INDIA – CDSCO

Introduction:

Drug Controller General of India (DCGI) under central drug standard control organization (CDSCO) has prime responsibility for regulating clinical trial in India.

Two drug organizations are functioning in India to exercise control over drugs:

- Central drug standard control organization (CDSCO)
- State drug control organizations

It is the sovereign function of the government to ensure safety, efficacy and quality of drugs supplied to the public. This function is performed by the Central Drugs Standard Control Organization (CDSCO). The role of CDSCO in early stages of drug development is minimal but it becomes more pronounced consequent to the lead obtained from animal pharmacology and toxicological studies and the need for its further testing on humans. The requirements of data submission on animal testing for permission to undertake Phase I, Phase II and Phase III clinical trials are laid down in Schedule Y of Drugs & Cosmetics rules. Central drug standard control organization of the government of India is headed by the drugs controller general (India). The prime responsibilities of this organization are:

- Controlling the quality of imported drugs;
- Co-ordinating the activities of the states and advising them on matters relating to the uniform administration of the Act in the country.
- Laying down rules and ancillary provisions of drug control and standards of drugs;
- Controlling the quality of drugs moving in inter-state commerce jointly with state drug control organizations;
- Granting approval to “New Drugs” proposed to be imported manufactured in the country;
- Controlling the quality of drugs which are exported from India;
- To regulate clinical research in India.
- Testing of drugs by Central Drugs Labs.
- To approve licenses to manufacture certain categories of drugs as Central License
- Approving Authority i.e. for Blood Banks, Large volume parenteral and vaccines & Sera.
- Monitoring adverse drug reactions (ADR)
- Arranging meetings of the two statutory bodies, namely the Drugs Technical Advisory Board (DTAB) and the drug consultative committee and also processing all matters connected with their functioning.

Drug Technical Advisory Board (DTAB): It has technical experts and advises the central and state governments on all technical matters arising out of the enforcement of drug control. No rules can be made by the central government without consulting this board.

Drugs Consultative Committee: It has the central and state drug control officials as members, and its main function is to ensure that the drug control measures are enforced uniformly in all states.

Genetic Engineering Approval Committee (GEAC): It is authority to approve rDNA pharmaceutical products. GEAC's role is to assess the bio-safety/environmental safety aspect of the biotechnological products.

Other Functions:

- Guidance on technical matters
- Publication of Indian Pharmacopoeia
- Screening of drug formulations available in Indian market
- Participation in the WHO GMP certification scheme
- Coordinating the activities of the State Drugs Control Organizations to achieve uniform administration of the Act; and policy guidance.

Clinical trials Guidelines in India: The guidelines that govern the conduct of clinical trials in India include: Schedule Y (Revised-2005) of Drugs and Cosmetics Act,1940. Ethical Guidelines for Biomedical Research on Human Subjects, 2006; Good Clinical Practices, 2001;

SCHEDULE Y (Revised-2005) of Drugs and Cosmetics Act,1940. [See rules 122A, 122B, 122D, 122DA, 122DAA and 122E]

- Rule 122 A - Permission to import new drug
- Rule 122 B - Permission to manufacture new drug
- Rule 122 DA - Definition of Clinical trials
- Rule 122 E - Definition of New Drugs*

The Requirements and guidelines for permission to Import and / or Manufacture of New Drugs for sale or to undertake Clinical Trials

122-DAA Definition of Clinical trial: "Clinical trial" means a systematic study of new drug(s) in human subject(s) to generate data for discovering and / or verifying the clinical, pharmacological (including pharmacodynamic and pharmacokinetic) and /or adverse effects with the objective of determining safety and / or efficacy of the new drug. Application for the permission of carrying out a clinical trial in India is made to the office of DCGI. General recommendations carrying out clinical trials in India as specified in Schedule Y are as follows:

o The requirements for carrying out clinical trials in India before a new drug is approved for marketing depend upon the status of drug in other countries.

o For new drugs approved outside India, Phase-3 trials are required to be conducted in India before permission to market the drug in India is granted. Prior to conduct of Phase-3 studies in India subjects, Licensing Authority may require pharmacokinetic studies to be undertaken to verify that data generated in India population is in conformity with data already generated abroad.

o For new drug substances discovered in India, clinical trials are required to be carried out in India right from phase-1. For new drugs substances discovered in countries other than India, phase-1 data should be submitted along with the application. After submission of phase-1 data generated outside India to the licensing authority, permission may be granted to repeat phase-1 trials and/or to conduct phase-2 trials and subsequently phase-2 trials concurrently with other global trials for that drug.

o Application for permission to import or manufacture new drugs for sale or to undertake clinical trials shall be made in "Form 44 format.

o If the study drug is intended to be imported for the purposes of examination, test or analysis, the application for import of small quantities of drugs for such purpose should also be made in Form 12.

o For drugs indicated in life threatening / serious diseases or diseases of special relevance to the Indian health scenario, the toxicological and clinical data requirements may be abbreviated, deferred or omitted, as deemed appropriate by the Licensing Authority.

o Laboratories used for generating data for clinical trials should be compliant with Good Laboratory Practices (GCP).

o In case of studies prematurely discontinued for any reason a summary report (in specified format) should be submitted within 3 months.

o Any unexpected serious adverse event (SAE) occurring during a clinical trial should be communicated promptly (within 14 calendar days) by sponsor to the licensing authority and to other investigator(s) participating in the study (appendix-9).

o The investigator has to give an undertaking on GCP compliance as per the format specified in appendix -7.

o The investigator has to report all serious and unexpected adverse events to the sponsor within 24 hours and to the Ethics committee within 7 working days of their occurrence.

o Ethics committee should have written standard operating procedures and should maintain a record of its proceedings. In case an ethics committee revokes its approval accorded to a trial protocol, it must record the reasons for doing so and at once communicate such a decision to the investigator as well as to the licensing authority.

o Geriatric patients should be included in phase-3 clinical trials if the disease intended to be treated is characteristically a disease of aging or when the new drug is likely to the geriatric patient's response compared with that the non- geriatric patient.

o Paediatric subjects are legally unable to provide written informed consent, and are dependent on their patient(s)/legal guardian to assume responsibility for their participation in clinical studies.

o Subsequent to approval of the product, new drugs should be closely monitored for their clinical safety once they are marketed.

o The Periodic Safety Update Reports (PSURs) shall be submitted every six months for the first two years after approval of the drug is granted to the applicant.

o For subsequent two years PSURs need to be submitted annually.

o Licensing authority may extend the total duration of submission of PSURs if it is considered necessary in the interest of public health.

o PSURs due for a period must be submitted within 30 calendar days of the last day of the reporting period.

The global clinical trials are classified into 2 categories on their approval duration:

Category A and Category B

Category A: Clinical trials approved by USA, UK, Switzerland, Australia, Canada, Germany, South Africa, Japan, and EMEA. DCGI will grant the approved within2-4 weeks.

Category B: Clinical trials approved by other countries not listed under category

A. Regulatory turnaround time would be approx 8-12 weeks.

Protocol amendments have been classified into three categories:

1. Those amendments which do not require any information or permission,

   a. Administrative and logistic changes

   b. Minor protocol amendments and additional safety assessments in case the IEC

2. Those amendments which require being informed but need not wait for permission,

   a. Additional investigator sites

   b. Amended investigator's brochure, amended ICD

3. Those amendments which require prior permission before implementation of the amendments,

   a. Changes of principal investigator

   b. Additional patients to be recruited

   c. Major changes in the protocol with respect to the study design, dose and treatment options.

Clinical trial on a new drug shall be initiated only after the permission has been granted by the licensing authority under rule 21 (b), and the approval obtained from the respective ethics committee.

Appendices: Provide a study synopsis, copies of the informed consent documents (patient information sheet, informed consent form etc.); CRF and other data collection forms; a summary of relevant pre-clinical safety information and any other documents referenced in the clinical protocol. has already approved these changes.

APPENDIX I;

Data to be submitted along with the application to conduct clinical trials / Import / manufacture of new drugs for marketing in the country

1. Introduction

2. Chemical and pharmaceutical information

3. Animal Pharmacology (refer Appendix IV)

4. Animal Toxicology (refer Appendix III)

5. Human / Clinical pharmacology (Phase I)

6. Therapeutic exploratory trials (Phase II)

7. Therapeutic confirmatory trials (Phase III)

8. Special studies

9. Regulatory status in other countries

10. Prescribing information

11. Samples & testing protocol

APPENDIX I-A;

Data required to be submitted by an applicant for grant of permission to import and / or manufacture a new drug already approved in the country.

1. Introduction

2. Chemical and pharmaceutical information

3. Marketing information

4. Special studies conducted with approval of Licensing Authority

Appendix II; Structure, contents and format for clinical study reports

Appendix III; Animal toxicology (non-clinical toxicity studies)

Appendix IV; Animal pharmacology

Appendix V; Informed consent

Appendix VI; Fixed dose combinations (fdcs)

Appendix VII; Undertaking by the investigator

Appendix VIII; Ethics Committee

Appendix IX; Stability testing of new drugs

Appendix X; Contents of the proposed protocol for conducting clinical trials

Appendix XI; Data Elements for reporting serious adverse events occurring in a clinical trial .

