Rajiv Gandhi University of Health Sciences Karnataka

(Syllabus)

Clinical Research

REZA RAHIMI

DOCTOR OF PHARMACY

5TH PHARMD

CONTENTS

Second Year

2.1 CLINICAL RESEARCH (THEORY)

Theory : 3 Hrs. /Week

1. **Drug development process:**
   Introduction
   Various Approaches to drug discovery
   1. Pharmacological
   2. Toxicological
   3. IND Application
   4. Drug characterization
   5. Dosage form

2. **Clinical development of drug:**
   1. Introduction to Clinical trials
   2. Various phases of clinical trial.
   3. Methods of post marketing surveillance
   4. Abbreviated New Drug Application submission.
   5. Good Clinical Practice – ICH, GCP, Central drug standard control organisation (CDSCO) guidelines
   6. Challenges in the implementation of guidelines
   7. Ethical guidelines in Clinical Research
   8. Composition, responsibilities, procedures of IRB / IEC
   9. Overview of regulatory environment in USA, Europe and India.
   10. Role and responsibilities of clinical trial personnel as per ICH GCP
       a. Sponsor
       b. Investigators
       c. Clinical research associate
       d. Auditors
       e. Contract research coordinators
       f. Regulatory authority
   11. Designing of clinical study documents (protocol, CRF, ICF, PIC with assignment)
   12. Informed consent Process
   13. Data management and its components
   14. Safety monitoring in clinical trials.

A

Pharmacological Approaches

•Drug development is the process of bringing a new pharmaceutical drug to the market once a lead compound has been identified through the process of drug discovery.

Drug Development Process:

1- Screening of thousands of active compounds by means of biological assays ALS F STP

2. Choice of the lead compound

3. Synthesis and physico-chemical characterization of the lead compound

4- Formulation of the drug product consisting of the drug substance, excipients and delivery system

5- Scale-up of production and quality control

6. Toxicology

7. Preclinical pharmacology, composed of pharmacokinetics and pharmacodynamics.

#Pharmacological Approches:

Pharmacological studies fall into two categories:

1. Research pharmacological studies
2. Safety pharmacological studies

1-Research Pharmacological Studies:

- Mainly conducted at the start of a drug development Program
- They do not need to be performed at GLP standard

There are two types:

1. Primary research pharmacological studies
2. Secondary research pharmacology studies

Primary research pharmacological studies:

- Primary actions are related to proposed therapeutic-use
- These studies focus on the mechanism of action of drug and can be conducted in vitro and in vivo.
- Studies conducted in vitro include radioligand binding studies and focus on drug action on specific receptor site.
- Studies conducted in vivo investigate the pharmacological action of the drug in animal models.
- This study is useful in predicting potential safety

issues, drug interaction and other undesired effects.

Secondary research pharmacology studies

- Secondary actions focus on the overall pharmacological activity of the drug compound
- And also relates to the actions that occur which is not directly related to the proposed therapeutic use
- This can be concluded in vitro and in vivo. --- In vitro studies investigate the binding of drug molecule with the non-target receptors.
- In vivo studies investigate the general pharmacological actions in animal models.

Safety Pharmacological Studies:

- Safety pharmacological studies investigate potentially undesirable effects of the drug compound
- They are conducted in animal models
- These are single dose studies using intended

therapeutic dose

- They focus on functional changes in major organ systems within the body
- These studies investigate the undesirable effect on the functioning of CNS, CVS and respiratory system

Eg: CNS

Skeletal muscle tone
locomotion
reflexes

CVS

BP
H.R
ECG changes

Respiratory system

rate and depth of breathing

□ Estimating the Maximum recommended Starting Dose (MRSD) in Clinical Trials for A NEW DRUG in Adults Healthy Volunteers:

Introduction:

- Maximum recommended starting dose (MRSD) for first-in-human

- clinical trials of new molecular entities in adult healthy volunteers

The goals of this guidance are to:

- Establish a consistent terminology for discussing the starting dose
- Provide common conversation factors for deriving a human equivalent dose (HED)
- To derive a strategy for selecting the MRSD for adult healthy volunteers, regardless of the projected clinical use.

Glossary

Body surface area conversion factor (BSA-CF): A factor that converts a dose (mg/kg) in an animal species to the equaling dose in humans (also known as the human equivalent dose), (HED) based on differences in body surface area.
-A BSA-CF is the ratio of the body surface areas in the tested species to that of an average human.

Human equivalent dose (HED): A dose in humans anticipated to provide the same degree of effect as that observed in animals at a given dose.

- In this guidance, as in many communications from sponsors, the term HED is usually used to refer to the human equivalent dose the NOAEL.

K: A dimensionless factor that adjusts for differences in the surface area to weight ratio of species because of their different body shapes.

K_m: Factor of converting mg/m^1 dose to mg/m^2 dose

Maximum recommended starting dose (MRSD):

The highest dose recommended as the initial dose in a clinical trial. In clinical trials of adult healthy volunteers the MRSD is predicted to cause no adverse reactions.

- The units of the dose (e.g mg/kg or mg/m^2) may vary depending on practices employed in the area being investigated.

- No observed adverse effect level (NOAEL): The highest dose tested in an animal species that does not produce a significant increase in adverse effects in comparison to the control group. Adverse effects that are biologically significant, even if not statistically significant, should be considered in determining an NOAEL.

- Safety factors (SF): A number by which the HED is divided to introduce a margin of safety b/w the HED and the maximum recommended starting dose. MRSD = HED/SF

Human Equivalent Dose Calculation

Conversation Based on Body Surface Area

- An analysis of the effect of the allometric exponent (b) on the conversion of an animal dose to the HED was conducted.

HED = animal NOAEL x (W animal/W human) (1-b)

Based on this analysis and on the fact that correcting for body surface area increases clinical trial safety by resulting in a more conservative starting dose estimate, it was concluded that the approach of converting NOAEL doses to an HED based on body surface area correction factors (i.e., WO.67) should be maintained for selecting starting doses for initial studies in adult healthy volunteers.

Conversion Of Animal Doses to Human Equivalent Doses(HED) Based on Body Surface Area
(only for reference)

Species	To convert Animal Dose in mg/kg to Dose in mg/m2, multiply by km	To Convert Animal Dose in mg/kg to HED in mg/kg, either:	
		Divided Animal Dose By	Multiply Animal Dose By
Human	37	---	---
Child(20 kg)b	25	---	---
Mouse	3	12.3	0.08
Hamster	5	7.4	0.13
Rat	6	6.2	0.16
Ferret	7	5.3	0.19
Guinea pig	8	4.6	0.22
Rabbit	12	3.1	0.32
Dog	20	1.8	0.54
Primates:			
Monkeys	12	3.1	0.32
Marmoset	6	6.2	0.16
Squirrel	7	5.3	0.19
monkey	20	1.8	0.54
Baboon			
Micro-pig	27	1.4	0.73
Mini-pig	35	1.1	0.95

ONLY FOR REFERANCE

Most appropriate species selection

Factors that can influence:

- Differences in the absorption, distribution, metabolism, and excretion(ADME) of the therapeutic between the species.
- Class experience that may indicate a particular animal model is more predictive of human toxicity. Selection of the most appropriate species for certain biological products (e.g. human protein)

APPLICATION OF SAFETY FACTOR (SF)

- To provide a margin of safety for protection of human subjects receiving the initial clinical dose.

- This safety factor allows for variability in extrapolating from animal toxicity studies to studies in humans resulting from:
- Uncertainties due to enhanced sensitivity to pharmacologic activity in humans V.S animals.
- Difficulty in detecting certain toxicity in animals (e.g. headache, myalgias, mental disturbances)
- Differences in receptor densities or affinities
- Unexpected toxicities interspecies differences in ADME of the therapeutic.

Toxicological Approach to Drug development:

- A typical non clinical safety program requires a staged approach.
- With the staged approach, non clinical toxicity studies required to support the next clinical phase are conducted and data made available prior to initiation of that clinical phase, the so-called "just in time" approach to drug development.
- For a first dose-in-humans study, the non clinical safety program generally consists of single dose toxicity studies (two species), repeated-dose toxicity studies (one two species: one rodent one non rodent), local tolerance (generally part of the repeated-dose toxicity studies), and genotoxicity (bacterial mutation assay and in vitro chromosomal damage with mammalian cells or in vitro mouse lymphoma assay) studies.
- These studies usually provide sufficient information to allow dose selection for the first Phase 1 study

Two important determinants of toxicity are:

1. Dose
2. Time

There are three time scales:

1. Dynamic
2. Kinetic
3. Frequency of dosing

- All three are thought to play a role in determining the circumstances leading to toxicity.
- The purpose of the toxicity studies in pharmaceutical development is to provide data in animals that can be used to assess the safety of a compound for human use.

Toxicology and pharmaceutical development:

- For pharmaceutical products, safety must be demonstrated

1. Clinically
2. Non clinically

-Non clinically it is accomplished by conducting:

1. Single dose toxicity
2. Repeated dose toxicity
3. Reproduction toxicity
4. Genotoxicity
5. local tolerance studies

- Depending upon the clinical indication and the level of concern carcinogenicity studies may be required.

- Other studies such as safety pharmacology, special toxicity and pharmacokinetics studies may be required and/or provide supportive data for risk assessment.

Single dose toxicity study:

- These guidelines deal with the qualitative and quantitative study of toxic phenomena and their occurrence related to time after a single administration of the substance, or combination of substances.

- These studies may give some indication of the

likely effects of acute overdosage in man and may be useful for the design of toxicity studies requiring repeated dosing on the relevant animal species.

- The single-dose toxicity tests should be conducted in such a way that signs of acute toxicity are revealed and the mode of death determined. In suitable species a quantitative evaluation of the approximate lethal dose and information on the dose-effect relationship should be made, but a high level of precision is not required.

#Repeated-dose toxicity:

- Repeated dose toxicity testing using oral administration of a test substance in rodents for 28 and 90 days is used to evaluate chronic toxic effects, primarily effects on various organ system, and to establish a no observed effect level (NOEL).

- Depending on the potential route of human

exposure to the substance, similar testing using dermal and inhalation dosing may also be assessed.

- Doses are selected to be sublethal but still cause toxic effects.
- Long-term chronic toxicity studies with a minimum duration of 12 months are sometimes required.

Reproduction toxicity:

- Reproductive toxicity refers to structural and functional alterations that affect reproductive competence (كفاءة) in sexually mature males and females.
- Reproductive toxicity includes effects on male fertility and female fertility, parturition and lactation.

- Male fertility:

Male reproductive toxicity includes damage to the reproductive organs, alterations in endocrine regulation of gamete maturation and release, reduction in sperm count, alterations in sperm

motility or morphology, aberrant (غير عادي) mating behavior, altered ability to mate, alterations in endocrine function, or overall reduction in fertility.

- Female Fertility:

Female reproductive toxicity includes damage to the reproductive organs, alterations in endocrine regulation of gamete maturation and release, aberrant mating behaviour, altered ability to mate, or overall reduction in fertility.

- Diminished fertility in female animals is typically detected by reductions in the fertility index, the number of implantation sites, time to mating, or fecundity.

Genotoxicity:

Germ cell mutagens / genotoxins are substances that cause heritable (passed on to progeny) changes in the genetic material in germ cells, namely spermatocytes or oocytes. The term mutagen refers to a substance that includes transmissible

- A poisonous substance which damage DNA. A genotoxin can cause mutations in DNA (and so be a mutagen), it can trigger cancer (and so be a carcinogen), or it can cause a birth defect (and so be a teratogen).

changes in DNA structure involving a single gene or a group of genes.

-Genotoxins are a broader category of substances that induce changes to the structure or number of genes via chemical interaction with DNA and/or non-DNA targets.

*Carcinogen: A substance capable of causing cancer in living tissue.

→ the ability or tendency to produce CANCER.

- Carcinogenicity Studies:

It is required for pharmaceuticals intended for continuous use for atleast 6 months and/or there is a cause for concern.

Causes for concern include:

- Evidence of carcinogenicity in the compound class
- Structure activity relationship suggesting carcinogenic risk
- Evidence of pre neoplastic lesions in repeated-dose toxicity studies
- Long-term tissue retension of parent compound and/or metabolites resulting in local tissue reactions.

Doses of carcinogenicity studies may be based on one of the following:

- Comparison of AUC in animals and man
- Saturation of absorption
- Pharmacodynamics
- Maximum feasible dose
- Maximum tolerated dose
- limit dose

-Thus two of the six criteria require the use of pharmacokinetic data for selection of the high dose for a carcinogenicity study.

- Chronic toxicity studies consist of six months studies in rodents and nine or twelve months toxicity studies in non rodents.

-This is required only when the duration of clinical use of pharmaceutical is greater than three months.

Outline of Typical Safety Program:

- A typical non clinical safety program requires a staged approach.

- With the staged approach, non clinical toxicity studies required to support the next clinical phase are conducted and data made available prior to initiation of that clinical phase, the so-called "just in time" approach to drug development.
- For a first dose-in-humans study, the non clinical safety program generally consists of single dose toxicity studies (two species), repeated dose toxicity studies (one two species: one rodent one non rodent), local tolerance (generally part of the repeated dose toxicity studies), and genotoxicity (bacterial mutation assay and in vitro chromosomal damage with mammalian cells or in vitro mouse lymphoma assay) studies
- These studies usually provide sufficient information to allow dose selection for the first phase I study.
- As data becomes available from the initial toxicity studies the toxicologists assesses the findings reassesses the clinical development plan. And prepares for the next toxicity studies.

•These studies involve the conduct of longer-term repeated dose toxicity, reproductive toxicity and in vivo genotoxicity studies.

•The final type of toxicity is the special toxicity study it is conducted when an issue arises and there is a need to better understand.

#Factors in Designing Studies:

•Several factors must be considered when designing toxicity studies.

•These include the use of main study or satellite animals for collection of pharmacokinetic data, the total blood volume that can be extracted from animals during a given period of time, as well as the amount of blood that can be collected at each time point, route of exposure, Sampling time point, number of animals per time point, number of sampling days and bioanalytical support.