Ethical Guidelines for Biomedical Research on Human Subjects, 2006:

The Indian Council of Medical research brought out the 'Policy Statement on Ethical Considerations involved in Research on Human Subjects' in 1980 and revised these guidelines in 2000 as the 'Ethical guidelines for Biomedical Research on Human subjects'. This statement of Ethical Guidelines for Biomedical Research on Human Participants shall be known as the ICMR Code and shall consist of the following:-

(a) Statement of General Principles on Research using Human Participants in Biomedical Research

(b) Statement of Specific Principles on Research using Human Participants in specific areas of

Biomedical Research Good Clinical Practices, 2001:

Good clinical practice is a set of guidelines for bio medical studies which encompasses the design, conduct, termination, audit, analysis, reporting and documentation of the studies involving human subjects.

Conclusion:

The manufacturer / sponsor have to submit application on Form 44 for permission of New Drugs Approval under the provisions of Drugs and Cosmetic Act 1940 and Rules 1945. As the Form 44 is an application for grant of permission to import or manufacture a new drug or to undertake Clinical Trial the Central Drugs Standard Control Organization.

REGULATORY ENVIRONMENT IN US [chapter 2 (i)- USA]

Regulatory Authority: U.S – FDA

Introduction:

The U.S. Food and Drug Administration (FDA or USFDA) is an agency of the United States Department of Health and Human Services and is responsible for regulating and supervising the safety of foods, dietary supplements, drugs, vaccines, biological medical products, blood products, medical devices, radiation- emitting devices, veterinary products, and cosmetics. The FDA also enforces section 361 of the Public Health Service Act and the associated regulations, including sanitation requirements on interstate travel as well as specific rules for control of disease on products ranging from pet turtles to semen donations for assisted reproductive medicine techniques. The FDA is an agency within the United States Department of Health and Human Services responsible for protecting and promoting the nation's public health. The FDA is headquartered in Rockville, supported by 13 laboratories located throughout the United States. The agency is organized into the following major subdivisions, 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 Biologics Evaluation and Research (CBER)

The Center for Food Safety and Applied Nutrition (CFSAN)

The Center for Devices and Radiological Health (CDRH)

The Center for Veterinary Medicine (CVM)

The National Center for Toxicological Research (NCTR)

The Office of Regulatory Affairs (ORA)

The FDA works in conjunction with other Federal agencies including the Department of Agriculture, Drug Enforcement Administration, Customs and Border Protection, and Consumer Product Safety Commission. The local and state government agencies also work in cooperation with the FDA to provide regulatory inspections and enforcement action.

USFDA Guidelines for Clinical Research:

The CDER was developed to provide a user-friendly resource for obtaining information on the Centre’s processes and activities of interest to regulated industry, health professionals, academia, and the general public. The mission of FDA's Center for Drug Evaluation and Research is to assure that safe and effective drugs are available to the American people.

The CDER Center is involved in 4 important activities like:

- New Drug Review
- Generic Drug Review
- Over-the-Counter Drug Review
- Post Drug Approval Activities.
- Post Drug Approval Activities.

New drugs receive extensive scrutiny before FDA approval in a process called a New Drug Application or NDA. New drugs are available only by prescription by default. A change to Over the Counter (OTC) status is a separate process and the drug must be approved through an NDA first.

Synthesis and Purification:

The research process is complicated, time Guaranteed. FDA estimates that it takes approximately eight test a new drug before it can be approved for the general public. This estimate includes early lab human subjects.

Pre-Clinical Research:

Under FDA requirements, a sponsor must first submit data showing reasonably safe for use in initial, small-scale clinical studies.

The sponsor may have several options for fulfilling this requirements:

(1) Compiling existing nonclinical data from past in vitro laboratory or animal compound;

(2) Compiling data from previous clinical testing or marketing of the States or another country whose population is relevant to the U.S. population;

(3) Undertaking new preclinical studies designed to provide the evidence necessary to support the safety of administering the compound to humans.

During preclinical drug development, a sponsor evaluates the drug's toxic and pharmacologic effects through in vitro and in vivo laboratory animal testing. Genotoxicity screening is performed, as well as investigations on drug absorption and metabolism.

At the preclinical stage, the FDA will generally ask, at a minimum that sponsors:

- Develop a pharmacological profile of the drug.
- Determine the acute toxicity of the drug in at least two species of animals.
- Conduct short-term toxicity studies ranging from 2 weeks to 3 months depending on the proposed duration of use of the substance in the proposed clinical studies

Animal Testing:

In animal testing, drug companies make every effort to use as few animals as possible and to ensure their humane and proper care. Generally, two or more species (one Rodent, one Non-rodent) are tested because a drug may affect one species differently from another. Animal testing is used to measure how much of a drug is absorbed into the blood, how it is broken down chemically in the body, the toxicity of the drug and its breakdown products (metabolites), and how quickly the drug and its metabolites are excreted from the body.

Short-Term Testing: Testing in animals ranges in duration from 2 weeks to 3 months, depending on the proposed use of the substance.

Long-Term Testing: Testing in animals ranges in duration from a few weeks to several years. Some animal testing continues after human tests begin to learn whether long-term use of a drug may cause cancer or birth defects. Much of this information is submitted to FDA when a sponsor requests to proceed with human clinical trials. The FDA reviews the preclinical research data and then makes a decision as to whether to allow the clinical trials to proceed. After the completion of preclinical testing, the company/sponsor files and IND (Investigational New Drug Application) with the FDA to begin to test the drug in humans. It is the means through which sponsor obtain the legal status to call its new investigational molecule as new drug.

Generally, this includes data and information in three broad areas:

Animal Pharmacology and Toxicology Studies- Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans.

Manufacturing Information- Information pertaining to the composition, manufacture, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed as to ensure the company can adequately produce and supply consistent batches of the drug.

Clinical Protocols and Investigator Information- Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks.

Medical review, Chemistry review, Pharmacology/Toxicology review, Safety review are carried out on the IND application. Pharmacology and Drug Distribution are carried according to 21 CFR 312.23(a)(8)(I)rules .Toxicology Data regulations are carried according to 21 CFR 312.23(a)(8)(ii)(a) rules. The IND becomes effective if FDA does not disapprove it within 30 days.

Sponsor/FDA Meetings (Pre-IND):

Prior to clinical studies, the sponsor needs evidence that the compound is biologically active, and both the sponsor and the FDA need data showing that the drug is reasonably safe for initial administration to humans

Phase 1 Clinical Studies:

Phase 1 includes the initial introduction of an investigational new drug into humans. These studies are closely monitored and conducted in healthy volunteer subjects. These studies are designed to determine the metabolic and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. Phase 1 studies also evaluate drug metabolism, structure-activity relationships, and the Mechanism of action in humans. During Phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase 2 studies.

Phase 2 Clinical Studies:

Phase 2 includes the early controlled clinical studies conducted to obtain some preliminary data on the effectiveness of the drug for a particular indication or indications in patients with the disease or condition. This phase of testing helps determine the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well-controlled, closely monitored, and conducted in a relatively small number of patients, usually involving several hundred people. Phase 2 studies lasts from six months to two years.

Phase 3 Clinical Studies:

Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained in Phase 2, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug. Phase 3 studies also provide an adequate basis for extrapolating the results to the general population and transmitting that information in the physician labeling. Phase 3 studies usually include several hundred to several thousand people.

New Drug Application (NDA):

An NDA is an application submitted to the USFDA for permission to market a new drug product in the United States. To obtain this permission, company/sponsor submits an NDA form along with nonclinical and clinical test data and analyses, drug information and description of manufacturing procedures. As outlined in Form FDA-356h, Application to Market a New Drug for Human Use NDAs can consist of as many as 15 different sections:

_ Index;

_ Summary;

_ Chemistry, Manufacturing, and Control;

_ Samples, Methods Validation Package, and Labeling;

_ Nonclinical Pharmacology and Toxicology;

_ Human Pharmacokinetics and Bioavailability;

_ Microbiology (for anti-microbial drugs only);

_ Clinical Data;

_ Safety Update Report (typically submitted 120 days after the NDA's submission);

_ Statistical;

_ Case Report Tabulations;

_ Case Report Forms;

_ Patent Information;

_ Patent Certification; and

_ Other Information

After a NDA is received by the FDA, it undergoes a technical screening generally referred to as a completeness review. At the conclusion of FDA review, there are three possible action letters that can be sent to the sponsor:

_ Not Approvable Letter: Lists of deficiencies in the application and reasons why the application cannot be approved.

_ Approvable Letter: The drug can be approved, with the list of minor deficiencies that can be corrected.

_ Approval Letter: The drug is approved. It can be issued directly or it may follow an approvable letter

Phase 4 Clinical Trials (Post-Marketing Surveillance):

Sometimes adverse drug effects of drug comes after the drug has been in the market for a long time or been used by very large number of patients. Phase IV clinical trials mainly aim at identifying such problems. Withdrawal of a drug from the market is done based on the results of Phase IV clinical trials.

ROLE AND RESPONSIBILITIES OF CLINICAL TRIAL PERSONNEL AS PER ICH GCP [chapter 2 (j)- (1)]

Sponsor;

Quality Assurance and Quality Control;

 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.

 Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

 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.

Contract Research Organization (CRO);

 A sponsor may transfer any or all of the sponsor's trial- related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The CRO should implement quality assurance and quality control.

 Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing

 All references to a sponsor in this guideline also apply to a CRO to the extent that a CRO has assumed the trial related duties and functions of a sponsor.

Medical Expertise; The sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose.

Trial Design; 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.

 For further guidance: Clinical Trial Protocol and Protocol Amendment(s), the ICH Guideline for Structure and Content of Clinical Study Reports, and other appropriate ICH guidance on trial design, protocol and conduct.

Trial Management, Data Handling, and Record Keeping;

 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.

 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. The IDMC should have written operating procedures and maintain written records of all its meetings. When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

(a) Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e. validation).

(b) Maintains SOPs for using these systems.

(c) Maintain a security system that prevents unauthorized access to the data.

(e) Maintain a list of the individuals who are authorized to make data changes

(f) Maintain adequate backup of the data.

(g) Safeguard the blinding, if any (e.g. maintain the blinding during data entry and processing).

Investigator Selection;

 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. If organization of a coordinating committee and/or selection of coordinating investigator(s) are to be utilized in multicentre trials, their organization and/or selection is the sponsor's responsibility.

Allocation of Responsibilities; Prior to initiating a trial, the sponsor should define, establish, and allocate all trial-related duties and functions.

Compensation to Subjects and Investigators; If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence.

Financing; The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

Notification/Submission to Regulatory Authority(ies);

 Before initiating the clinical trial(s), the sponsor (or the sponsor and the investigator, if required by the applicable regulatory requirement(s)) should submit any required application(s) to the appropriate authority(ies) for review, acceptance, and/or permission (as required by the applicable regulatory requirement(s)) to begin the trial(s).

Manufacturing, Packaging, Labelling, and Coding Investigational Product(s);

 The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterized as appropriate to the stage of development of the product(s),

is manufactured in accordance with any applicable GMP, and is coded and labelled in a manner that protects the blinding, if applicable. In addition, the labelling should comply with applicable regulatory requirement(s).

 The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g. protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any.

 In blinded trials, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding.

 If significant formulation changes are made in the investigational or comparator product(s) during the course of clinical development, the results of any additional studies of the formulated product(s) (e.g. stability, dissolution rate, bioavailability) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product should be available prior to the use of the new formulation in clinical trials.

Record Access;

 The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator (s)/institution(s) provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection.

Safety Information;

 The sponsor is responsible for the ongoing safety evaluation of the investigational product(s).

Adverse Drug Reaction Reporting;

 The sponsor should expedite the reporting to all concerned investigator(s)/institutions(s), to the IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all adverse drug reactions (ADRs) that are both serious and unexpected.

Monitoring;

a) Selection of qualified Monitors

b) The sponsor should ensure that the trials are adequately monitored.

c) Assign Monitor's Responsibilities

d) Verifying for the investigational product(s)

e) Establish SOP’s as well as procedures that are specified for monitoring a specific trial

f) Monitoring Reports should be evaluated on timely basis.

INVESTIGATOR [chapter 2 (j)- (2)]

Investigator's Qualifications and Agreements;

 The investigator(s) 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(s), 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 (ies).

 The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.

 The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements

 The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority (ies).

 The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

Adequate Resources;

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

 The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

 The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

Medical Care of Trial Subjects;

 A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.

 During and following a subject's participation in a trial, 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.

 Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

Communication with IRB/IEC;

 Before initiating a trial, the investigator/institution 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 (e.g., advertisements), and any other written information to be provided to subjects.

 During the trial the investigator/institution should provide to the IRB/IEC all documents subject to review.

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(ies) and which was given approval/favorable opinion by the IRB/IEC.

 The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favourable opinion.

Investigational Product(s);

 Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution. The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, 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(s).

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

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.

 Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

 All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

Records and Reports;

 The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsorin the CRFs and in all required reports.

 Data reported on the CRF, that are derived from sourcedocuments, should be consistent with the source documentsor the discrepancies should be explained.

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.

Safety reporting ;

 All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports.

Premature Termination or Suspension of a Trial;

 If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies).

Final Report(s);

 Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the trials outcome, and the regulatory authority(ies) with any reports required.

CLINICAL RESEARCH ASSOCIATE [chapter 2 (j)- (3)]

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. Consequently, the CRA must be knowledgeable about both the regulatory and sponsor-specific requirements for reporting serious and non-serious adverse events in clinical trials.

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

o Providing initial training on adverse event reporting requirements for investigators ;

o Reviewing data to assure accuracy and completeness of reported events;

o Providing new information to the investigator;

o Monitoring the clinical trial to detect potentially unreported adverse events; and

o Assuring follow-up data is reported for adverse events when require

RESPONSIBILITIES:

Evaluating &Selecting the investigators;

The Monitor is responsible for selecting the investigator/institution. Each investigator should be qualified by training experience and should have adequate resources to properly conduct the trial for which the investigator is selected

Pre Study Visit (site selection visit);

Conducted at a potential research site Assess the investigator's experience, staff, facility and potential patient population Introduce the study & obligations to the potential investigator & staff

Site Initiation Visit;

Conducted at a confirmed research site Verify the confirmed investigator's experience, staff, facility and potential patient population Detail the study & obligations to the potential investigator & staff.Collect all essential documents before this visit.

Routine Monitoring Visit;

CRA's main activity – study monitoring

Purpose of monitoring:

 Rights& well being of subjects are protected reported data are accurate, complete & verifiable from source documents

 Rrial conduct is in compliance with protocol, GCP & applicable regulatory requirements

Routine Monitoring Visit;

 Review IP handling, storage conditions, receipt, use, return and disposition

 Review all informed consent forms

 Review protocol compliance

 Review CRFs, source documents, site file

 Review AEs/SAEs

 Review facilities, resources, staffing

 Address questions and/or concerns

Site Close out Visit;

Site close out visit is conducted when

 Study is complete & finished

 Enrollment has stopped

 All subjects have completed their study related activities

 Data are complete & correct

 Final IP accountability is done

Site Close out Visit;

Site close out visit is conducted to

 Retrieve all appropriate study supplies

 Verify that study documentation is complete & accurate

 Ensure that site is in compliance with regulatory & GCP guidelines

Brief List of 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.

QUALIFICATION:

A Bachelors Degree in a medical, health, or science related area; MS degree preferred. Minimum of 2 years medical / science background and relevant experience; experience of clinical trial management would be preferable.

 Knowledge of SFDA regulations and ICH/GCP guidelines.

 General knowledge of clinical/ laboratory terminology.

 Good problem solving and analytical skills.

 Computer literacy desirable.

 Strong oral and written communication skills in English.

 Must be able to travel if required.

ROLES AND RESPONSIBILITIES OF AUDITOR [chapter 2 (j)- (4)]

Audit is 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, analysed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), good clinical practices (GCP), and the applicable regulatory requirements. Investigator sites, Sponsor, CRO, ERB are liable to get audited. The auditors are independent individuals appointed by sponsors/regulatory authorities to conduct a systematic and in- depth examination of trial conduct, and compliance with Protocol, SOPs, GCP, GLP, GPP and the applicable regulatory requirements. An audit is separate from routine Monitoring or quality control functions. The regulatory auditor is a suitably qualified employee of the FDA/DCGI/Other regulatory bodies whose responsibility is to conduct announced or unannounced inspection visits at clinical trial sites as required/instructed by the regulatory bodies. Most auditors visits are prearranged but some may not, especially where there is suspected serious breathes of the GCP or malpractices.

Regulatory auditor is responsible to perform following types of audits:

1.Investigational site audits

2.Clinical department process audits

3.Data management audits

4.Safety department audits

5.GCP laboratory audits

6.Sponsor central file audits

Investigational Site Audits; These audits of study sites can be routine: to assess a site's performance; identify deficiencies and develop a corrective action plan; determine the sponsor's level of risk Audits can be conducted "for cause" that is, when the sponsor believes that a site is non-GCP compliant or is suspicious of investigator gross negligence or fraud.

Clinical Department Process Audits; The clinical research departments of clinical trials sponsoring companies and firms responsible for post marketing surveillance are being audited here. Reasons for conducting these audits are:

- potential for a regulatory inspection
- desire to improve effectiveness and efficiency
- benchmarking against other clinical departments
- satisfying concerns of upper level management

Data Management Audits; Sponsor companies and CRO's data management departments are being audited during these audits. Some of the objectives of these audits are to:

 compare data in data sets against data in CRFs

 review error programs and the query system

 assess treatment of outlier data

 review data transformation and imputation methods

 review file structure and merger of data sets

 check security and backup procedures

Safety Department Audits; Here auditors examine a sample of serious adverse events, either pre or post marketing for the following criteria:

 accuracy of reports and coding

 timelines of regulatory submission

 completeness and follow-up where necessary

 Match with adverse event data

 Thoroughness of analysis (signal and trend analysis)

 Potential "hidden SAE" within the SAE

 Down coding or down grading

 appropriate use of technology in processing events.