Compound libraries:

- If the lead compound is found to be toxic, it is kept in the compound library for future use.
- A compound library is a collection of compounds
- Compound libraries from past project are kept and may be screened for the biological activity you are looking for in a new project.
- New compounds may also be made "in-house" but nowadays specialist chemical companies are often contracted to simply make NCEs for big-pharmaceutical companies.
- A disadvantage of synthetic libraries is that often limited.

lead compound in drug discovery is a chemical compound that has pharmacological or biological activity likely to be therapeutically useful, but may still have suboptimal structure that requires modification to fit better to the target.

IND Application

The United States FDA's Investigational New Drug (IND) program is the means by which a pharmaceutical companies obtains permission to ship an experimental drug across state lines (usually to clinical investigators) before a marketing application for the drug has been approved.

- The FDA reviews the IND application for safety to assure that research subjects will not be subjected to unreasonable risk.
- If the application is cleared, the candidate drug usually enters a phase 1 clinical trial.

Criteria for application:

An IND is required for a clinical study if it is intended to support a:

- New indication
- Change in the approved route of administration or dosage level
- Change in the approved patient population (e.g paediatric) or a population at greater or increase of

risk (elderly, HIV positive, immunocompromised)
- Significant change in the promotion of an approved drug

Exemption from IND application:

The FDA or an IRB may grant an exemption from IND requirements for the clinical investigation of a drug or biologic that is lawfully marketed in the United States if all six of the following conditions are met:

1. It is not intended to be reported to FDA in support of new indication for use or to support any other significant change in the labeling for the drug.
2. The drug is lawfully marketed as a prescription drug product and its proposed use is not intended to support a significant change in the advertising for the product.
3. It does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks

associated with the use of the drug product.
4. It is conducted in compliance with the requirements for IRB review and informed consent.

-It is conducted in compliance with the requirements concerning the promotion and sale of drugs and in addition, the investigator must not intend to invoke an exception from informed consent for emergency research.

□When to use IND application:

Conditions in which IND application need to be submitted:

1. Drug intended to treat or diagnostic serious or life threatening condition;
2. No satisfactory alternative available.
3. Controlled clinical trials in progress under IND or when trials completed and FDA review of request to market is pending.
4. Sponsor activity pursuing device marketing approval with FDA

5. Need FDA authorization to use experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21 CFR Part 312.

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

□ Application Categories: < commercial / research (non-commercial)

There are two main categories of IND:

1. Investigator-initiated
2. Sponsor-initiated

Both of these types of studies require approval by an institutional review board (IRB), an independent body constituted of medical, scientific, and non-scientific members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial.

Three IND types:

1. (Regular) investigator IND

- Submitted by a physician who both initiates and conduct an investigation, and under whose immediate direction the investigational drug is administered or dispensed.

2. Emergency Use IND:

- Allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21CFR, Sec. 312.23 or Sec. 312.34.

- It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.

3. Treatment IND:

- It is submitted for experimental drugs showing promise in clinical testing for serious or immedi-

ately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

•The IND application must contain in three broad areas:

1. Animal pharmacology and toxicology Studies:

Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans. Also included are any previous experience with the drug in humans (often foreign use).

2. Chemistry manufacturing information:

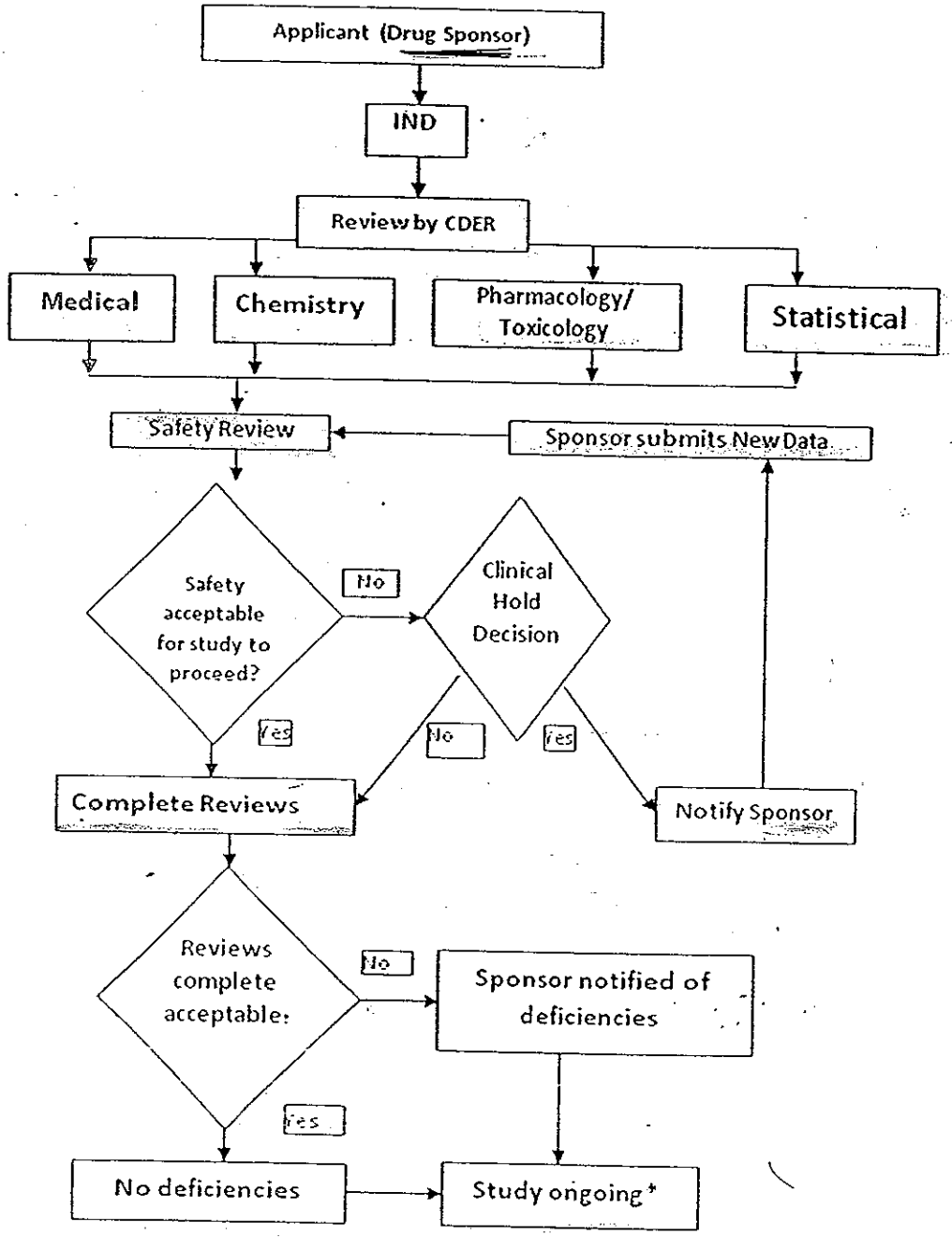
Information pertaining to the composition, manufacturer, stability and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug.

3. Clinical protocols and investigator information:

Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks. Also, information on the qualifications of clinical investigators-professionals (generally physicians) who oversee the administration of the experimental compound-to assess whether they are qualified to fulfill their clinical trial duties. Finally, commitments to obtain informed consent from the research subjects to obtain review of the study by an Institutional Review Board (IRB), and to adhere to the investigational new drug regulations.

-Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials. During this time, FDA has an opportunity to review the IND for safety to assure that research subjects will not be subjected to unreasonable risk.

IND CHART



* While sponsor answers any deficiencies

IND application contents:

1. Cover sheet / application form (Form FDA-1571)
2. Table of contents
3. Introductory statement
4. General investigational plan
5. Investigator brochure
6. Protocol(s)
7. Chemistry, manufacturing and control info
8. Pharmacology and Toxicology info
9. Previous human experience with drug
10. Additional information as required by FDA:
    - Drug dependence/abuse potential
    - Radioactive drugs
    - Pediatric studies

IND application contents:

1. Application form (Form FDA-1571)

- Required for initial IND and all subsequent submissions.
- Provides basic info about sponsor and submission contents

- Must be signed and dated
- Obligates sponsor to comply with laws and regulations

2. Introductory Statement.

- Drug name, structure, pharmacological class, development history, foreign testing.

3. General investigational plan:

- Summary of studies anticipated in first year
- Study rationale.

4. Investigator brochure

- Package insert
- Early versions contain more pre-clinical data
- Later versions more heavily weighted with clinical area.

5. Protocol(s):

- Must include at least initial protocol
  - No subjects planned
  - Eligibility requirements

- Dosing
- Safety assessments.
- Phase II and III - detailed protocols

6. Chemistry, manufacturing and control info:

- Manufacturing process
- Raw materials and finished product testing
- May refer to drug master file or previous application

7. pharmacology and toxilology info:

- Non-clinical study summaries of pharmacological and toxicological effects.

8. Previous human experience with drug

- Foreign trials
- Data from other INDs, NDAs

9. Additional information as required by FDA:

- Other relevant info
- Copies of referenced materials
- Address issues are possible drug abuse,

dependence, radioactivity etc.

IND Amendments::

1. New protocol introduced
2. Changes made to protocol that may affect
   - Scientific Soundness of study
   - Rights, Safety or welfare of study subjects
3. Addition of new study investigators (FDA Form 1572)
4. New/revised information not related to protocol
   - New pharmacology, toxicology, chemistry, clinical info
   - Discontinuance of a study

Drug Characterization

- Drug characterization involves finding of biological and physiochemical properties of potential drug molecule.

- Two types of DC:

→ 1. Biological characterization

Interaction of drug molecule with biological systems

→ 2. Chemical characterization:

Physical and chemical characterization of a potential drug

#Biological characterization:

Biological characterization is needed to assess whether the molecule will likely work in humans

- Goals of biological characterization:

a- To find efficacy

b- Assess toxic effects

- Studied at the level of biochemical, cell, tissue, organ and organism level.

- Biochemical assays:
  - 1. Mechanism of action at a molecule level
    - Receptor binding (affinity and selectivity) assays
    - Enzyme inhibition. activity: Km, selectivity
  - 2. Metabolic processing - metabolic activation

- Cellular assays:
  1. Cell cultures: Cell penetration, receptor activity, transport.
  2. Isolated tissues: Effects on specific tissue - possible toxicity
  3. Liver tissues (microsomes): Drug metabolism, drug interaction

Systemic / whole animals:

→ Rat, mouse: toxicity, LD_{50}, organ-specific efficacy

→ Dog, rabbit, guinea pig, monkey: pharmacokinetic, BA, toxicity

→ Lab animal models for disease: efficacy, toxicity

#Chemical Characterization:

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

→ Chemical structure: Mass spectroscopy, NMR, X-ray crystallography

→ Solubility, pK_a

→ Partition coefficient: octanol: water

→ Stability

→ Impurities: TLC, HPLC, GC, mass spectroscopy

→ ADME

• Physico chemical properties are closely related to drug absorption and their values are used in predicting bioavailability and interpreting other in vitro and in vivo findings. Different approaches have been developed to address these properties at different stages in drug discovery, including hit finding, lead finding and optimization and nomination for development condition.

Main sources of drug leads :-

- 1970's and 1980.
  - Around 1970 large empirically based screening programs
  - From then on knowledge base grew for rational drug design.
  - Most leads had already been in a range of physical properties previously known to be consistent with oral activity.
- 1989 and on
  - High through screening of hundreds of thousands of compounds across in vitro assay.
  - Soon after combination chemistry.
  - Rapid progress in molecular genetics expression of receptors.
  - Drugs were dissolved in DMSO.(dimethyl sulfoxide)
  - The recent trend in medical chemistry leads towards larger molecule and increased Lipophilicity.
  - The candidate with the right balance of activity and availability is more desirable.

One further aspects is that "drug-likeness" profile of oral drugs is far beyond these simple rules and includes properties such as dissolution, absorption, metabolism, clearance and protein binding. A good drug candidate needs to have favorable above mentioned properties to ensure good pharmacokinetic (PK) outcome.

ADME and PK properties

Property	Describes	Comment	Models
Passive transmembrane diffusion	Ability to cross a membrane bilayer in a concentration gradient-driven fashion	Usually the major component of cell permeability and drug absorption	IAM, PAMPA
Cell permeability	Ability to traverse an Intact cell monolayer unchanged in an in vitro system	For compounds stable to first pass effect and with no solubility and dissolution, limitations, often correlates with oral bioavailability	Caco-2, MDCK, e.t.c
Absorption	Ability to pass the first biological barrier to entry into the body	Not as the same as the ability to reach portal blood by this definition	ROF, COMPUTATIONAL MODELS
BIOAVAILABILITY	Fraction of administrated drug that ultimately reaches the site of action, although in practice concentrations in systemic circulation are usually measured	Includes absorption and first pass effect	In vivo PK studies, computational models

#Solubility

- Importantly, two different kinds of "solubility" encountered in drug discovery need to be distinguished.
- Thermodynamic or equilibrium solubility is the true amount of compound that will go into insulin from the solid phase given an infinite amount of time. This is approximated by shaking it in a flash with the solvent for 24-72hr, filtering or centrifuging and then quantitating the amount dissolved by using HPLC standards. Obviously this is not a high-through put method.
- Kinetic solubility is typically observed when a stock solution of a compound dissolved in DMSO is diluted into water or aqueous buffer, as is done in preparing HTS samples. Although precipitation might not be observed immediately. It often happens a few hours or days later. Here a supersaturated solution is formed upon dilution, which eventually reaches equilibrium but takes some time to do so.
- In contrast to equilibrium solubility, though, kinetic solubility is easy to measure quickly, making it more suitable for high-through put determination using a method like nephelometry or turbidimetry.

Problems resulting from poor solubility

- Good solubility is important for oral bioavailability.
- Poor solubility and differences between kinetic solubilities and equilibrium solubilities can cause problem at many points in the drug discovery process.
- Poor solubility introduces uncertainty into the concentration of compounds in the wells of HTS plates.
- Different solubilities of different solid forms can make compounds hard to test and results hard to compare

Key points about solubility

- Kinetic solubility is easy to measure in high – throughput
- Thermodynamic solubility is harder to measure but ultimately more relavent
- Solubility for a given compound depends on its crystalline or amorphous form
- Inadequate solubility can
    - Make for poor absorption
    - Lead to erroneous SAR & poor compound prioritization
    - Mask other problems
- The minimum solubility a drug will need depends on its potency & permeability
- Poor solubility can be improved by
    - Reducing hydrophobicity
    - Adding polarity
    - Disrupting crystal packing interactions
    - Making appropriate salts

➢ Using a prodrug approach

Solubility leads

- In DMSO , even very insoluble drugs could be tested.
- As a result – in vitro activity could be detected in compounds with very poor thermodynamic solubility properties.
- The physico-chemical profile of leads does not depend on compound solubility.

Target dataset with good absorption properties

- Compounds that entered clinical phase 2 stage.
- Poorly soluble compounds or compounds with poorer physical and chemical properties, as well as insoluble and non-permeable compounds would have been filtered out at earlier stages.
- Data taken from world drug index(WDI) - a computerized database of about 50000 drugs.
- USAN – united nation adapted name
- INN – international non-proprietary name.
- These names are applied upon entry to phase 2
- Database size- about 2500 compounds.

Selected parameters for testing:

- Molecular weight - known relationship between poor permeability & high molecular weight.
- Lipophilicity (ratio of octanol solubility to water solubility – measured through LogP.
- Number of hydrogen bond donors and acceptors – high numbers may impair permeability across membrane bilayer.

LIPINSKI'S the rule of five

Poor absorption or permeation are more likely when:

- There are more than (5) H-bond donors.
- The molecular weight is over (500)
- The LogP is over(5).
- There are more than (10) H-bond acceptors.

Lipophilicity

Lipophilicity describes the likelihood of a molecular to participate into a lipid phase with respect to a hydrophilic phase, and to penetrate the lipid bilayer to reach the therapeutic target site.

Therefore, Lipophilicity has a wide impact on the oral absorption, distribution within the body, as well as metabolism and elimination (ADME) of drug candidates.

The terms are commonly utilized to describe Lipophilicity: LogP and LogD, referring to the logarithms of partition coefficient and distribution coefficient of new chemical entities (NCEs) in a lipophilic phase (e.g. 1-octanol) and an aqueous phase, respectively.

Specifically, the former represents the partition of neutral species only, where as LogD reflects partitions of both neutral and ionized species at a particular pH and there by pH dependent.

Charged or ionized species are less favorable for partitioning into the lipophilic phase.

Partition coefficient (PC):

The ratio of the equilibrium concentrations of a dissolved substance in a in a two-phase system containing two largely immiscible solvents(water & n-octanol

$$\text{Partition coefficient} = \frac{\text{conc. of drug in oil phase}}{\text{conc of drug in water phase}}$$

The higher the PC, the better is its lipid solubility.

Exception to the rule of five:

Compound classes that are substrates for biological transporters:

- Antibiotics.
- Fungicides – protozoacides – antiseptics.
- Vitamins.
- Cardiac glycosides.

Isonization

Most drug candidates contain at least one ionizable group and therefore can be ionized within the physiological pH range.

Interestingly, 90% of NCEs are ionized to variable extent at different pH, leaving only 10% of them non-inonizable within pH 2-12.

At pH 7.4 at which most drugs are absorbed through gastro-intestinanes, 36% NCEs are more than 50% ionized.

Ionization is closely related to solubility and membrane permeability, thus the oral absorption of the drug.

The charge of a drug also affects the binding at the active site, thereby influencing not only CYP or hERG activity but also therapeutic efficiency.

Most frequently used techniques to improve efficiency or activity is to introduce ionizable groups to the lead or modifying the ionization of the lead.

Potentiometric titration is considered as the measurement of choice for pKa determination.

Poor solubility can be impaired by:

- Reducing hydrophobicity
- Adding polarity
- Disrupting crystal packing interactins
- Making appropriate salts
- Using a prodrug approach.

Chemical & plasma stability

- Like insolubility, compound instability can make assay results false & potentially misleading.
- Drugs need to be stable at every stage of discovery & development. Besides confounding early biochemical assay values. Instability will affect everything there after including cellular values, invivo results, a compound's ability to survive the pH range in the GI tract, & even shelflife.

Three kinds of instability often encountered are:

- **Oxidative instability:-**
  Organic chemists are quite aware of the tendency of ether & THF to form hydro peroxides & of thiols to form disulfides given a little bit of air & a lot of time. These types of reactions usually occur in solutions by free radical mechanisms & can be catalyzed by various metal ion are light.
- **Chiral instability:-**
  Chiral purity is important since drugs are increasingly being introduced as single stereoisomers. For drugs that are racemic to begin with the equilibration of each epimer amounts to stability.
- **Hydrolytic instability:-**
  This can be a problem for certain functional groups like esters, amides, carbomates, sulphanamides, lactones & lactams. Hydrolytic instability for such compounds spans the

range of simple, pH dependent, non-enzymatic hydrolysis to hydrolytic cleavage of peptides by specific peptidases.

Key points about chemical & plasma stability

- Chemical & plasma stability screening can help to
  - Identify problem compounds early
  - Select compounds for invivo studies
  - Study prodrugs & antidrugs
- Stability in plasma, serum, or blood is species dependent
- Stability can be enhanced by isosteric replacement or through wide variety of modifications

Metabolic stability

Metabolically unstable compounds will tend to have poor PK properties like bioavailability & in vivo half life due to rapid degradation. Metabolic instability can also make for other problems like toxicity or drug -drug interactions caused by metabolites.

Common metabolic transformations

Xenobiotics are transformed & cleared from the body through a highly evolved system that efficiently prevents the accumulation of lipophilic & potentially toxic substances. The process involves often 2 stages(in the first, phase I metabolism, drug's polarity is slightly increased though what's usually an oxidative or hydrolytic process like hydroxylation or ester hydrolysis. This can be followed by phase 2 metabolism, where the polarity is further increased through an enzyme-catalyzed conjugation of the resulting compound with glucuronic acid, sulphate, etc.)

Assessing Metabolic Stability

1) Recombinant Drug Metabolizing Enzymes

Individual drug metabolizing enzymes (DMEs) like CYPs, FMOs, &UGTs are now routinely expressed, usually in insect cells using a baculo virus.
The stability of a given compound could be assayed against a full collection of these individual DMEs or a cocktail there of as a primary screen for stability to Phase I metabolism.

2) Liver Microsomes

Screening for metabolic stability using Microsomes is the most popular way of looking at a compound's stability to most, but not all important metabolic transformations. Microsomes from many different species (mouse, rat, monkey, etc) including man are commercially available & are stable for months when kept at 80° C although their

activities drop off at room temperature after an hour or two making them less useful for long time-course experiments.

3) **Liver Cytosol & S9 Sub cellular Fractions**

Hepatic Cytosol contains three important soluble DMEs that aren't found in Microsomes, N-acetyl transferase (NAC). Sulfotransferase (SULT sometimes abbreviated ST) & glutathione S-transferase (GST). When the appropriate co-factors like Acetyl CoA for NAC are added stability to these three conjugating enzymes can be studied.

4) **Hepatocytes**

Fresh primary human Hepatocytes are the gold standard for metabolism research. Advances in cryopreservation techniques have recently made it possible to store frozen human Hepatocytes for up to a year, then out & use them with only a slight loss of activity. As a result, human Hepatocytes stability screening has become widespread in drug discovery recently.

Improving Metabolic Stability

1) **Metabolic Identification**

Knowing what the compound's metabolic hotspots are, structural modifications to prevent these reactions can be carried out if the aim is to prolong in vivo exposure to the parent compound, which is normally the case except for prodrugs & ante drugs.

2) **Structural Modifications to Improve Metabolic Stability**

Site-directed methods

- Replace atoms (i.e., with a bioisostere) at the site of metabolism
- Alter electronic or steric effects to disfavor metabolism

Lipophilicity- directed method

- Reduce Log P (or Log D) by adding in polarity
  "If you can't beat'em....." method
- Pre-form a stable active metabolite.

Key points about metabolic stability

Metabolic stability is normally essential for good PK properities.

Commonly observed metabolic reactions include the following:

- Hydrolysis of esters and amides(phase1)
- Hydroxylation of arenes and alkanes(phase1)
- Epoxidation of alkenes and alkynes(phase1)

- oxidations at heteroatom's(phase1)
- O- N- or S-GLUCURONIDATION (phase2)

Metabolic stability is typically assessed by incubation with liver Microsomes or Hepatocytes.

Fixing a metabolic stability problem might:
Cause new instability somewhere else on the molecule.
Decrease cell stability and absorption.
LEAD to faster excretion.
Turn the compound into CYP inhibitor.
Not improve stability in a different species.

Ways to increase metabolic stability include the following:

Bioisosteric replacement at the metabolic site altering electronics, sterics or conformation to disfavor metabolism. Reducing Log P by adding in polar groups pre-forming an active active metabolite.

Plasma protein Binding

Plasma protein binding reduces the amount of free drug available to the target

- It can also however, increase a compound's in vivo half life
- Many marketed drugs display high plasma protein binding.
- Many acidic compounds bind to albumin many basic ones to AAG.
- Species differences in plasma protein binding are common.

Measuring plasma protein binding:

1) Equilibrium dialysis is considered the "gold standard" method. A sample of the compound in plasma at PH7.4 and at 37_C is dialyzed through a membrane with a 10kDa cut off into buffer for some hours. After standard sample preparation, detection and quantitation of both solutions are done by LC/MS.

2) Ultra filtration - centrifugal force is applied for a few minutes to a sample of the compound in a plasma , pushing the unbound fraction through a permeability selective membrane. LC/MS analysis of the ultrafilterate and retenate is then done.

3) Computational methods - for predicting plasma protein binding have appeared in recent years, and such software is now commercially available.

Plasma protein Binding can be minimized by:

- Removing or reducing acidity.
- Adding in amines.
- Lowering Lipophilicity.
- Given enough information, using SBDD to disfavor binding.

Dosage Form Development

•Formulation developing during early drug discovery and lead optimization, involve several challenges including limited drug supply, the need for rapid turnaround, limited development time.

Its also desirable to develop initial formulation that will be representative of final commercial formulation.

Nanoparticles offer a unique platform for the formulation of poorly soluble drug such formulation can be injected (IV, SC, IM), as well as administered through routes, such as oral, ocular and inhalation.

-Rapid formulation and identification of an appropriate formulation are crucial for an accurate assessment of compound in a drug discovery setting. The challenges involved with formulation during this stage are, the limited availability of compound, limited drug characterization data and a need for rapid turnaround.

Given these challenges, screening technologies are required to be versatile, robust and scalable.

- Two approaches can be taken to formulate compounds in this stage of discovery:

a- Rapid formulation development wherein compound are formulated rapidly for in vivo testing, not necessarily considering the commercial viability of the formulation (ie. the powder in a bottle approach).

b- Robust and thorough formulation development, wherein effort is made to make the formulation commercially viable.

- The rapid formulation development is desirable in situations involving screening of multiple candidates with a limited assigned probability of success.

A more detailed formulation development is desired early on especially in situation involving time constraints and for leads with higher probability of success. There is a further desire to converge these two approaches, by the development and use of rapid formulation

techniques that are scalable and commercially viable.

-The drug discovery process:

A biopharmaceutical classification system (BCS) has been developed to categories hit compound, based on their aqueous solubility and GI permeability.

Class 1: High permeability, High solubility

Eg: propranolol, diltiazem, verapamil

- Those compounds are well absorbed and their absorption rate is usually higher than excretion.

Class 2: High Permeability, Low Solubility

Eg: Glibenclamide, mefenamic acid

-The bioavailability of those product is limited by their solvation rate.

Class 3: Low permeability, High solubility

Eg: Captopril, cimetidine

The absorption is limited by the permeation rate

but the drug is solvated very fast. If the formulation does not change the permeability or gastro intestinal duration time, the class 1 criteria can be applied.

Class 4: Low permeability, Low Solubility

Eg: Taxol, hydrochlorothiazide

- Those compounds have a poor bioavailability. Usually they are not well absorbed over the intestinal mucosa and high solubility (class 1) are generally easiest to formulate - a simple powder for reconstitution is sufficient or early studies. However, poorly soluble and or poorly permeable compounds pose a significant challenge. Such compounds often require an array of technologies to provide a viable formulation Early screening dose not differentiate compounds based on their solubility, therefore there is an increasing bias toward lipophilic (and consequently poorly soluble) drugs entering and processing through the development pipeline.

Furthermore, retrospective analysis suggests that drug discovery methodologies are biases towards low potency compounds, with a typical potency in the range of 1mg/kg.

Formulation tools for drug development:

Two of the most important per formulation factor that are considered during compound screening are Solubility and permeability. Both these factors directly affect the oral bioavailability of the compound. Solubility of the drugs is estimated in silico based on structure and can be experimentally verified using techniques such as Laser Nephelometry.

Similarly, permeability can be estimated from several semi-empirical models [such as those based on quantitative-SARs (QSAR).

Additionally, software programs are now available to estimate intestinal absorption. Compounds that are identified as poorly soluble and/or show

poor bioavailability might require additional formulation expertise at the development stage, as discussed in subsequent sections. However, irrational decisions based on these factors can lead to elimination of compounds that might otherwise be promising.

□ The term solid dispersion defined as the dispersion of one or more active ingredients (hydrophobic) in an inert carrier or matrix (hydrophilic) at solid stated by the melting (fusion), solvent or melting-solvent method.

Class	Solubility	Permeability	Absorption Pattern	Rate-limiting Step in Absorption
I	High	High	Well absorbed	Gastric emptying
II	Low	High	Variable	Dissolution
III	High	Low	Variable	Permeability
IV	Low	Low	Poorly absorbed	Case by case

- Enabling formulation technologies:

Novel enabling technologies are desired for challenging drugs where conventional technologies do not provide a viable solution. Through drug delivery research, several enabling technologies are now becoming available to formulate compounds that are poorly soluble. At the same time, formulation scientists can not merely depend on these technologies to assist development at a later stage. The use of these technologies and subsequent experimental demonstration of this are crucial elements required in lead optimization. Hence there is a need for such enabling technologies to be tested at small scales in a drug discovery setting.

- Solid dispersions.