The audits evaluate departmental processes and procedures with the objective of achieving regulatory and industry standards and for making improvements.

GCP Laboratory Audits; Clinical, analytic, and reference laboratories often participate in clinical trials by processing blood, urine, and saliva samples. It is vitally important that test results are valid and accurately reported. Regulatory auditors examine data records and record keeping and transmittal procedures at these laboratories to determine if these data are accurate. In part, this review establishes that each sample for each patient is reported correctly. Thus auditor is responsible to establish that research was conducted under proper authority with sound scientific rationale, rights/safety/well-being of research subjects was protected and final study data supports the conclusions.

Sponsor Central File Audits; All inspection of sponsors, CROs are conducted without prior notification unless otherwise instructed by the assigning center.

Inspection are conducted to determine :

 How sponsor assure to validity of data submitted to them by Clinical Investigator.

 The adherence of sponsors to applicable regulations.

CLINICAL RESEARCH COORDINATOR [chapter 2 (j)- (5)]

The CRC is a vital link between the research subjects and their family, the investigator, and other site team members. They are also the liaison between the Sponsor, CRO, SMO, Central laboratory, Courier, the Institutional Review Board (IRB), and other players involved in the trial. Because of an increase in the number of clinical trials and the need for complicated and data intensive research, many sponsors today are reluctant to place a trial at a site that does not have a trained CRC to work along with the investigator.

Responsibilities Of CRC's

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:

 General responsibilities

 Trial specific responsibilities

General responsibilities;

Capacity Building

The CRC ensures that the potential pool of potential Investigators and Sites keep increasing. The CRC is always on the lookout for new trial sites with Investigators who are research naïve. They conduct an in-depth survey of the new sites to assess:

o Manpower presence and competence

o Support staff and constant support

o Infrastructure

o Presence of a functional Ethics Committee

o Compatible management

o Major diseases – incidence and prevalence rates

Training new CRCs;

Experienced CRCs are an asset and often are the best persons to hand-hold and train the newcomers in the field of clinical research. The training may include conducting feasibility studies, designing trial documents, setting up of sites, conduct of the trial and trial closeout.

Trial - related Responsibilities;

Site Identification;

A key responsibility of the CRC is to identify the right site for the trial – one that fulfills all the criteria set forth by the clinical trial guidelines and trial protocol. A CRC who has worked at a particular site earlier is often the best judge to identify the site for another trial. Having worked at a site for over a period of time, the CRC understands the needs, expectations, and the potential of the site. He/she knows how the site can function to its optimum.

Pretrial Documentation;

A CRC has to collect the updated and signed resume of each member of the site team. He/She must ensure that the o following pretrial documents are completed within the specified timeline:

Form 1572

o Financial Disclosure Form

o Undertaking from the PI

o Confidentiality Non-Disclosure Agreement

Coordinating with the IRB;

You can actively follow up through the site team with the IRB for a faster approval of the trial. You will also look into the timely submission of all the safety reports and the amendments of the trial documents to the IRB.

Financial Responsibilities;

Sometimes a senior CRC may be empowered to negotiate thetrial budgets at the site. This includes the investigator fees, the IRB fees, the site administration fees, laboratory costs, study subject travel and other reimbursements. Track the trial on a routine basis. Inform the concerned personnel on reaching specific milestones. All milestone-related payments will be followed up by you.

Training the Site Staff;

The CRC must be ready to train the site staff on a regular basis throughout the trial. He/she can highlight on:

o Inclusion criteria

o Exclusion criteria

o Schedule of visits

o Window period

o Visit specific activities

o Safety guidelines and reporting timelines as per the protocol

Investigators' Meeting and Site Initiation Visits ;
The CRC may be in charge of conducting the entire investigators' meeting for the trial. They also have to ensure that all the requirements are in place for the site initiation visit.

Informed Consent Forms ;

The CRC ensures that the informed consent form sent by the sponsor is translated and back-translated into the local language as advised by the investigator.

Patient recruitment and follow up;

During the subject enrollment, he/she ensures that all queries are clarified up to the subjects' satisfaction and that the ICF is administered by the Investigator as per the ICH GCP guidelines.

Research Pharmacy, Drug Accountability, and Laboratory Responsibilities;

The CRC also have to manage the storage of the study drug -account for study drug received from sponsor, distributed to the patient, returned from the patient and finally back to the sponsor. They ensure that all laboratory specimens such as blood, urine, tissue etc are properly labeled, packaged and stored before shipment to the central lab. They even coordinate with the central lab on a regular basis for the timely receipt of the reports.

Amendments;

They follow up with the sponsor for any amendments in the study protocol or the ICF and ensure that the amended versions are implemented at the site only after the favorable written approval by the IRB.

Post-trial activities;

Once the hospital phase of the trial is over, completing the study documentation will become the key focus3. They do a final check of the case report forms (CRFs), maintain an archival inventory of records and CRFs in a secure place and coordinate the close out visits.

REGULATORY AUTHORITY [chapter 2 (j)- (6)]

1) Must act according to laws to implement and enforce the laws .
2) In general, the regulatory authority bears responsibility for:

o Allowing a protocol to proceed

o Ensuring the quality of the investigational product

o Ensuring subject rights and safety during a study

o Assuring and using quality study data for regulatory decision-making

o Inspecting the parties who conduct or oversee the study

o Receiving and acting on complaints about a clinical study

o Educating the parties who conduct or oversee the study

Allowing a Protocol to Proceed;

Should ensure that both scientific and ethical review have been performed

* Regulatory Authority's Review;

May include inspection of non-clinical (animal toxicology) studies/facilities supporting the protocol

*Independent review(s);

Expert review(s);

Ethics Committee review Should include authority for the regulator to NOT allow the protocol to proceed or to require modification of the protocol l before proceeding

Ensuring the Quality of the Investigational Product;

In accordance with national/local laws and regulations, regulators may

o Establish Good Manufacturing Practice (GMP) requirements for investigational products

o Review manufacturing data submitted in support of research permits

o Inspect manufacturing facilities

o Establish requirements for the import of investigational products.

Ensuring Subject Rights and Safety during the Study;

o Should include the regulator's receipt and review of safety information (especially serious and unanticipated adverse experiences) during the study

o Should include knowledge by the regulator of safety concerns with the investigational product in other studies of the product

o May include the regulator's requesting or requiring independent data and safety monitoring boards (DSMBs) for the study

o Should include assurance to the regulator that informed consent and ethical (IEC) review is conducted prior to initiating the study and continued during the study

o Regulatory authorities also need to be alert to the issue of subject confidentiality and any applicable national/local laws and regulations for handling private medical information

o Regulators should have the authority to stop a study if they find that subjects are or will be exposed to an unreasonable risk

The regulatory authority should implement procedures to receive, review, evaluate, and as appropriate, follow-up (e.g., by inspection) on any such complaints

Ensuring the Quality of the Investigational Product;

In accordance with national/local laws and regulations, regulators may

 Establish Good Manufacturing Practice (GMP) requirements for investigational products

 Review manufacturing data submitted in support of research permits

 Inspect manufacturing facilities

 Establish requirements for the import of investigational products.

*Establishing a System of Ethical Review States should promote the establishment of Ethics Committees (WHO)

*Promote development of independent ethical review within a country

*Ensure clear and efficient communication between committees

*Ensure ongoing education of IEC members

*Establish procedures for the review of protocols carried out at more than one site in a country or in more than one country

*Receiving and Acting On Complaints Ensuring Subject Rights and Safety during the Study.

Designing (CRF) [chapter 2 (k)- CRF]

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 subject's 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 vanous 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, blinding, 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

PURPOSE OF INFORMATION TO BE COLLECTED;

The data collected through CRF should address two main issues:

1.Study hypothesis.

2.Drug safety.

The CRF should provide the accurate data to achieve the objectives proposed in the study protocol. The honest and complete recording of information in a GCP compliant pattern avoids discrepancy and speeds up drug approval process

FORMATTING CRF;

The assessment parameters should be presented in a logical sequence, which ensures careful and accurate completion of CRF is important for quick data processing. A complicated CRF is an invitation to error and misinterpretation at all steps particularly in the hands of a busy investigator. Thus, a good quality CRF ensures complete, credible and reliable data generation .

*Ideally multiples assessments done on each patient should appear in the CRF in the same format and sequence as performed, for all visits. This not only helps the investigator to complete all assessments but also assists in database building and quick data entry.

*The various assessments should be separated by white space not to be utilized for writing notes/remarks by the investigator. However, a separate global comments page should be provided with the CRF for his remarks.

* An easily readable font style should be selected which encourages detailed review of the CRF and its filling, (e.g. Helvetica or Arial).

* All text should preferably be 12 point size, which is neither too small not too large. Moreover the text should be well-spaced with proper page breakup for easy reading.