Solid dispersion technologies involve stabili-

zation of the drug in its amorphous form, within a carrier matrix. The amorphous form allows faster dissolution of the drug and is particularly promising for orally administered drug (because of the wider choices of carrier matrices).

- Typical carrier used for this technology include water soluble polymer, such as polyvinyl pyrrolidone, polyethylene glycol.
- The drug carrier screening tool can be used in conjunction with miniaturized proceeding equipment (such as the micro-spray dryer developed by particle and coating technologies) to develop and screen solid dispersion formulation of poorly soluble drugs.

- **Solubilizing agent:**

Complexation using carriers such as

Cyclodextrin is another approach that can be used for solubilization and screening of poorly soluble compounds.

. The beta- and gamma- cyclodextrins and several of their derivatives are unique in having the ability to form molecular inclusion complexes with hydrophobic drugs having poor aqueous solubility.

. These are versatile in having a hydrophobic cavity of size suitable enough to accommodate the lipophilic drugs as guests; the outside of the host molecule is relatively hydrophilic.

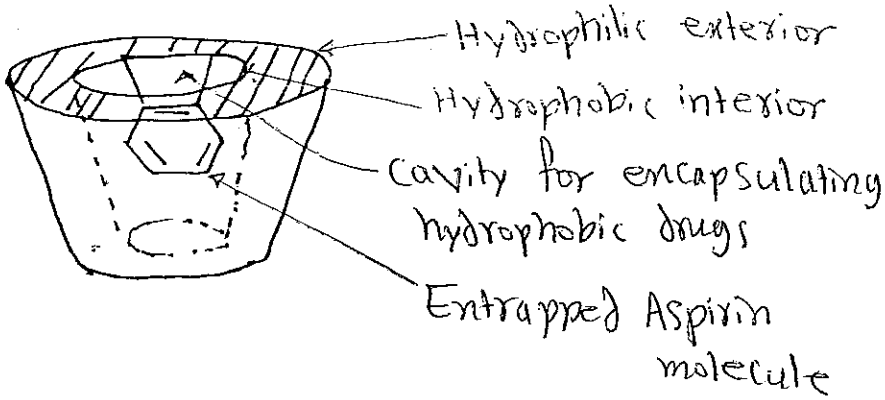


Fig- Functional and structural feature of a cyclodextrin molecule showing an encapsulated drug.

- Thus, the molecularly encapsulated drug has greatly improved aqueous solubility and dissolution rate.

-limitations:

1- Several naturally occuring and commercially available cyclodextrins have exhibited toxicity.

2. Cyclodextrins require the drug to have specific molecular properties to efficiently form a complex.

□Lipid-based complexation:

- Complexation using lipids is another strategy that can be adopted for poorly soluble drugs. Various complexes can be formed including liposome, micelles, cubosomes and solid lipid nanoparticle.

- Lipid can also be used in developing

Self emulsifying drug delivery system (SEDDS), lipid vesicle, particularly liposomes, have been used extensively for targeting of chemotherapeutic drugs to tumours.

- Liposomes provide an additional benefit of being applicable for both water soluble drugs (whereby the drug is encapsulated in the lipid bilayers. Finally, for oral applications, lipid vesicles might serve as permeation enhancers, increasing the bioavailability of drugs. Furthermore the presence of high amounts of lipid might provide an analytical challenge in identifying the effect of the drug versus the excipient.

- **Particle size reduction:**

- Poorly soluble drugs can be formulated as nanoparticles with high surface area, which

enhances dissolution rates in accordance with Noyes-Whitney equation:

$$\frac{dQ}{dt} = \frac{D}{h} S(C_s - C_g)$$

C_s — concentration of drug in bulk of the soln

C_g — ... in the stagnant layer

h — thickness of the stagnant layer

Where, the rate of dissolution ($\frac{dQ}{dt}$) is proportional to the diffusion coefficient of the drug (D), the available surface area(S) and the difference b/w Saturation solubility of the drug in the boundary layer (C_s) and concentration of drug in the bulk fluid (C_g).

o Particle size reduction can be achieved mainly by two of processes:

1. Particle formation processes (microprecipitation, chemical synthesis, complexation).
2. Particle comminution (size reduction) processes: homogenization, milling, grinding.

The two types of processes can also be combined for a synergistic effect as adopted by the Nanoedge technology platform. A particle formation step (micro precipitation) is employed just before a particle comminution step in this platform, a particle formation step is designed to produce customized, friable particles that are amenable to comminution via high pressure homogenization.

Besides enhanced dissolution, nanoparticles offer the potential for passive or active targeting of drugs. When administered intravenously, nanoparticles have a tendency to be taken up by the reticuloendothelial system (RES). This provides a potential for targeting for macrophage related disorders.

Nanoparticles can be coated with hydrophilic polymers, such as polyethylene glycol, to prevent

RES uptake. Such particles have a tendency to circulate for longer periods of time, and are typically taken up by tumour cells via the enhanced permeation and retention (EPR) effect. Furthermore, nanoparticles can be coated with specific functional groups for active targeting. For example, thiamine coated nanoparticles demonstrated preferential uptake in the brain, via the blood-brain-barrier thiamine transporters. Nanoparticles can also be administered via multiple routes of administration, as a solid or a suspension.

Thus a single formulation can lead to multiple dosing options early in the development program.

•Nanoparticles further provide clinical benefits including enhanced bioavailability,

reduced fed-fasted ratio (for oral applications). Given these factors it is anticipated that nanoparticles could offer potential solution for expending the lead selection and the drug development process.

Route of administration	Potential benefit
oral	Rapid onset, reduced fed-fasted ratio, improved bioavailability
IV	Rapid dissolution, tissue targeting
SC/IM	Rapid onset, reduced tissue irritation, Higher bioavailability
Inhalation	Higher bioavailability ,more consistent dosing
ocular	Higher bioavailability more consistent dosing

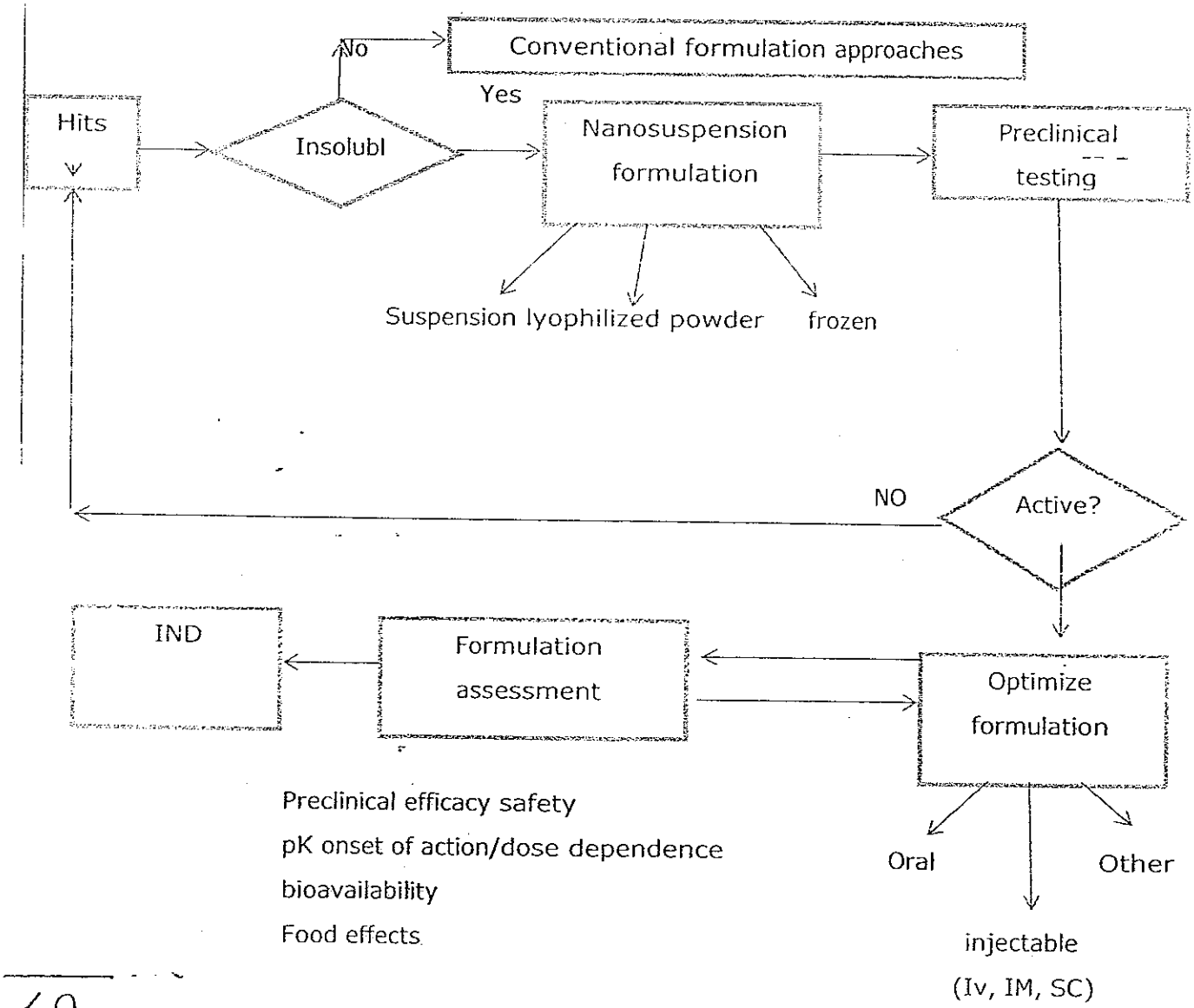
Rapid formulation screening:

Several platforms have been developed to provide rapid formulation screening. These platform involve a combination of one or more traditional and novel enabling technologies.

Poorly soluble drugs(solubility less than 500nm)are processed rapidly(& in small quantities)as nan suspensions that are stabilize either in suspension or frozen or lyophilized. The suspension is tested in animals for efficacy & the process is repeated iteratively till the hit compounds with desired efficacy is identified.

More rigorous testing can be performed at this stage to assess the formulation before scale up.

It is anticipated that other versatile technologies with rapid screening functionalities might also be used in a similar fashion.



Introduction To Clinical Trials

□ A clinical trial or study is defined by the International Conference on Harmonisation Principles of Good Clinical Practice (ICH GCP) as being any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study ADME of an investigational product(s) with the object of ascertaining its safety and/or efficacy...

<u>what are the different types of clinical trials?</u>

- Treatment
- Prevention
- Early detection/ Screening
- Diagnostic
- Quality of life/Supportive care

□ <u>Treatment Trials:</u>

What new treatments can help people with a particular disease?

- what is the most effective treatment for people with that disease?

□ Prevention Trials:

Evaluate the effectiveness of ways to reduce the risk of a particular disease

- Enroll healthy people at high risk for developing that disease
- Unlike treatment trials, prevention clinical trials are studies involving healthy people who are at high risk for developing a particular disease.
- These studies try to answer specific questions about and evaluate the effectiveness of ways to reduce the risk of disease.

□ Randomized Trials:

Participants have an equal chance to be assigned to one of two or more groups:

- One gets the most widely accepted treatment (standard treatment)

- The other gets the new treatment being tested, which researchers hope and have reason to believe will be better than the standard treatment.
- Phase 3 trials are randomized clinical trials, and some phase 2 trials may also be randomized.
- Randomization is a method used to prevent bias in research.
- Treatment assignments are generated by a computer, and each participant has an equal chance of being assigned to one of two or more groups, the control group and the treatment group.
- The control group is made up of the people who get the most widely accepted treatment (standard treatment) for the disease.

- Randomization in clinical Trial Studies

Randomization is of central importance in clinical trials. It prevents selection bias and insures against accidental bias. It produces comparable groups, and

eliminates the source of bias in treatment assignments. Finally, it permits the use of probability theory to express the likelihood of chance as a source for the difference b/w outcomes.

Introduction:

-A good clinical trial minimizes variability of the evaluation and provides an unbiased evaluation of the intervention by avoiding confounding from other factors. Randomization insures that each patient have an equal chance of receiving any of the treatments under study, generate comparable intervention groups which are alike in all important aspects except for the intervention each group receives. It also provides a basis for the statistical methods used in analyzing data.

Criteria For Randomization:

1. Unpredictability

- Each participant has the same chance of

receiving any of the interventions.

- Allocation (تخصيص) is carried out using a chance mechanism so that neither the participant nor the investigator will know in advance which will be assigned.

2. Balance:

- Treatment groups are of a similar size and constitution, groups are alike in all important aspects and only differ in the intervention each group receives.

3. Simplicity:

- Easy for investigator / staff to implement

#Methods of Randomization:

The common types of randomization include 1-simple 2-block 3-Stratified and 4-unequal randomization. Some other methods such as biased coin, minimization and response-adaptive methods may be applied for specific purposes.

1. Simple Randomization:

This method is equivalent to tossing a coin for each subject that enters a trial, such as Heads = Active, Tails = Placebo. The random number generator is generally used. It is simple and easy to implement and treatment assignment is completely unpredictable. However, it can get imbalanced in treatment assignment, especially in smaller trials. Imbalanced randomization reduces statistical power.

2. Block Randomization:

The basic idea of block randomization is to divide potential patients into m blocks of size 2n, randomize each block such that n patients are allocated to A and n to B. then choose the blocks randomly. This method ensures equal treatment allocation within each block if the complete block is used. Example: Two treatments of A, B and Block size of $2 \times 2 = 4$ Possible treatment allocations within each block are (1) AABB

2) BBAA 3) AB AB 4) BABA 5) ABBA 6. BAAB

طبقه‌بندی کردن

3. Stratified Randomization:

Imbalance randomization in numbers of subjects reduces statistical power, but imbalance in prognostic factors is also more likely inefficient for estimating treatment effect. Trial may not be valid if it is not well balanced across prognostic factors. Stratification can balance subjects on baseline covariates. tend to produce comparable groups with regard to certain characteristics (e.g. gender, age, race, disease severity) thus produces valid statistical tests. The block size should be relative small to maintain balance in small strata.

4. Unequal Randomization:

Most randomized trials allocate equal numbers of patients to experimental and control groups. This is the most statistically efficient randomization ratio as it maximizes statistical power for a

"Stratified randomization refers to the situation in which strata are constructed based on values of prognostic variables and a randomization scheme is performed separately within each stratum.

given total sample size. However this may not be the most economically efficient or ethically/practically feasible. When two or more treatments under evaluation have a cost difference it may be more economically efficient to randomize fewer patients to the expensive treatment and more to the cheaper one. The substatistical cost saving can be achieved by adopting a smaller randomization ratio such as a ratio of 2:1 with only a modest loss in statistical power. When one arm of the treatment saves lives and the other such as placebo/medical care only does not much to save them in the oncology trials. The subject survival time depends on which treatment they receive. More extreme allocation may be used in these trials to allocate fewer patients into the placebo group. Generally randomization ratio of 3:1 will lose considerable statistical power more extreme than ..... which leads to much longer sample size.

- The investigational group is made up of the people who get the new treatment being tested.
- Why is randomization important?

So all groups are as alike as possible

Provides the best way to prove the effectiveness of a new agent or intervention

- Clinical trial protocol:

→ A recipe or blueprint.

→ Strict scientific guidelines:

- Purpose of study
- How many people will participate
- Who is eligible to participate
- How the study will be carried out
- What information will be gathered about participants
- End points

- Clinical trials follow strict scientific guidelines. These guidelines clearly state the study's design and who will be able to participate in the study.

- Every trial has a head person in charge, usually a doctor, who is called the principal investigator.

- The principal investigator prepares a plan for the study, called a protocol, which acts like a "recipe" for conducting a clinical trial.

- Every doctor or research center that takes part in the trial uses the same protocol. This ensures that participants are treated identically no matter where they are receiving treatment, and that information from all the participating sites can be combined and compared.

- The case report form:

CRF is the document which collects all the data necessary for analysis is to be recorded.

CRF is to be filled by investigator or any person formally delegated to carry out the procedure in question.

- Finding suitable patients

They must pass the inclusion and exclusion criteria and the consent to the study.

- They must also be deemed likely to complete the study.

• Why do research Studies?

• To collect data on usual and unusual events, conditions and population groups.

• To test hypotheses formulated from observations and/or intuition

• Ultimately, to understand better one's world and make "sense of it".

Epidemiology:

The study of the distribution of a disease or condition in a population and the factors that influence that distribution.

• Classifications of research studies:

i- Observational Studies:

• Groups are studied and contrasts made b/w groups.

• The observed data collected are analyzed

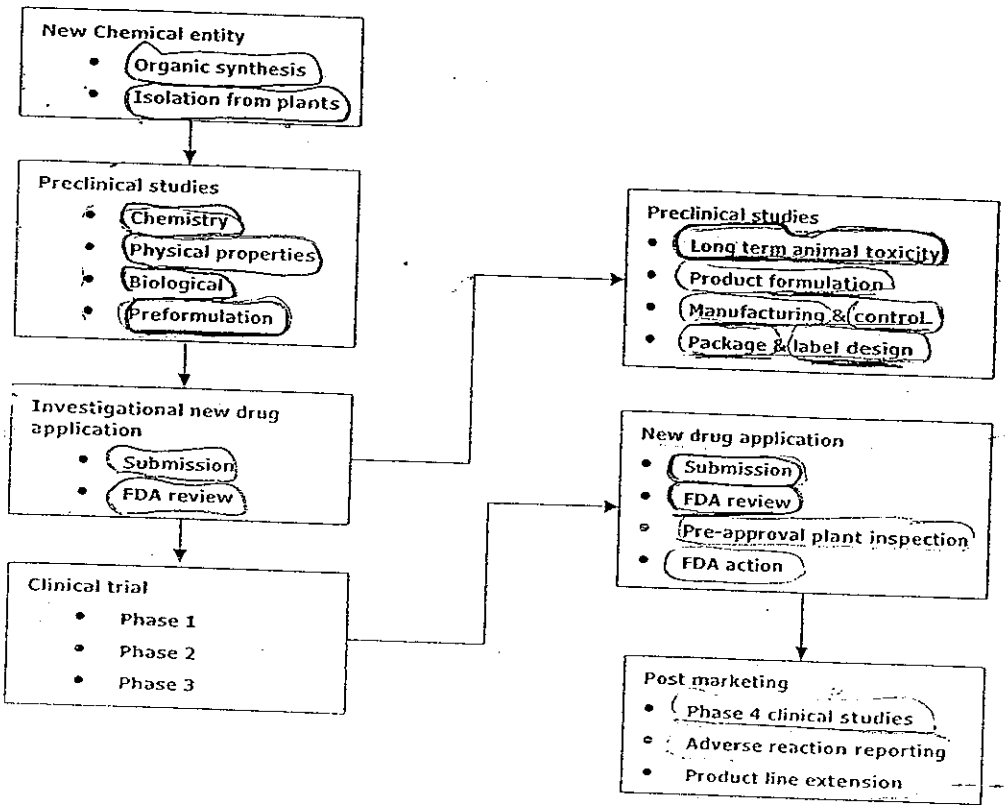
ii- Analytic Studies:

- Also called experimental
- Study the impact of a certain therapy
- ultimately the investigator controls factor being studied.

iii- Clinical Trial:

- Considered the "true" experimental study
- "Gold Standard" of clinical research
- Often a prospective study that compares the effect and value of an intervention against a control in human subjects

Steps involved in clinical trial:



5M

- Preclinical Studies:

- Choice of animal model:

- Typically, in drug development studies animal testing involves two species.

The most commonly used models are murine and canines, although primate and procaine are also used.

- The choice of species is based on which

will give the best correlation to human trial.

- Difference in the gut, enzyme activity, circulatory system or other consideration make certain models more appropriate based on the dosage form, site of activity, or noxious metabolite.

- Acute toxicity:

Acute toxicity studies are required for all drugs. These studies involve single administration of the agent up to the lethal level in at least two species, one rodent and one non rodent.

Sub acute and chronic toxicity:

These studies are required for most agent especially those intended for chronic use. Tests are usually carried out for at least

the amt of time proposed for human application ie. 2-4 weeks (sub acute) or 6-24 month (chronic) in atleast two species.

Types of animal testing:

- Pharmacological profile
- Teratogens
- Mutagenesis
- Carcinogenesis

- Based on pre-clinical trial, No observable effect level (NOEL) on drug are established, which are used to determine initial phase 1 clinical trial dosage levels on a mass API per mass patient basis.

- Pre clinical studies involve in vitro (test tube) and in vivo (animal or cell culture)

experiment using wide ranging dose of the study to obtain preliminary efficacy, toxicity, and pharmacokinetic information.

- Such test assists pharmaceutical companies to decide whether a drug candidate has scientific merit for further development as an investigational new drug.
- Each class of product may undergo different type of preclinical research. For instance, drugs may undergo pharmacodynamics (PD), pharmacokinetic (PK), ADME and toxicity testing through animal testing.
- This data allows researcher to estimate a safe starting dose of the drug for clinical trials in human.
- Studies of drug's toxicity includ which organ are targeted by the drug.

◦Types of clinical trials: 2m

The U.S. National institutes of Health (NIH) organize trials into 5 different types:

1. Prevention trials:

- Look for better way to prevent disease in people who have never had the disease or to prevent a disease from returning.
- This approach may include medicine, vitamin, vaccines, minerals or life style changes.

2. Screening trial:

Test the best way to detect certain disease or health condition.

3. Diagnostic trials:

Conducted to find better test or procedure for diagnosing a particular disease or condition.

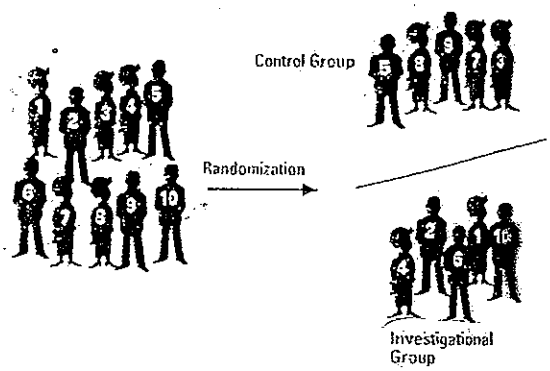
4. Treatment trials: test experimental treatment, new combination of drugs, or new approaches to surgery or radiation therapy

5. Quality of life trials: explore way to improve comfort and the quality of life for individual with a chronic illness.

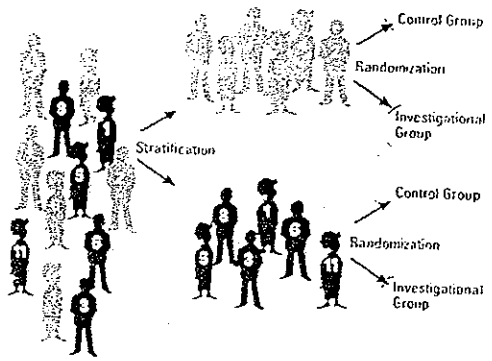
☐ Clinical Trial Study Design: 5M

- Randomized
- Non-randomized
- Blinded: Participants do not know if in experimental or control group
- Double blinded: Participants and staff do not know group assignment
- Placebo: inactive pill with no therapeutic value

Randomization



Stratification



- Clinical trial protocol: 5M

- The protocol describes the scientific, objective, design, methodology, statistical consideration and organization of the planned trial.

- Detail of the trial is also provided in other documents referenced in the protocol such as investigator's brochure.

- The protocol contains a precise study plan for executing the clinical trial, not only to assure safety and health of the trial subjects, but also to provide an exact template for trial conduct by investigators at multiple locations (in a multicenter trial) to perform the study in exactly the same way

- The protocol also gives the study administrator (often a contract research organisation) as well as the site team of physicians, nurses and clinic administrator a common reference document for site responsibilities during the trial.

- The format and content of clinical trial protocols sponsored by pharmaceutical, biotechnology or medical device companies in the United States, European Union, or

Japan has been standardized to follow Good Clinical Practice guidance issued by the international conference on Harmonization of Technical Requirement for registration of pharmaceutical for Human Use (ICH).

- Regulatory authorities in Canada and Australia also follow ICH guideline.

- Components of clinical Trial Protocols:

  - Investigating two or more conditions so have two (+) groups

    -Ex: drug vs. placebo; medicine vs surgery

  - Specific inclusion/exclusion criteria

  - Sample size and power calculations

- Study participant recruitment:

  - Identify eligible participants

  - Explain study

- Provide informed consent
- Reassess eligibility
- Assign to one group

- Participants should be told:
  - May have side effects (adverse effects)
  - Time commitment
  - Benefits and risks
  - May withdraw at any time
  - Enrollment 100% voluntary

- Design feature:

1. Informed consent: informed consent is a legally-defined praess of a person being told about key facts involved in a clinical trial before deciding whether or not to participate.
  - The research team provides an informed consent document that include trial details,

such as its purpose, duration required procedures, risks, potential benefits and key contacts. The participant then decides whether or not to sign the document in agreement.

- Informed consent is not an immutable contract, as the participant can withdraw at any time without penalty.

2. Statistical power:

The Sponsor's goal usually is to obtain a statistically significant result showing a significant difference in outcome b/w the groups of patients who receive the study treatment. The number of patient enrolled in study has a large bearing on the ability of the study to reliably detect the size of the effect of the study intervention.

This is describing as a power of the trial. The larger the sample size or number of participants in the trial, the greater the statistical power.

3. Administration:

Clinical trials designed by a local investigator and federally funded clinical trials are almost always administered by the researcher who designed the study and applied for the grant. Phase 3 and phase 4 clinical trial of new drugs are usually administered by a contract research organisation (CRO) hired by the sponsoring company.

A CRO is a company that is contracted to perform all the administrative work on a clinical trial. It recruits participating researchers, train them, provide them with supplies, coordinates

Study administration and data collection, set up meetings, monitors the sites for compliance with the clinical protocol and ensures that the sponsor receives clean data from every site.

4. Ethical conduct:

All studies that involve medical or therapeutic intervention on patients must be approved by a supervising ethics committee before permission is granted to run the trial.

- In the U.S., this body is called the Institutional Review Board (IRB).
- ICH GCP is set of standard used internationally for the conduct of clinical trials. The guideline aim to ensure that the right, safety and well being of trial subjects are protected.

5. Sponser:

-Sponsor is responsible for:

Accurately informing the local site investigator of true historical safety record of drug, device or other medical treatment to be tested and of any potential interaction of the study treatment with already approved medical treatment, monitoring the results of the study as they come in from the various site, as the trial proceeds, collecting adverse event reports from all site investigators in the study, and for informing all the investigaters of the sponsor's judgment as to whether these adverse events were related or not related to the study treatment. The sponsor and the local site investigators are jointly responsible for writing a site specific informed consent that accurately inform the

potential subjects of the true risks and potential benefits of participating in the study.

6. local Site investigators:

If a physician investigator believes that study treatment may be harming subject in the study, the investigator can stop participating at any time.

- The local investigator is responsible for:

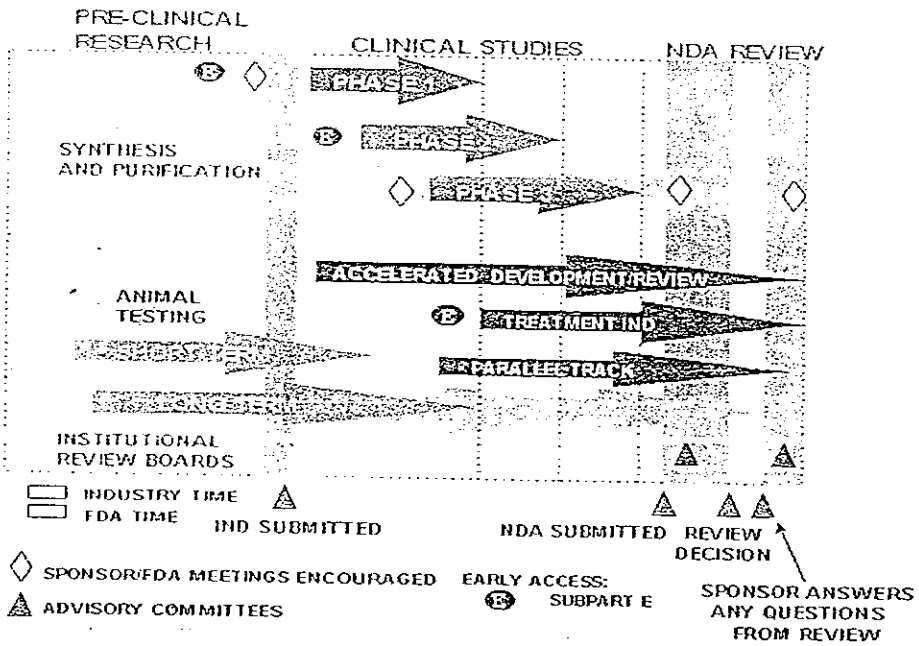
- Conducting the study according to the study staff throughout the duration of the study
- Ensuring that potential subjects in the study understand the risk and potential benefit of participating in the study.
- Reviewing all adverse event reports sent by the sponsor.
- Being truthful to the local IRB in all

Communication relating to the study.