* The margins should be identical in all CRF pages, text needs to be turned 90 degrees e.g,, column holders, the text should be turned as complete words and not printed as individual letter, stacked on top of other.

* Avoid using hyphenation in the CRF text. It may convey a different meaning if used liberally e.g., therapist may read as the-rapist.

ENTERING DATA INTO DATABASE;

1. The CRF should be formatted such that repeated observations taken (e,g., temperature, blood pressure, pulse etc) can be recorded in separate lines rather than single line horizontally.

2. The units of all measurements should be specified in the CRF to maintain uniformity, and appropriate boxes should be provided to avoid confusion

3. The CRF entries should be neatly written preferably in block letters to avoid errors. Appropriate space should be provided in each column to avoid overriding, abbreviations or cryptic comments overflowing the allotted space. The data management personnel may have tough time to figure out the medical terms, medication, microbial species, laboratory tests, etc., if the text is illegible. This becomes more pronounced in multinational studies since different nations have different fonts.

4. Attempts should be made to minimize,v_aphical. data e.g., visual Analogue-Scale. The linear scale may be intercepted in different ways causing inconsistency. If graphics are unavoidable, the CRF designer should first decide on data coding for the database in consultation with the data manager and then design the graphic to reflect that code.

INSTRUCTIONS FOR CRF COMPLETION;

The investigator should be provided clear instructions for CRF completion with respect to subject eligibility, assessments. On every visit, subject's compliance, concomitant medication, adverse event recording reporting etc. The instructions can be presented in the form of instruction manual or instruction page that accompanies CRF. This includes the general instructions for collecting the data, completion of CRF and dealing with correction of entries made in error. Date and time format should also be explained at this point. Moreover, the page should also guide to account for missing or unknown data. Graphical representations can be helpful. It may be good to include a list of assessments (or flow chart) to be carried out at the beginning of each visit, which will remind the investigator to ask the relevant questions and take appropriate actions. Moreover, reminders should appear at appropriate place in the CRF e.g., enquiring adverse events, ensuring laboratory reports, ECG etc., for recording and completing the CRF. Method to record dosages and frequency should be indicated. Similarly, list of prohibited medicines can be put against the concomitant page. Instructions for deviations from CRF items should also be highlighted

FRAMING THE QUESTIONS FOR CRF;

As we have seen in the earlier sections, a good CRF should be clean, precise and easy for the study co-ordinator or the investigator to enter the data with no ambiguity. Therefore, it is essential that the questions be framed in a manner that elicits a suitable answer. The question and response formats in a CRF are grouped as follows:

a. Alphanumeric and free text.

b. Multiple choice including binary options.

c. Matrix arrays.

d. Analogue scales.
A CRF designer uses a combination of these sets.

Alphanumeric and Free Text;

This method is used to indicate certain data such as the patient identification adverse event and treatment responses. The responses utilize words and/or numbers. To enter these data, either a free space or constrained space with character separators is provided. Free space gives psychological freedom to the investigator/CRC but, increases the chances of wrong entries, cancellations and re-entries. Character separators ensure that the first entry is the right entry.

Multiple Choice Questions;

In certain instances like collection of demographic data, it is easier for a CRC/ investigator to tick an answer from the options given rather than writing a self- generated answer. Multiple choice questions are, therefore, the most preferred format of questionnaire that saves time and also reduces the ambiguity. Designing these questions must be done skilfully. Although the answers appear simple, the questions must be specific and the expected answer should not have any other options than the mentioned ones. Furthermore, the lay out of questions must also be considered. For instance, while framing questions on eligibility criteria, it is always advisable that the answer is YES as the desired option for all inclusion criteria and NO for all.

Matrix Arrays;

These are utilized to obtain specific information on different categories collectively. The questions are usually arranged in rows and each question has an option from the choices arranged in columns, The options for each question can be ticked. This format provides comprehensive information during analysis

Analogue Scales;

In a clinical trial, it is necessary to asses the progress of the disease or the response to the treatment by comparing the base line observations with the ones observed in the follow-up visits. Analogue scales are often used for some of the assessment

FORMATTING A QUESTIONNAIRE;

Sections of CRF may involve a questionnaire to be filled by the patients valuable especially in cases of evaluations of quality of life. The questionnaires need to be designed keeping in mind that they are to be filled by patients speaking different languages of different backgrounds, age group, etc.

General guidelines:

a. Use simple and non-technical language.

b. Use examples wherever necessary.

c. Minimize free text entry.

d. The duration of recording in daily card should preferably not exceed 2-4 weeks. Fresh cards are to be provided after two weeks.

e. Font size should be more than 1.0 to enable comfortable reading by the aged.

PRINTING REQUIREMENTS;

The efforts of designing and formatting the CRF can be translated into use only if good printing is ensured. Printing plays an important role in adding values to the quality of CRF. It is desirable to coordinate between the project manager and the printer resolving queries. The printer needs to be well-informed about various requirements of a CRF such as:

i. The dimensions of the paper to be used.

ii. The weight and the colour of the paper.

iii. The margin to be allocated so that binding does not go through the printed text.

iv. Font sizes for header, footer and the text.

v. Colour of ink to be used.

vi. Logo formats.

If the material is supplied to the printer as an electronic file, the printer must have an access to the same program and templates that have been used in the design.

PACKAGING AND ORGANIZING THE CRF BOOK;

Once the final version is ready for printing, it has to undergo a proofreading by at least two members of the team, after which it is approved for final printing. The next step is to decide the number of copies required per page. Ideally three copies should be printed per page considering one for the investigative site, second for the sponsor and third to be used as a worksheet for corrections. It is advisable to use a different colour for each of the copies. The usage of No Carbon Required (NCR) paper is recommended. The enormous data collected in the case 'Tort form neceitates that the forms be bound in copies the form of a booklet. This ensures the ease of usage and integrity of the data. The CRFc can be prepared by doting different types of binding such as:

 Stapled

 Stitched and glued

 Spiral bound

 Wire bound

 Three ring binder.

ERRORS IN CRF ENTRY;

Inspite of the instructions and guidelines provided for CRF completion several errors have been identified during monitoring visits and at data entry level. Incomplete and missing information leads to poor quality of data which may affect the study outcome. All the errors identified need to be rectified before data entry and analysis. The common errors encountered in the filled CRF are as follows:

1. Inconsistencies between the source document and CRF

2. Missing data

3. Inconsistencies across the visits

4. Illegible data

5. Spelling errors

6. Blank 'mandatory comment fields'

7. Unacceptable terminology

8. Missing investigators signature.

Errors identified in the CRF have to be dealt with the help of an query form that is specific to the CRF of the particular study provided by the sponsor.

PROCEDURE FOR MAKING CORRECTION IN THE CRF;

Query can be generated by the CRA or data entry operator. The identified errors must be discussed by the CRA with the investigator and CRC to obtain the explanation. The CRC must make the necessary corrections by striking a line through the incorrect entry, entering the correct data with date and initials. The reason for the change has to be explained. The original entry should not to be whiteout or erased from the CRF as one must be able to see the original incorrect value, i.e. no corrections should obscure the original entry.

ELECTRONIC CASE RECORD FORM (eCRF);

Among the various challenges in the drug developmental process, one of the key challenges faced by the sponsor, investigators and CROs is how to manage the large volume of clinical data generated in an efficient, secure and cost effective manner. Electronic version of Case Report Form is getting importance due to the ease of application as compared to the paper based CRF. Due to the

advancement of information technology and the need for better data management, the present focus has been shifted to electronic version CRF. Electronic CRF initially started as scanned copy of filled paper CRF This partially solved the problems associated with data analysis, but data was still recorded on paper. With the advent of electronic data transfer and electronic signature, the security of data was well assured and it made the remote data entry possible. This minimized the data entry errors and reduced the time required to lock the database at the end of the study. This has to be in compliance with international standards as described in 21 CFR Part 11. The use of electronic device/software that enables the investigator to enter the patient data directly into eCRF electronically is called electronic data capture (EDC) process. Among the different types of data, laboratory results get entered directly into eCRF.The results generated from analytical instruments and from automated machines get transferred electronically into electronic database. Though vital parameters can be recorded digitally, usually they are first recorded in paper CRF and later gets transcribed to eCRF. Various methods of electronic data capture such as Interactive Voice Response System (IVRS), Interactive Web Response System (IWRS), etc. are employed to collect data and the same is electronically represented in eCRF. Electronic data capture (EDC) has been an effective tool to speed up the process of data entry and enhancing the quality of data obtained during a trial. With the advent of Internet Based Clinical Trials (IBCT) and Clinical Data Interchange Standards Consortium (CDISC), many pharmaceutical companies have initiated enforcing eCRF based eTrials. It is a fundamental GCP requirement for investigator to "maintain" a copy of eCRF as per 21 CFR 312 62.b section. These are the investigator's records, which must be prevented from being modified without their knowledge.