- The drug development and approval process:

1. Early research and preclinical testing
2. IND application filed with FDA
3. Clinical trials (phases 1, 2, and 3)
4. NDA filed with FDA
5. FDA validates claim and approves drug

Phases of Clinical Product Development



Various phase in clinical trials:

	phase1	*Phase 2*	*Phase 3*	*phase4*
objective	Determine the metabolic& pharmacological action & the maximally tolerated dose.	Evaluate effectiveness, determine the short term side effect & identify common risk ~~for specific risks~~ for a specific population & disease.	Obtain additional information about the effectiveness in clinical outcomes & evaluate the overall risk benefit ratio in demographically diverse sample.	Monitor ongoing safety in large population & identify additional uses of the agent that might be approved by FDA.

Phases of clinical Trials:

Phase 1:

- 15-30 people
- What dosage is safe?
- How should treatment be given?
- How does treatment affect the body?
- Initial administration of drug to humans
- Assessment of human toxicology
- Determine Maximum Tolerated Dose (MTD)

or optimal Biological Dose (OBD)

Phase 2:

- Less than 100 people
- Begin if phase 1 studies do not reveal unacceptable toxicity.
- Primarily focus on collection of preliminary data on whether the drug has effect in a defined patient population
- The relationship between dose and effectiveness
- Continue to evaluate safety and short-term side effects.
- For controlled trials, patients receiving the drug are compared with similar patients receiving a different treatment, usually a placebo or a different drug questions asked.

Does treatment do what it is supposed to?

How does treatment affect the body?

Phase 3:

- From 100 to thousands of people
- Compare new treatment with current standard
- Begin if preliminary evidence of effectiveness is shown during phase 2.
- Gather more information about safety and effectiveness in a defined population.
- May form the primary basis of an efficacy claim

Post marketing surveillance phase 4:

- From hundreds to thousands of people
- Usually takes place after drug is approved
- Used to further evaluate long-term safety and effectiveness of new treatment.

- Methods involved in post marketing surveillance:

non-experimental studies (observational)

1. Descriptive non experimental studies
   - A. Case reports
   - B. Case series

2. Analytical non-experimental studies
   - A. Case control
   - B. Cohort study
   - C. Cross sectional study

A. Case control:

- By definition, a case control study involves two population - case and control.
- In this study, cases and controls must be comparable with respect to known 'confounding factors' such as age, sex, occupation, social status.

- For example, the link btw use of oral contraceptive and occurrence of ovarian cysts in women of child bearing can be conducted. Here prior use of oral contraceptive in the age group can be selected as the cases.
- The controls are those without the prior use of oral contraceptives.
- In case control, matching is important.
- Case control studies are used when outcomes and exposure to the drug are rare.
- The case control studies are widely used to assess the safety of medicines.
- Ex of association btw the drugs and adverse events:
  - NSAIDs and peptic ulcer
  - Oral contraceptives and venous thromboembolism
- Data from case control studies are used to

calculate an odd ratio, which is the ratio of the odds of developing the disease for exposed patient to the odds of developing the disease for un-exposed patients.

The basic design of a case control study is

Suspected or Risk factors	Cases (disease present)	Control (disease absent)
present	a	B
absent	c	D
	a+c	b+d

- To illustrate, if it is our intention to test the hypothesis that cigarette smoking causes lung cancer, using the case control method, the investigation begins by assembling, a group of lung cancer cases (a+c) and a group of suitably matched control (b+d)
- One then explores the past history of these two groups for the presence or absence of smoking, which is suspected to be related

to the occurence of the lung cancer.

- If frequency of smoking, a/(a+c) higher in cases than in controls, b/(b+d), an association is said to exist b/w smoking and lung cancer.

Advantages:

1. Relatively easy to carry out
2. Rapid and inexpensive
3. Require comparatively few subjects
4. No risk to subjects
5. Allows the study of several different etiological factors (eg: smoking, physical activity and personality characteristics in myocardial infarction).
6. Ethical problems minimal

Disadvantages:

1. Problems of bias relies on memory or past records.

2. Selection of an appropriate control group may be difficult.

3. We cannot measure incidence and can only estimate the relative risk.

4. Not suited to the evaluation of therapy or prophylaxis of disease.

b. Cohort Study:

Cohort Study are Studies that identify subsets of a define population and follow them over time, looking for differences in their outcome.

- Cohort studies generally are used to compare exposed patients to unexposed patients, although they can also be used to compare one exposure to another.
- The term "cohort" is defined as the group of people who share a common characte-

ristic or experience within the defined time period eg. Age, occupation, exposure to a drug or vaccine, pregnancy, ensured person.

Indication for cohort studies:

a. When there is good evidence of an association b/w an exposure and disease as derived from clinical observations and supported by descriptive and case control studies.

b. When exposure is rare, but the incidence of disease high among exposed e.g: special exposure groups like those in industries, exposure to X-ray.

c- When attrition of study population can be minimized e.g. follow up is easy, cohort is stable, cooperative easily accessible.

d. When ample funds are available.

Framework of a cohort study

- The basic design of a simple cohort study is shown. We begin with a group of cohort (a+b) exposed to a particular factor thought to be related to disease occurrence, and a group (c+d) not exposed to that particular factor. The former is known as study cohort , and the latter control cohort.

cohort	yes	no	total
Exposed to putative etiologic factor	a	b	a+b
Not exposed to putative etiologic factor	c	d	C+d

• Types of cohort study:

1. Prospective cohort study
2. Retrospective cohort study
3. Combination of retrospective and prospective cohort study.

1. Prospective cohort study:

A prospective cohort study or current cohort study is one in which the outcome (e.g Disease) has not yet occured at the time the

investigation begins.

- Most prospective studies begin in the present and continue into future.
- For eg: The long term effects of exposure to uranium was evaluated by identifying a group of uranium miners and a comparison group of individual not exposed to uranium mine and by assessing subsequent development of lung cancer in both the groups.

2. Retrospective Cohort Studies:

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

- The investigator goes back in time, sometimes 10 to 30 years, to select his study groups from existing records of past employments

medical or other records and traces them forward through time, from a past date fixed on the records, usually up to the present.

3. Combination of retrospective and prospective cohort studies:

In this type of study, the retrospective and prosp-ective elements are combined.

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

- Cohort study example:

- The news's health study followed more than 160,000 American nurses over time, starting in 1976. the exposure of interest was oral contraceptive use.

- The researcher on that project were able to prospectively examine different outcomes such as cancers (i.e breast, colon, skin), deaths, thromboembolism and skeletal problems.

- Advantages:

- Incidence can be calculated.
- Several possible outcomes related to exposure can be studied simultaneously.
- It provide direct estimate of relative risk
- Dose response ratio can also be calculated.

- Disadvantages:

- Studies involve a large no. of people
- It takes a long time to complete the study.

- Certain administrative problems such as loss of experienced staff, loss of funding.
- There may be changes in the standard methods or diagnostic criteria of the disease over prolonged follow-up.
- The study itself may alter people's behavior
- Expensive

C- Cross-Sectional Study:

- Cross sectional study may be of descriptive or analytical nature.
- Cross sectional study are also known as instantaneous studies, simultaneous studies or prevalence studies.
- There are studies of use of drugs at the specific point of time and are conducted through surveys, data base analysis or

medication chart reviews.

- They help the collection of data on a cross section of population, which may comprise the whole population or a population (sample) of it.
- This type of studies provides information about the situation that exists at a single time.

Advantages:

- The studies can be short term.
- Relatively inexpensive to conduct.
- It can only measure disease prevalence rather than incidence.

Disadvantages:

- No direct estimate of risk and the slope for bias. Since exposure and disease are measure at the same point of time.

- It is not possible to establish temporality, that is, whether the exposure or presence of a characteristic preceded the development of the disease or condition.

MAIN DIFFERENCE BETWEEN CASE CONTROL AND COHORT STUDII

CASE CONTROL STUDY	COHORT STUDY
1) Proceeds from effect to cause.	1) Proceeds from cause to effect
2) Starts with the disease .	2) Starts with people exposed to risk factor or suspected cause.
3) Tests whether the suspected cause occurs more frequently in those with the disease than among those without the disease.	3) Tests whether disease occurs more frequently in those expose than in those not similarly exposed.
4) Usually the first approach to the testing of hypothesis, but also useful for exploratory study.	4) Reserve for testing of precisel formulated hypothesis.
5)Involves fewer No .of subjects	5)Involves larger No .of subjects
6)Yields relatively quick results	6)Long follow up period often needed involving delayed result
7)Suitable for study of rare disease	7)Inappropriate when the disease or exposure under investigation is rare
8)Generally yields only estimate of RR(odds ratio)	8)Yields incidence rates, RR as we as AR
9) Cannot yield the information about disease other than selected for study	9) Can yield the information about more than one disease outcome
10)Relatively inexpensive	10)expensive

-The Final Step: FDA approval

- Review of New Drug Application (NDA) or

Biologics License Application (BLA)

- Labeling
- Continued monitoring
- Feedback

- Releasing the results of clinical trials:
  - Peer-reviewed journals
  - Public announcements
  - Results not made public until end of trial.

Methods of post marketing surveillance

Phase IV Studies

Also known as post marketing surveillance trials involve the safety surveillance (pharmacovigilance) and ongoing technical support of drug after it receives permission to be sold.

- Phase IV studies may be required by regulatory authorities or may be undertaken by sponsoring company for competitive (finding a new market) or other reasons (for eg, the drug may not have been tested for interactions with other drugs, or on certain population groups such as pregnant women, who are unlikely to subject themselves to trials).
- The safety surveillance is designed to detect any rare or long-term ADR over much larger patient population and longer time period than was possible during the phase I-III clinical trials.
- Harmful effects discovered by phase IV may result in a drug being no longer sold, or restricted

to certain uses: recent examples involve. cerivastatin, troglitazone, rofecoxib.

□ Purposes of clinical Studies in phase IV:

1. Address questions that arose during phase I to III, but which have not yet been completely answered or adequately addressed. These clinical trials include comparisons with other drugs, cost-effectiveness studies.

2. Continue clinical trials initiated in phase III.

3. Investigate interactions with food, drugs and environmental factors.

4. Expose more patients to new drug to confirm efficiency better understanding of safety (delayed effects, prolonged use effects) to quantify rates of nonadverse reactions.

5. Also drug should be evaluated in special patient like pregnant, nursing mothers, elderly

6. Determine whether the results obtained from tertiary care hospital during phase I and III can be confirmed in other hospitals.

7. Evaluate whether any rare but serious ADR occur.

8. Discover new indications that may be explored and developed in phase II and III discoveries may occur to serendipity.

9. Evaluate pattern of drug utilization in specific or general population.

10. Study the clinical characteristics of over dosage and the means of counteracting the problem.

11. Assess the costs of ADR to various sectors of society and possibly develop and approach to meet these costs.

Methods:

1. Descriptive studies
2. Cross-sectional studies
3. Case control studies

exposure to a drug or vaccine, pregnancy, ensured person.

- If the case and controls both come from the same population the results of the study are more easily validated.
- There is no randomization and blinding.
- Patients can be directly monitored to ensure they take the drug appropriately, and to observe drug effects.
- With less control, a larger cohort can be followed, but bias is thus increased.

□ Controlled clinical trials

- The term "controlled" refers to the trials that adhere strictly to a designed protocol.
- The purpose is to reduce the variability of many factors and biases that might influence the results.
- Control features include the double-blind procedure, where neither the patient, nor the

investigator is aware of which treatment the patient is receiving.

- The greater the number of factors of the study or trial design that are specified and the greater the control that is built into the study.
- Used to identify drugs beneficial as well as ADR.
- How often the effects occur (frequency).

Abbreviated New Drug Application (ANDA)

- An Abbreviated New Drug Application (ANDA) is specifically designed for an approval of a generic drug product.
- When data within an ANDA are submitted to the Food and Drug Administration's Center for Drug Evaluation and Research (CDER), office of Generic Drugs, the applications are reviewed and approved from that division.
- On approval of the application the applicant may manufacture and market the generic drug product with the purpose of providing consumers with a safe, effective, and low cost alternative of the generic form of a brand name drug.

- A generic drug must be a drug product that is comparable to an innovator drug product in dosage form, strength, route of administration,

quality, performance characteristic and intended use.

Using bioequivalence as the basis for approving generic copies of drug products was established by the "Drug Price Competition and Patent Term restoration Act of 1984, also known as the Waxman-Hatch Act. This act permits the FDA to approve ANDAs submitted to market generic versions of brand-name drugs without conducting costly and duplicative preclinical and clinical trials.

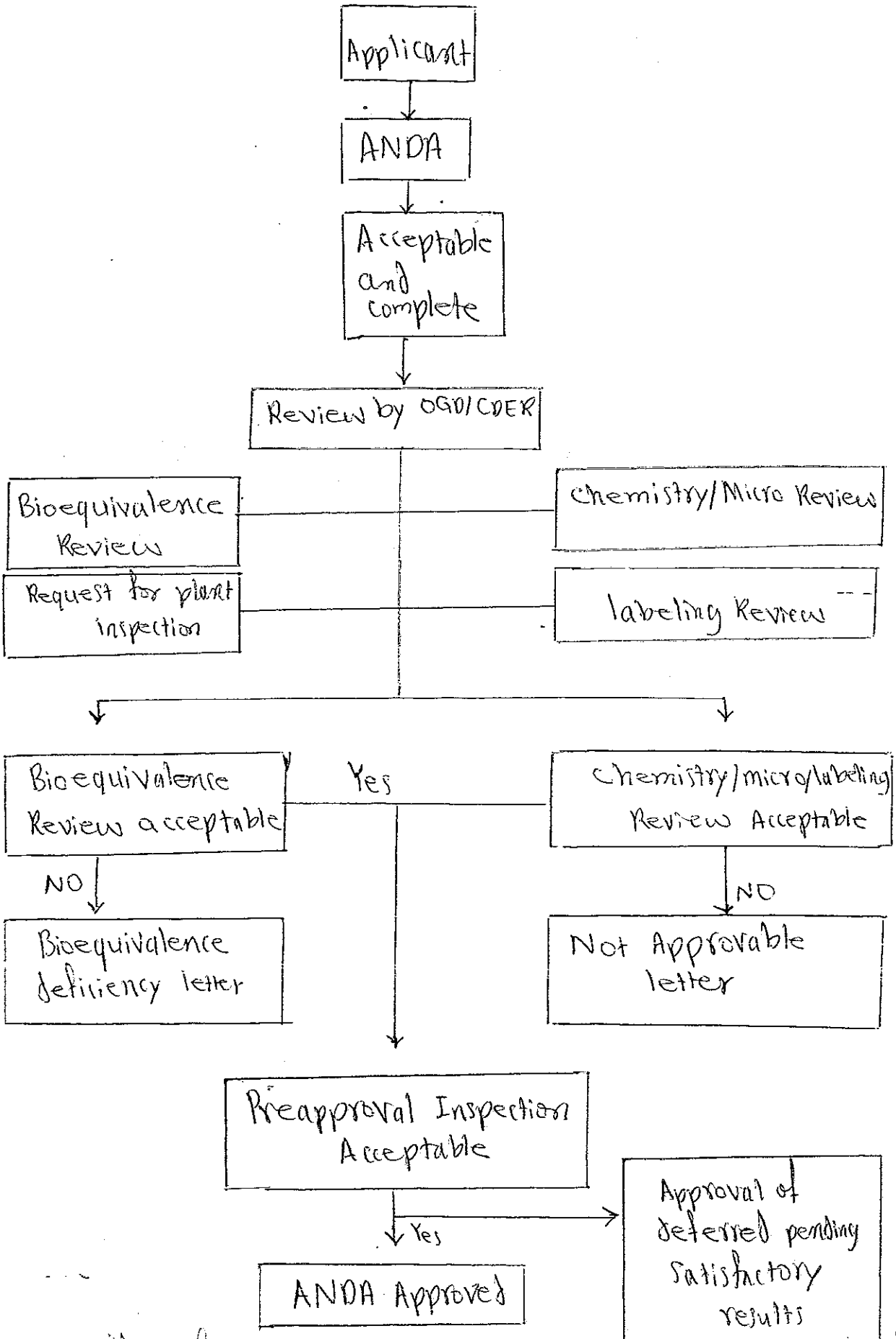
☐ Hatch-Waxman Act:

- Commonly known as "Drug Price Competition and Patent Term Restoration Act" of 1984.
- The Hatch-Waxman Act" is an act dealing with the approval of generic drugs and associated conditions for getting their approval from

FDA, patent term extension and Orange Book Listing.

- It is because of this Act that there is the availability of less costly generic drugs into the market without conducting costly and duplicative clinical trials.
- As the same time, the brand-name companies (innovators) can apply for upto five additional years longer patent protection for the new medicines that they developed to make up the time lost while their products were going through FDA's approval process.

ANDA review process



OGD: Office of Generic Drugs
CDER: Center for Drug Evaluation and Research

Guidance documents for ANDAs

- **Generics**
  - Generic (Draft - Distributed for comment purposes only)
  - Procedural Draft: Applications covered by Section 505(b)(2). This provision permits FDA to rely, for approval of an NDA, on data not developed by the applicant.

- **Biopharmaceutics**
  - Bioavailability and bioequivalence studies for orally administered drug products - general considerations. This guidance should be useful for applicants planning to conduct bioavailability (BA) and Bioequivalence (BE) studies during the IND period for an NDA, BE studies intended for submission in an ANDA and BE studies conducted in the post approval period

for certain changes in both NDAs and ANDAs.

- Drug master files

- A Drug Master File (DMF) is a submission to the FDA that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging and storing of one or more human drugs.

- Required specifications for FDA's, IND, NDA and ANDA Drug Master File Binders.

- Guidance for industry

  - changes to an approved NDA or ANDA

  - Refusal to receive

  - clarifies CDER's decisions to refuse to receive an incomplete application.

- Inactive ingredient database:

  - This database contains all inactive ingredients

present in approved drug products or conditionally approved drug products currently marketed for human use.

D Biopharmaceutics

Bioavailability and Bioequivalence Studies for orally Administered Drug Products - General Considerations.

1. Introduction

2. Background

a. General

b. Bioavailability

c. Bioequivalence

3. Methods to document BA and BE

a. pharmacokinetic Studies

b. Pharmacodynamic Studies

4. Comparison of BA measures in BE studies

5. Documentation of BA and BE.

a. Solutions

b. Suspensions

c. Immediate-Release Products: Capsules and Tablets

d. Modified-Release Products

e. Miscellaneous Dosage Forms

6. Special Topics:

a. Food-Effect Studies

b-Moieties to be measured

c. Long-Half-life Drugs

d. First Point Cmax

e. Orally Administered Drugs Intended for Local Action

f. Narrow Therapeutic Range Drugs

I. ANDA Content:

A. General:

•The term abbreviated is used in generic drug applications because they are generally not

required to include preclinical and clinical data to establish safety and efficacy.

- A sponsor of a generic drug must scientifically demonstrate that the product is bioequivalent i.e. performs in the same manner as the innovator drug.

- One way scientists demonstrate bioequivalence is to measure the time it takes the generic drug to reach the blood stream in 24 to 36 healthy volunteers. This gives them the rate of absorption, or bioavailability of the generic drug, which they can then compare to that of the innovator drug. This generic version must deliver the same amount of active ingredients into a patient's bloodstream in the same amount of time as the innovator drug.

B. Legal Requirements and Guidance Documents

- Guidance documents represent the Agency's current thinking on a particular subject. These documents are prepared for FDA review staff and applicants or sponsors to provide guidelines for the processing, content, evaluation, and approval of an application and also to the design, production manufacturing and testing of regulated products.
- They also establish policies intended to achieve consistency in the Agency's regulatory approach and establish inspection and enforcement procedures. It must be guidance documents are not regulations or laws and as a result are not enforceable either through administrative actions or through the courts.

The guidelines to assist in preparing ANDAs include:

1. Format and content for:

a. Application summary

b. chemistry, manufacturing and control section.

c. Nonclinical pharmacology and toxicology section.

d. Human pharmacokinetics and bioavailability section.

e. clinical and statistical section

f. Microbiology section.

2. Guideline for post marketing reporting of adverse reactions.

3. Guideline for the submission in microfiche of the archival copy of an application.

4. Guideline for submitting supporting documentation for the manufacture of drug substance.

5. Guideline for submitting supporting docu-

mentation for the manufacture of finished dosage forms.

6. Guideline for submitting supportive analytical data for methods validation in new drug applications.

7. Guideline for submitting supporting documentation for stability studies of human beings and biologics.

8. Guideline for packaging.

II. ANDA check list:

The ANDA check list provides the applicant with an itemization of all the necessary components for an ANDA submission.

III. Additional comments Regarding the ANDA:

Each component and section of the checklist

should be carefully reviewed for content and completeness. Every precaution must be taken so that the applicant does not receive a letter of Refusal to Receive that clarifies the CDER's decision to refuse to receive an incomplete application. The specific copies i.e, archival, reviews, and field to be submitted in the ANDA, outlined in the beginning of the checklist, should follow the NDA format as stated below:

a. Archival copy:

- Cover letter
- Application form
- ANDA Suitability statement
- Chemistry, manufacturing and controls
- Human pharmacokinetics and bioavailability
- Samples and labeling section
- Other information

b. Review copy:

Each of the technical sections in the review copy of the ANDA must be separately bound in its own particular color folder, and a copy of the application form must also be included. Although an integrated summary is not required, a summary that would help in reviewing chemist may expedite the ANDA approval.

C. Field copy:

A field copy certification with an original signature of the chemistry, manufacturing and control with a copy of application form and any reference to Drug Master Files should be clearly explained.

Summary:

ANDAs are specifically designed to help

the manufacturers of generics to provide these products rapidly to the consumer at lower cost than those of brand names.

ANDA (Abbreviated new drug application)

- ANDA is an application for a U.S. generic drug approval for an existing licenced medication or approved drug.
- ANDA is submitted to FDA's center for drug evaluation and Research office of generic drugs (OGD), which provides review and ultimate approval of generic drug product.
- Once approved, an applicant may manufacture and market the generic drug product to -- provide safe, effective and low cost alternative to the American public.
- 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 and

generic are listed in FDA's approved drug products ē therapeutic equivalence eval... (orange book).

- Generic drug applications are termed as abbreviated because they are generally not required to include preclinical (animal and in vitro) and clinical (human) trial data to establish safety and effectiveness.
- Scientific demonstration of bioequivalence-- is important and must insted, generic applicant must scientifically demonstrate that their product is bioequivalent (performs in same manner as innovator drug).
- One way scientistis demonstrate bioequivalence is to measue time it takes the generic drug to reach the blood stream in 24-36 healthy volunteers.
- This gives them the rate of absorption or bioavailability of generic drug, which they can them compare to that of the innovator drug.

#Necessary items of ANDA:

- → Composition of drug:
  - → name
  - → Amount of each ingredient < active / inactive

- Identify place of drug { manufactured / Processed / Packaged / labeled }

  name of supplier

- Identify any person other than applicant who performs a part of operation
- Certifications from applicant and method used in { Process / facilites / Controls → use in { mfg / Processing / Packaging / labeling }

- Assure that dosage form and comply ~ specifications and tests ~ official compendi

component

- if drug differ from compendium drug, the specification and tests applied to drug and its components are adequate to assure their identify, strength, quality, quantity.

- Outline { method used
  facility
  control used } for < mfg, Processing, packaging

- if drug require a long ANDA
  require adequate data to assure bioavailability

□ Goals of ANDA:

↓ price of drug
↓ time of development
↑ bioavailability of drug (compare to reference list drug)

□ WAXMAN-HATCH ACT:

- Using the bioequivalence as the basis for approving generic copies of products was

established by drug price and patent term restoration act" of 1984 is known as Waxman-hatch act.

- This act expedites the "availability" of less costly generic drugs by permitting FDA to approve application to market generic versions of brand names without conducting costly clinical trials.

- Also it provides mechanism to grant drug companies upto 5years additional parent --- protection to compensate patent life lost as a result of time consumed during test required by FDA.

□ Condition to ask an extension:

- Patent must not have expired at time of filling the request for extension.

- Product must have been subjected to examination by FDA.

- Request for extension must have been filled

at least during the last three months of life of patent.

- A fee of 750 $ is paid.

#ANDA requirements:

1- labeling

2- Pharm/tox

3- Chemistry
   Manufacturing
   controls

4- Microbiology

5- Inspection

6- Testing

7- bioequivalence

1- Labeling:

- Same information as brand name labeling
- May differ in excipients and description (color- shapes).

2- Pharm/tox:

- All inactive ingredients must be approved in either reference list or similar NDA in same or higher levels.

3. Chemistry, manufacturing and controls:

- Component and composition
- Mfg and controls
- Batch formulation and records
- Description of facilities
- Packaging
- Stability

4. Microbiology:

- for antiinfective drug
- A complete description of biochemical basis of drug action on microbial physiology.
- Clinical microbiology laboratory methods
- Assure the sterility of products especially c injectables.

□ Inspection / testing:

- Assure mfg facilites are incompliance c̄ current GMP's.
- Assure bioequivalence. sites are in compliance c̄ GCP's.

□ Bioequivalence:

A generic drug is considered to be bioequivalent to brand name if rate and extent of absorption not show a significant difference from listed drug.

- ICH-GCP is an International Conference on Harmonization Good Clinical Practice.
- The guideline was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and the World Heath Organization.
- The birth of ICH (International Conference on Harmonization) took place at a meeting in April 1990, hosted by the European Federation of Pharmaceuticals Industries and Association (EFPIA) in Brussels.
- The ICH screening Committee which was established at the meeting has since met at least twice in a year, with the location rotating between the three regions.

- Sponsors and regions of ICH-GCP:

.EMEA: The European Medicines Agency

.EFPIA: European Federation of Pharmaceutical Industries Association.

PhRMA: Pharmaceutical Research and Manufactures of America

- JMHW: Japanese Ministry of Health Welfare
- JPMA: Japanese Pharmaceutical Manufacture Association

□ Members of ICH:

- All the Sponsors are members of ICH. Additional members include observers from WHO, European Free Trade Association (EFTA), Canada and Switzerland.
- European commission: represents 25 members of the EU. The commission has set up the European medicines agency (EMEA) and the committee for medicinal products for human use (CHMP) of the EMEA provides the technical and scientific support for all the ICH activities. EMEA is situated in London.
- EFPIA: situated in Brussels and comprises 25 national pharmaceutical industry associations, including 6 associations with liaison status;

and 43 leading pharmaceutical companies involved in research, development and manufacturing of medicinal products in Europe, for human use.

- JMHW: All technical support and scientific support for ICH related activities are provided by the pharmaceuticals and medical device agency, national institute of health sciences and other expert academic bodies.

- JPMA: Consist of 90 major research based pharmaceutical manufacturers in Japan.

- USFDA: largest regulatory agency in the world, is responsible for the approval of all drug products used in US. Two centres namely, Centre for Research and the Centre for Biologics evaluation and research give technical advice for ICH work.

PhRMA: 67 member companies and 24 research affiliates involved in the discovery, development

and manufacture of prescription medicines.