Types of eCRF;

eCRF exists in two formats

I. Tagged Image File Format (TIFF)

2. Portable Document Format (PDF)

DESIGNING OF eCRF;

Designing of a CRF is an important process since it is essential to collect all the data specified in the protocol. The process of designing an eCRF involves various steps. Designer should draft the first version of CRF based on the protocol requirements and sponsor's specifications. Once the basic design of CRF is drafted, the programmer can begin to generate the data entry screens of eCRF. This will be reviewed by the original designer for accuracy and errors detected in the design will be rectified. During this review period, online edit checks too will be programmed into eCRF by providing sites with immediate feedback to coned the errors or missing data, thereby ensuring clean data which helps in locking the database. It will be further subjected to scrutiny for overall navigation layout (the visits and forms associated with each visit), form content and edit checks for both accuracy and completeness of eCRF, after which the final version will be approved and released.

DIFFERENCES BETWEEN eCRF VERSUS PAPER CRF;

Though there are intrinsic differences between electronic and paper CRF, visual impressions of both should remain the same.

1. Paper CRF can be viewed as a booklet, whereas, in eCRF only a single page is displayed on the screen.

2. In a paper-based CRF, cleaning and reviewing data is a difficult and time consuming process which has been simplified with eCRF.

3. High cost and delay associated with printing, binding, shipping, tracking of paper CRF can be avoided with eCRF. It also minimizes the generation of wastes arising from unused printed CRF records.

4. Unlike paper CRF, eCRF avoids double key data entry, spelling errors and issues regarding legibility while entering the data.

5. Recording of surplus information in paper CRF may lead to overcrowding which can be avoided in eCRF, just by clicking on the icon "add another."

6. The problems associated with archival of paper CRF viz., space, storage conditions, retrieval of data, etc. is not encountered with eCRF.

7. The confidentiality of data is high in eCRF in comparison with paper CRF due to security provided through password protection.

8. The quality of data can be checked by remote review without any personal visit to the site and timelines of data entry can be controlled in eCRF which is not possible with paper CRF.

DESIGNING INFORMED CONSENT FORM (ICF) [chapter 2 (k)- ICF]

Informed consent is an essential part of the design of every research project involving human subjects. Researchers who involve human subjects in their research have both an ethical and legal obligation to secure the informed consent of the potential research subjects prior to initiation of the research.

I. General Elements of Informed Consent;

The basic elements of effective informed consent are:

A. the full disclosure of the nature of the research, any risks and benefits, and a description of what the subjects will experience;

B. adequate information for the potential subjects to make an informed choice about participating in the research;

C. disclosure of measures to protect privacy and confidentiality;

D. affirmation of the subject's voluntary choice to participate.

II. Specific Elements of an Informed Consent Document;

In order to assure that these general elements are included, an appropriate informed consent document should include the following written to and in understandable language for potential subjects:

A. A general description of the study and its purpose or goal.

B. A description of the procedures and measures or observations involved in the study (tell them what they will experience)

C.A statement indicating how much time participation in the study is expected to take.

D.A description of any benefits which may be reasonably expected for both

E. A description of any foreseeable risks or discomforts to the potential research subject. This section should include information from your IRB application regarding possible stress or risks for the research subjects, information regarding personal or sensitive questions, and disclosure if any of the materials to be presented might be considered offensive, threatening or degrading. the potential research subject and society. If there is no direct benefit for subjects, that should be stated.

F. An explanation as to what medical and/or mental health care services are available and contact information (the name, location, and phone number of the UCO Student Counseling Services or Mercy Health Clinic) in cases where research involves more than minimal risk.

G. Phone and email contact information for questions or concerns about the research (for each Principal Investigator and Co-PI).

H. Contact information for UCO IRB for questions about research participation.

I. A description of how the confidentiality of records identifying the subject will be maintained. This section should include information from your IRB application. We strongly urge that, where possible, data be stored on campus in a secure office file. You must specify the location of all documents related to the study and the person responsible for them in case these records need inspection. Federal guidelines require that signed consent forms be kept at least 3 years following the end of the study. Contact the ORC to discuss storage issues. Completely de-identified data records may be kept as long as needed.

J. A statement that participation in the research is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits

III. Informed Consent Modifications & Waivers;

In special situations, evaluated on a case-by-case basis, the UCO IRB may approve a consent procedure which modifies or waives the requirement to obtain written informed consent under one or more the following conditions:

A. The research cannot practicably be carried out without the waiver; e.g., research that must, due to the requisites of its design, purposefully mislead/deceive research subjects.

B. It is research that involves no more than minimal risk to the research subjects;

C. Subsequent to the research, the research subjects will be provided a statement (information sheet) containing the basic elements of the consent form which describe the research project.

DESIGNING PROTOCOL [chapter 2 (k)- protocol]

 Study Summary:

Study summary should include the following:

 Protocol title (The title on related IRB submissions (e.g., applications for new study, changes in procedure, research progress reports) must match the title of the protocol)

 Study phase

 Duration of the study

 Methodology

 Study site

 Approximate number of subjects

 Name, title, address, and telephone number of the PI, Co-PI, sponsors and study coordinators

 Investigator's affiliation

* List of Abbreviations:

Provide a list of abbreviation used in the study protocol.

* Background Information/Significance;

 Name and description of the investigational product, and in case of retrospective reviews, justification for the chart and medical record reviews.

 Summary of results from prior clinical studies and clinical data to date.
• Human subjects risks and benefits.

 Description of the population to be studied.

 Description and justification for the dosing regimen and treatment period.

 A paragraph stating that the clinical study will be conducted in compliance with the protocol, SOPs and the federal, state and local regulations.

 Citations from the references and data relevant to the study that also provides background for the trial.

* Objectives/Rationale/Research Question;

 Include a detailed description of the primary and secondary objectives and the purpose of the study and clearly state your research hypothesis or your question.

 Discuss the project's feasibility.

 Give details of resources, skills and experience to complete the study.

 Include any pilot study information

* Clinical Study Design:

 Primary and secondary endpoints, if any, to be measured during the study.

 Include the information that is needed to answer the research question.

 Include the study design e.g. single, double-blind, observational, randomized, retrospective etc. A schematic diagram of the study design would be helpful.

 Include the amount of dosage, dosing regimen of the drug, packaging and labelling of the experimental drug.

 Explain how the study drug will be stored and dispensed.

 Include the expected duration of the study and subject's participation and a description of the sequence and duration of all study periods.

 Include any follow up visits.

 Describe when a subject's participation in the trial may be discontinued.

 Maintenance of randomization codes and confidentiality.

 Describe the potential risks and step s taken to minimize the risks.

 Identify possible benefits of the study.

* Inclusion and Exclusion criteria of the Subjects;

 Include subjects inclusion criteria.

 Include subjects exclusion criteria. Women of childbearing potential may not be routinely excluded from participating in research, however, pregnant women should be excluded unless there is a clear justification to include them.

 Include enrolment of persons of diverse racial and ethnic back grounds to ensure that the benefits of the research study are distributed in an equitable manner.

* Informed consent form process;

 Provide information about the regulatory requirements of the consent form and which languages will be used.

 Include a discussion of additional safeguards taken if potentially vulnerable subjects will be enrolled in the study e.g., children, prisoners, cognitively impaired and critically ill Subjects .

 Specify Code of Ethics under which consent will be obtained.

 Include a copy of the proposed informed consent along with the protocol.

* Adverse Event Reporting;

 Describe your plan to report any adverse event.

 Anticipated adverse events should be clearly documented.

 Identify the type and duration of follow up and treatment for subjects that experience an adverse event.

* Assessment of Safety and Efficacy;

 Be specific about the efficacy parameters.

 Include the methods and timing for assessing, recording, and analyzing efficacy parameters.

 Specify the safety parameters.

 Record and report properly all the ad verse events and inter current illnesses.

*Treatment of Subjects:

 List all the treatments to be administered including product's name, dose, route of administration, and the treatment period for subjects.

 Include all medication permitted before and during the clinical trial.

 Include the procedures for monitoring subject compliance.

* Data Collection Plan:

 Define the type of data collection instrument that will be used and list all the variables.

 Specify if computerized databases will be used.

 Identify what software will be used.

 Explain precautionary steps taken to secure the data.

* Data Access;

 Inform who will have access to the data and how the data will be used. If data with subject identifiers will be released, specify the person(s) or agency to whom the information will be released and the purpose of the release.

 Address all study related monitoring, audits, and regulatory inspections.

Statistical Methods;

 Describe the statistical methods in detail.

 Include the number of subjects you are planning to enroll. For multi-center studies, include the total number of sites expected and the total number of subjects to be enrolled across all sites.

 Provide the rationale for the sample size , the calculations on the power of the trial and the clinical justification.

 Procedure of accounting for missing, unused and spurious data

 Procedures for reporting deviations from the original statistical plan.

 Include the selections of subjects to be included in the analyses

*Conflict of Interest:

Identify and document clearly any consultative relationship that the principal or co-investigators has with a non-USF entity related to the protocol that might be considered a real or apparent conflict of interest.

* Publication and Presentation Plans:

List any meetings or conference you will be presenting the data and the results of your study.

* Timeline:

 A short paragraph stating when you plan to start and complete the study.

 Include a description e.g. subjects enrolment within a month, data collection within 6 months etc.

* References:

List all the references used in the back ground section at the end of the protocol.

INFORMED CONSENT PROCESS [chapter 2 (L)]

Informed Consent of Subject:

Prior to the beginning of the Study the Investigator(s) should obtain the Ethics Committee's approval for the written informed consent form and all information being provided to the Subjects and / or their legal representatives or guardians as well as an impartial witness. None of the oral and written information concerning the Study, including the written informed consent form, should contain any language that causes the Subject(s) or their legal representatives or guardians to waive or to appear to waive their legal rights, or that releases or appears to release the Investigator, the Institution, the Sponsor or their representatives from their liabilities for any negligence.

The information should be given to the Subjects and / or their legal representatives or guardians in a language and at a level of complexity that is understandable to the Subject(s) in both written and oral form, whenever possible.

Subjects, their legal representatives or guardians should be given ample opportunity and time to enquire about the details of the Study and all questions answered to their satisfaction. The Investigator(s), Sponsor or staff of the Institution should not coerce or unduly influence a potential Subject to participate or to continue to participate in the Study. Careful consideration should be given to ensuring the freedom of consent obtained from members of a group with a hierarchical structure- such as medical, pharmacy and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, and members of the armed forces. Persons with incurable diseases, in nursing homes, in detention, unemployed or impoverished, in emergency rooms, homeless persons, nomads, refugees and any ethnic or racial minority groups should be considered as vulnerable population whose mode of consent should be carefully considered and approved by the Ethics Committee.

Prior to the Subject's participation in the Study the written Informed Consent form should be signed and personally dated by

1. (i) The Subject or (ii) if the Subject is incapable of giving an Informed Consent for example children, unconscious or suffering from severe mental illness or disability, by the Subject's legal representative or guardian or (iii) if the Subject and his legal representative or guardian is unable to read / write,

2. An impartial witness who should be present during the entire informed consent discussion

3. The Investigator

By signing the consent form the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the Subject or the Subject's legal representative or the guardian, and that informed consent was freely given by the Subject or the Subject's legal representative or the guardian. The Subject's legal representative or guardian (if the subject is incapable of giving an Informed Consent for example children, unconscious or suffering from severe mental illness or disability), the inclusion of such patients in the study may be acceptable if the ethics committee is in principle, in agreement, and if the investigator thinks that the participation will promote the welfare and interest of the Subject. The agreement of a legal

representative or the guardian that participation will promote the welfare and interest of the Subject should also be recorded with dated signature. If, however, neither the signed Informed Consent nor the witnessed signed verbal consent is possible – this fact must be documented stating reasons by the Investigator and also brought to the knowledge of Ethics Committee without any delay.

Essential information for prospective research on subjects:

Before requesting an individual's consent to participate in research, the investigator must provide the individual with the following information in the language he or she is able to understand which should not only be scientifically accurate but should also be sensitive to their social and cultural context:

(i) the aims and methods of the research;

(ii) the expected duration of the subject participation;

(iii) the benefits that might reasonably be expected as an outcome of research to the subject or to others;

(iv) any alternative procedures or courses of treatment that might be as advantageous to the subject as the procedure or treatment to which she/he is being subjected;

(v) any foreseeable risk or discomfort to the subject resulting from participation in the study;

(vi) right to prevent use of his/her biological sample (DNA, cell-line, etc.) at any time during the conduct of the research;

(vii) the extent to which confidentiality of records could be able to safeguard, confidentiality and the anticipated consequences of breach of confidentiality;

(viii) free treatment for research related injury by the investigator / institution;

(ix) compensation of subjects for disability or death resulting from such injury;

(x) freedom of individual / family to participate and to withdraw from research any time without penalty or loss of benefits which the subject would otherwise be entitled to;

(xi) the identity of the research teams and contact persons with address and phone numbers;

(xii) foreseeable extent of information on possible current and future uses of the biological material and of the data to be generated from the research and if the material is likely to be used for secondary purposes or would be shared with others, clear mention of the same;

(xiii) risk of discovery of biologically sensitive information;

(xiv) Publication, if any, including photographs and pedigree charts.

The quality of the consent of certain social groups requires careful consideration as their agreement to volunteer may be unduly influenced by the Investigator.

Informed Consent in Non-Therapeutic Study:

In case of a Non-Therapeutic Study the consent must always be given by the subject. Non-Therapeutic Studies may be conducted in subjects with consent of a legal representative or guardian provided all of the following conditions are fulfilled:

1. The objective of the Study cannot be met by means of a trial in Subject(s) who can personally give the informed consent

2. The foreseeable risks to the Subject(s) are low

3. Ethics Committee's written approval is expressly sought on the inclusion of such Subject(s)

CLINICAL DATA MANAGEMENT [chapter 2 (m)]

All clinical trials are performed to answer certain questions about the efficacy and safety of a drug or device. The answers solely depend upon the quality of data, which are collected during the trial and submitted after the trial. The study data is an immense asset for the pharma and biotech companies. Probability of getting a drug or device being approved for marketing increases if the study data is in good shape. Hence data management plays a crucial role in ensuring the success of a trial. Adopting proper methods to manage the trial data helps in increasing the quality of data. Learning, practicing and improving upon these methods has lead to the creation of clinical data management as a subject. However these may overlap. A study starts with an objective, which gets translated to a protocol, proceeds with identification of sites and management of the trial. Actual process of data management is initiated with the collection of data

HISTORY OF CLINICAL DATA MANAGEMENT;

Clinical data management (CDM) has evolved from a data entry process into a diverse process referred to as "provide clean data in a useable format in a timely manner", "provide a database fit for use" or "ensure data are clean and database is ready to lock". Though clinical data management had to be done with whatever data was being collected for clinical trials from its earliest days, the processes were given a major focus in the early 1970s, when the Public Health Service recognized the need for good practices in clinical data management. With the advent of electronically transmitted clinical trial data, the standardized practices and procedures developed further. Regulatory requirements have advanced the necessity of clinical data management as a science. Quality of the trial data is much more critical as pharma companies invest vast amounts of money in drug research. It is also vital for regulatory submission and approval. Hence CDM has grown from a mere data entry process to a technology based science

OVERVIEW OF CLINICAL DATA MANAGEMENT;

Clinical data management consists of processes such as trial data acquisition ,validation, integration, database, administration,backup and quality assurance. The locked database undergoes a statistical analysis after which it is ready to be submitted to the regulatory authority for approval. Processes used to support the clinical data must be clearly defined and documented. Documents supporting CDM activities include protocol, standard operating procedures (SOP’s)

DATA MANAGEMENT PLAN;

Before starting with the data management processes, a data management plan (DMP) must be put in place. DMP helps to proactively assess and plan for the study-specific data management processes. The DMP serves as the backbone of overall quality system of data management (DM) and outlines:

- How and when each step of the CDM process must be carried out
- What documents are to be created and finalized
- Defines the data management tasks, responsibilities, deliverables and timelines
- Which SOPs or guidelines will apply to the various processes

 What document or output to collect or produce

 What level of quality must be achieved

DATA CAPTURE AND COLLECTION;

Data capture is a key concept in data management. This refers to procedures for gathering and recording data from or related to subjects in the study. It could either be paper-based or through electronic data capture (EDC). Promise of enhanced efficiency has led to increasing movement towards implementation of the electronic medical record and to computerized automation in the ICH Guideline for general.

DATA PRIVACY;

Good Clinical Practice (GCP) states, “The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirement(s)."

CRF DESIGN;

CRFs are instruments used to collect data from the clinical trials. They are designed to collect all data points specified in the protocol. CRFs standardize the collection of study data and also help in meeting the needs of medical, statistical, regulatory and data management personnel. The CRFs are filled in by the investigator and then forwarded to the data management unit for entry and review.

CLINICAL DATABASE;

A clinical data management system (CDMS) enhances the efficiency of the clinical trial process. Implementation of the CDMS involves planning and interaction of various teams. Design of CRF data flow into the system either manually or electronically is the first step. Subsequent steps are creating the global database, validation/derivation procedures, data extraction programs and reporting. One can also integrate dictionaries, AE reporting systems, EDC/RDC and CTMS with CDMS. It is essential to ensure that data is automatically transformed from a collection format to the reporting formats as needed by the sponsor and the regulatory authorities. The main objective of database design is to capture and store clinical data accurately. The essential° features of good design are ease of data capture, efficient creation of analysis data sets and accommodation of source data transfer formats

DATA ENTRY;

Data entry refers to the process of transferring data from the paper CRF to the database. This is also referred to as transcribing the data. Data entry results in creation of electronic data, which corresponds to the CRF data. Once data is entered into the database, it is reviewed and validated by the data editor. Emphasis for data entry is given on typing speed and typing skills, since this activity requires large amounts of data to be keyed into the database. Data entry consists of both double entry and single entry.

 Double Entry; This involves entry of the same CRF page by two independent data entry personnel. The first data entry personnel keys in the data into the database. Later, a second independent data entry personnel keys in the same data

 Single Entry; This involves entry by single data entry personnel. This process is used when there are sufficient and extensive checks built into the database that would detect certain errors that might be missed out by the data entry personnel. Single data entry is extensively used in EDC and RDC systems, where the investigator and site personnel directly key in the data.

 The data entry could be of two types:

1. Data entry is done locally at the site database and then transmitted periodically to the central database via internet or using a dialup line. Sometimes the data is also sent using other electronic media such as a CD, floppy or as a mail attachment.

2. Data entry is done online directly into the central database via internet. Usually these systems are web-based and the data is available in real time for review

DATA REVIEW AND VALIDATION;

Once data entry is complete, the data is ready to be reviewed by the data editor. The data editor ensures that all discrepancies are addressed and resolved, and that the database is finally clean and ready to be locked. Discrepancies are any inconsistencies found in the clinical trial data that needs to be addressed Discrepancies include incomplete data, illogical data, incorrect data and illegible data

 Point-by-Point Checks;

This refers to cross checking between the CRF and the database for every data point. If the data editor performs this check, it serves as a second quality check apart from double data entry Incorrect entries or entries missed out by data entry are corrected during this check. Special emphasis is given to dates, numerical values and header information, where there are likely to be more data entry misses.

 Missing Data or Blank Field Checks;

Missing data and blank fields must be queried for, unless indicated by the investigator as 'not done', 'not applicable' or 'not available'. It is better to program validations for missing data fields rather than review them manually. Examples of missing data include missing AE/medication term, missing start/stop dates, completely blank CRFs where none of the question responses are provided.

 Data Consistency Checks;

Checks are designed to identify potential data errors by checking corresponding ents, sequence of dates, missing data (indicated as existing elsewhere), etc. Checks include cross checking between data points both across different CRFs and also within the same CRF.

 Laboratory Data and Range Checks;

Laboratory data has to be treated in a special manner, as they are different from all other CRF data. This data has to be interpreted with the help of reference ranges and must be expressed in the specified units for proper interpretation. This is much more important when data are combined from multiple studies

 Header Inconsistency Checks;

Examples of discrepancies with the header information include (a) an incorrect visit date like 30-Feb-2005 (b) an incomplete visit date like 12-Jan, whereas the date is expected to be reported in the DD-MM-YYYY format (c) incomplete patient initials.

 Missing Pages Checks and CRF Tracking;

Details of transmittals and receipt processes of CRFs and DCFs are documented and maintained during all stages of the data management process. Missing and expected pages tracking systems are also planned and set up in the DMP

 Protocol Violation Checks;

Protocol adherence ought to be reviewed at all stages of data management. Violations found have to be queried. Special emphasis is given for reviewing primary safety and efficacy endpoints, adherence to inclusion and exclusion criteria, adherence to trial drug dosing regimen, study or drug termination specifications, etc.

 Dates Out of Sequence Checks;

Dates out of sequence refer to dates either in the header or the body of the CRF being inconsistent and out of sequence. Sequence of visits are reviewed and, if found to be out of sequence, will be either queried or corrected

 Continuity of Data Checks;

These are checks performed for ensuring continuity of events (AEs, medications, treatments/procedures, etc.) across the study and across visits. Overlapping start/ stop dates are checked across visits.

 Coding Checks;

All the data such as concomitant medications, adverse events, medical history, and diseases have to be substituted with a standard reference terminology. This is !mown as 'coding'. The reference terminology may come from sponsor specific dictionaries or other published dictionaries. The coding of data helps in grouping them under specific systems. Such groupings are required for summary analysis of these data. Some of the common standard dictionaries used are:

 MedDRA-Medical Dictionary for Regulatory Activities

 COSTART - Coding Symbols for a Thesaurus of Adverse Reaction Terms

 WHO-DRL - World Health Organization Drug Reference List

 WHO-ART - World Health Organization Adverse Reactions Terminology

 ICD-9-CM - International Classification of Diseases, Ninth Revision, Clinical Modification

 Duplicate Data Checks: This refers to duplicate data entries of a particular data value within a single CRF or across similar CRFs. Duplicate entries and duplicate records are generally deleted per guideline specifications.

 Textual Data: Checks All textual data are to be proofread and checked for spelling errors. Common examples of textual data include pre- existing conditions in medical history record, adverse events, medications/antibiotics, physical examination findings, etc.

 Database Closure: Database closure is done to prevent unauthorized or inadvertent changes to the database once the final analysis of the data has begun. This process is referred to as 'soft-locking' the database. This is done after completion of last patient last visit. (LPLV). Database lock is critical in randomized trials to ensure the integrity of the randomization process (as the blind has been broken).

QUALITY ASSURANCE AND QUALITY CONTROL (QA/QC);

QA/QC -audits are done periodically — on an ongoing basis as well as at or after the end of the study. QA audits are systematic and independent examinations of trial- related activities and documents to ensure that the CDM related activities and processes were conducted and completed, and that the data were accurately recorded, analyzed, documented and reported according to the protocol, SOPs, GCP and applicable regulatory requirements.

DATA STORAGE AND ARCHIVAL;

All trial related paper documents including CRFs and/or electronic files must be stored in a secure and controlled place. It is good to scan all paper documents so that they can be archived in an electronic form. Open formats such as CDISC or PDF are recommended for storage.

RECENT ADVANCES IN CDM;

Clinical trial systems to conduct clinical trials electronically has become a necessity today to increase the time to market as well as decrease the cost of trials. The various technologies utilized include EDC systems, adverse event reporting systems (AERS), OCR, OMR, IVRS, etc. These and many other technologies are providing number of benefits in the conduct of the clinical trial.

DATA STANDARDS.

Data standards are being developed to overcome the problems of data integration from different systems. Data structure (variable names, variable types, and labels), screen layout/paper CRF module, completion instructions, monitoring guidelines, standard reports, tables, listings, laboratory data, global libraries are all being standardized. Clinical Data Interchange Standards Consortium (CDISC) is at present leading the way. There are currently over 60 companies that are members of CDISC, and many companies are starting to adopt the CDISC models, even down to the variable name.

SAFETY MONITORING IN CLINICAL TRIALS [chapter 2 (n)]

INTRODUCTION:

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 (NO) 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.

GOOD CLINICAL PRACTICE (GCP);

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected. According to the Principles of ICH GCP guidelines .The rights, safety, and well-being of the trial subjects are the most important considerations.

Safety monitoring is done by

- Investigator
- IRB/IECs
- Sponsor
- Monitor

IRB — Responsibility:

- An IRB/IEC should safeguard the rights, safety, and well- being of all trial subjects. ICH GCP 3.1.1
- 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.

INVESTIGATOR — Responsibility:

- During and following subject participation in a trail, 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 trail. ICH GCP 4.3.2

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 ICH GCP 5.5.2

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. ICH GCP 5.18.4

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.

For drugs being studied under investigational new drug applications, the food and drug administration (FDA) published a regulation establishing a new safety reporting paradigm. According to this the clinical investigator and sponsor have to be more responsible in reporting and analysis of serious, unexpected events that might be caused by drug.

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. The need of DSMB will be decided by the principal investigator but the IRB may query the principal investigator regarding the need for a DSMB.

FUNCTIONS OF DSMB:

1. To ensure safety of the patient

2. To ensure that the protocol is designed in a ethical manner

3. To review interim analyses of outcome data and to recommend whether study needs to ki-changed or terminated

4. 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 (i.e. financial, intellectual, professional, or regulatory).

MEETINGS:

DSMB meetings will be held at least annually or as required by the timing of protocol specified interim analyses. The DSMB will review the status of the trials including toxicity, efficacy outcomes and next formal monitoring date as specified in the protocol. The review of each trial includes three parts. The first is an open session in which the principle investigator may be present to clarify the status of study. The second is a closed session limited to DSMB members and study statistician and the statistician presents the outcome results. Third is a closed session in which the DSMB members discusses outcome results and develops recommendations.

RESPONSIBILITIES IN MONITORING SAFETY:

DSMB might recommend the following

1. Change the eligibility criteria if risks seem to be concentrated in a particular sub group.

2. Altering the dosage of product if the adverse events are likely to be reduced by such changes.

3. Performing screening procedures which could identify the patients of high risk to a particular adverse event.

4. Informing the study participants about newly identified adverse events.

PHARMACOVIGILANCE:

It is science relating to detection, assessment and prevention of adverse effects and other problems related to the use of medicines.

ADVERSE EVENT:

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a casual relationship with this treatment.

SERIOUS ADVERSE EVENT:

Any untoward medical occurrence that at any dose:

•results in death

•is life-threatening

•requires inpatient hospitalization or prolongation of existing hospitalization

•results in persistent or significant disability/incapacity

•is a congenital anomaly/birth defect

METHODS OF COLLECTING ADVERSE EVENTS IN CLINICAL TRIAL:

- Volunteer reporting by the patient
- Investigator observation
- Standard Open question
- Checklist
- Subject diaries (written or electronic)
- Laboratory/Clinical values

A randomised controlled trial was conducted in California to determine better method of questioning patients regarding adverse event. Results showed that the percentage of patients reporting adverse event is much higher in case of checklist method when compared to standard open question.