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

□Objectives:

- To provide a unified standard for the European Union (EU), Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

• To identify and then to reduce differences in technical requirements for drug development among regulatory agencies.

AIMS:-

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

Principles of Guidelines:-

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

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

4. The available non-clinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

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

6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/Independent ethics committee

(IEC) approval/favorable opinion.

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.

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

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

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

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).

12. Investigational products should be manufactured, handled, and stored in accordance with the applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

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

□ The ICH topics are basically divided into four broad and major Categories:-

• Quality: relating to chemical and pharmaceutical quality assurance. These comprise of Q1-stability testing, Q3-impurity testing, Q5-quality of biotechnol-

ogical products and Q7- good manufacturing practices.

- Safety: topics related to invivo and in vitro preclinical Studies for eg, S1- carcinogenicity studies, S2- genotoxicity Studies, S5- reproductive toxicology S7- pharmacology studies.

- Efficacy- topics related to clinical studies in human subjects for eg, E4- dose response studies, and E7 clinical trials.

- Multidisciplinary: those that do not fit into one of the above. M1- medical terminology, M2- electronic standards for transmission of regulatory information (ESTRI), M3- timing of preclinical studies in relation to clinical trials, and M4- the common technical document.

Declaration of Helsinki

The Declaration of Helsinki is a statement of ethical Principles developed by the World Medical Association to "Provide guidance to physicians and other participants in medical research involving human subjects" (Para 1, Declaration of Helsinki)

- This includes research on people, identifiable human material or identifiable data.
- The Declaration was first adopted in 1964 and has since undergone several revisions (1975, --- 1983, 1989, 1996, 2000 and in 2008) to accommodate advances in medical science and ethical problems.

The Declaration includes principles on:

- Safeguarding research subjects
- Informed consent
- Minimising risk
- Adhering to an approved research plan/protocol

The Declaration is considered a fundamental document in the ethics of healthcare research.

As a result, the principles have been embodied in subsequent UK and International guidance and regulations.

CDSCO in clinical trials:

Central drug Standard control organization guidelines in clinical trials:

1- Application for permission

2. Clinical trial.

3. Studies in special population

Guidelines of CDSCO:

I. Application for permission:

1. Chemical and Pharmaceutical information as prescribed in item 2 of Appendix I.

2. Animal pharmacology Data as prescribed in item 3 of Appendix I and Appendix IV.

3. Animal toxicology data as prescribed in item 4 of Appendix I and Appendix III.

4. Human clinical pharmacology data as prescribed in item 5, 6 and 7 of Appendix I and as

Stated below:

- Regulatory Status in other countries as prescribed in item 9.2 of Appendix I, including information in respect of restrictions imposed, if any, on the use of the drug in other countries.
- The full prescribing information should be submitted as part of the new drug application for marketing as prescribed in item 10 of Appendix I. The prescribing information (package insert) shall comprise the following sections: generic name, composition, dosage form(s), indications, dose and method of administration; use in special populations (such as pregnant women, lactating women, pediatric patients, geriatric patients etc.); contraindications; warning; precautions; drug interaction; undesirable effects; overdose; pharmacodynamic and pharmacokinetic properties.

II- Clinical Trial:

1. Approval for clinical trial:

- 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(s).
- All trial investigator(s) should possess appropriate qualifications, training and experience and should have access to such investigational and treatment facilities as are relevant to the proposed trial protocol.
- Protocol amendments if become necessary before initiation or during the course of a clinical trial, all such amendments should be notified to the Licensing Authority in writing along with the approval by the ethics committee, which has granted the approval for the study.

2. Responsibilities of Sponsor:

- The clinical trial sponsor is responsible for implementing and maintaining quality assurance systems to ensure that the clinical trial is

conducted and data generated, documented and reported in compliance with the protocol and Good Clinical Practice (GCP) Guidelines.

- Sponsors are required to submit a status report on the clinical trial to the Licensing Authority at the prescribed periodicity.

3. Responsibilities of the Investigator:

- The investigator is responsible for the conduct of the trial according to the protocol and the GCP guidelines.
- Standard operating procedures are required to be documented by the investigators for the tasks performed by them.

4. Informed Consent.

- In all trials, a freely given, informed, written consent is required to be obtained from each study subject. The investigator must provide information about the study verbally as well as

using a patient information sheet, in a language that is non-technical and understandable by the study subject.

- Where a subject is not able to give informed consent (e.g. an unconscious person or a minor or those suffering from severe mental illness or disability the same may be obtained from a legally acceptable representative.

5. Responsibilities of the Ethics committee:

- It is the responsibility of the ethics committee that reviews and accords its approval to a trial protocol to safeguard (حفظ، حماية) the rights, safety and well being of all trial subjects.

6. Human pharmacology (Phase I):

- The objective of studies in this Phase is the estimation of safety and tolerability with the initial administration of an investigational new drug into humans(1). Studies in this Phase of

development usually have non-therapeutic objectives and may be conducted in healthy volunteers subjects or certain types of patients.

- Studies conducted in Phase I, usually intended to involve one or a combination of the following objectives:
  - Maximum tolerated dose
  - Pharmacokinetics
  - Pharmacodynamics

7. Therapeutic Exploratory Trials (Phase II):

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

8. Therapeutic confirmatory trials (Phase III):

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

9. Post Marketing Trials (Phase IV):

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

III. Studies in special populations:

1. Geriatrics:

- Geriatric patients should be included in Phase

III clinical trials (and in Phase II trials, at the Sponsor's option) in meaningful numbers, if:
→ The disease intended to be treated is characteristically a disease of aging or;
→ when the new drug is likely to alter the geriatric patient's response (with regard to safety or efficacy) compared with that of the non-geriatric patient.

2. Pediatrics

The timing of pediatric studies in the new drug development program will depend on the medicinal product, the type of disease being treated, safety considerations, and the efficacy and safety of available treatments.
- If the new drug is intended to treat serious or life-threatening disease, occuring in both adults and pediatric patients, for which there are currently no or limited therapeutic options, pediatric population should be included in

the clinical trials.

3. Pregnant or Nursing Women:

Pregnant or nursing women should be included in clinical trials only when the drug is intended for use by pregnant/nursing women or fetuses/nursing infants and where the data generated from women who are not pregnant or nursing is not suitable.

□ The Central Drugs Standard Control Organisation is the national regulatory body for Indian pharmaceuticals and medical devices, and serves parallel function to the European Medicines Agency of the European Union, the PMDA of Japan and the FDA of united States.

Challenges in implementation of guidelines

□ Challenges are of two types:

1. Technical Barriers for implementation of ICH-GCP regulations
2. Political Barriers for implementation of ICH-GCP regulation

1. Technical challenges:

• Four major categories of players can be identified in the ICH-GCP area:

i- The health authorities
ii- The academic institution
iii- The clinical investigators
iv the pharmaceutical industry

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

• Some of these common barriers are personnel's

knowledge, facility, equipment and finances.

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

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

2. Political challenges:

i-lack of or insufficient legislative/regulatory framework

ii-The most frequent areas of noncompliance

include: ethics committee, institutional review board (IRBs, composition and practices), informed consent issued (content, process, signature and dating), investigator dedication of authority (unreliable, excessive dedication), clinical monitoring (non existing adequate reporting of ADR, infrequent and/or inefficient).

◦General Ethical Principles:

- All research involving human subjects should be conducted in accordance with three basic ethical principles, namely respect for persons, beneficience and justice in varing circumstances that may be expressed differently and given different moral weight, and their application may lead to different decisions or courses of action. The present guidelines are directed at the application of these principles to research involving human subjects.

◦Respect for the persons incorporated at least two fundamental ethical considerations namely:

a- Respect for autonomy, which requires that, those who are capable of deliberation about their personal choices.

b- Protection of persons with impaired or diminished autonomy

◦Beneficence refers to the ethical obligation to

maximize benefits and minimize harms. Beneficence further prescribes the deliberate infliction of harm on person; non-malfeasance (Do not harm)

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

- The principle refers primarily to distributive justice, requires the equitable distribution of both the burdens and the benefits of participation in research.

The Guidelines:

Guideline 1: Ethical justification and scientific validity of biomedical research:
Ethical justification and scientific validity of biomedical research

Involving human being is the prospect of discovering new ways of benefiting people's health.

Such research can be ethically justifiable only if it carried out in ways that respect, protects and are fair to the subjects of that research and are morally acceptable within the communities in which the research is carried out.

Moreover, because scientifically invalid research is unethical in that it exposes research subject to risks without possible benefits.

Guideline 2: Ethical review committees

All proposals to conduct research involving human subjects must be submitted for review of their scientific merit and ethical acceptability to one or more scientific review and ethical review committees.

- The review committees must be independent of the research team and any direct financial or other benefit they may derive from the

research should not be contingent on the outcome of their review.

- The investigator must obtain their approval or clearance before undertaking the research. The ethical review committee should conduct further reviews as necessary in the course of research.

- Guideline 3: Ethical review of externally sponsored research:

- An external sponsoring organization and individual investigators should submit the research protocol for ethical and scientific review in the country of sponsoring organization.

And the ethical standards applied should be on less stringent that they would be, for research carried out in that country.

- As well as a national or local review committee, should ensure that proposed research is responsive to the health needs and priorities of the

host country and meets the requisite ethical standards.

Guideline 4: Individual informed consent

For all biomedical research involving humans the investigator must obtain the voluntary informed consent of the prospective subject or in the case of an individual who is not capable of giving informed consent, the permission of legally authorized representative in accordance with applicable law.

Waiver of informed consent is being regarded as uncommon and exceptional and must in all cases be approved by ethical review committee.

Guideline 5: obtaining informed consent

Essential information for prospective research subject before requesting an individual's consent to participate in research.

The investigator must provide the information, in language or another form of communication

that the individual can understand.

Guideline 6: Obtaining informed consent: Obligation of sponsors and investigators:

Sponsors and investigators have a duty to refrain (خودداری کردن) from unjustified deception, undue influence or intimidation.

Seek consent only after ascertaining that the prospective subject has adequate understanding of the relevant facts and of the consequences of the participation and has sufficient opportunity to consider whether to participate.

- Investigators should justify any exceptions to this general rules and obtain the approval of ethical review committee.

Renew the informed consent of each subject if there are significant changes in the conditions or procedures of research or if new information becomes available that could affect the willingness of subject to continue to participate.

Renew the new informed consent of each subject in long-term studies at pre-determined intervals, even if there are no changes in the design or objective of research.

Guideline 7: Inducement to participate

Subjects may be reimbursed for lost earning, travel costs and other expenses incurred in taking part in the study; they may also receive free medical services.

Subjects, particularly those who receive no direct benefit from research may also be paid or otherwise compensated for inconvenience and time spent.

The payment should not be so large, however or the medical services so extensive as to induce subjects to consent to participate in the research.

All payments, reimbursement and services provided to research subject must have been

approved by an ethical review committee.

Guideline 8: benefits and risks of study participation (2m)

For all biomedical research involving human subjects, the investigator must ensure that potential benefits and risks are reasonably balanced and risks are minimized.

Interventions or procedures of direct diagnostic, therapeutic or preventive benefit for individual subject must be justified by the expectation that they will be at least as advantageous to individual subject.

Guideline 9: Special limitation on risk when research involves individuals who are not capable of giving informed consent:

Research with individual who are incapable of giving informed consent, the risk from research interventions that do not hold up direct benefit for the individual subject should be

not greater than the risk attached to routine medical or psychological examination of such person.

Guideline 10: Research in populations and communities with limited resources:

Before undertaking research in a population or community with limited resources the sponsor and the investigator must make every effort to ensure that the research is responsive to health needs and the priorities of the community in which it is to be carried out; and any intervention or product developed on knowledge generated, will be made, reasonably available for the benefit of that population or community.

Guideline 11: Choice of control in clinical trials

As a general rule, research subjects in this control group of a trial of diagnostic, therapeu-

tic or preventive intervention should receive an established effective intervention.

- In some circumstances it may be ethically acceptable to use an alternative comparator such a placebo or no treatment.

Placebo may be used when:

There is no established effective intervention or when withholding a established effective intervention would expose subjects to at most, temporary discomfort or delay in relief of symptoms.

Guideline 12: Equitable distribution of burdens and benefits in the selection of group of subjects in research:

Group or communities to be invited to be subjects of research should be selected in such a way that the burdens, and benefits of the research will be equitably distributed. The exclusion of groups or communities that

might benefit from study participation must be justified.

Guideline 13: research involving vulnerable persons.

Special justification is required for inviting vulnerable individuals to serve as research subjects and if they are selected, the means of protecting their rights and welfare must be strictly applied.

Guideline 14: research involving children

Before undertaking research involving children, the investigator must be ensuring that:

i- research might not equally well be carried out with adults.

ii- The purpose of research is to obtain knowledge relevant to health needs of children.

iii- Parent oralegal representative of each child has given permission

iv. The agreement of each child has been obtained to

the extent of the child capabilities.

V. A child's refusal to participate or continue in the research will be respected.

Guideline 15: research involving individuals who by reason of mental or behavioural disorders are not capable of giving adequate informed consent:

The investigator must ensure that:

i. Such a person will not be subjects of research that might equally well be carried out on persons who is giving adequately informed consent.

ii - The purpose of the research is to obtain knowledge relevant to health needs of persons with mental or behavioural disorders.

iii - The consent of each subject has been obtained to the extent of person's capabilities.

iv. Prospective Subject's refusal of participate in research always respected, unless in exceptional circumstances, there is no reasonable medical alternatives.

- In cases where the subject is incapable of giving informed consent the latter must be given from the family member or legally authorized representative in accordance with applicable law.

Guideline 16: Women as research subjects

Investigators, sponsors or ethical review committees should not exclude women of reproductive age from biomedical research.

The potential for becoming pregnant during study should not be used as reason for limiting participation.

The sponsors or investigators should guarantee the prospective subject a pregnancy test and access to effective contraceptive methods before the research commences.

Where such an access is not possible for legal or religious reasons investigators should not recruit.

Guideline 17: Pregnant women as research participant

Pregnant women should be presumed to eligible for participation in biomedical research.

Investigators and ethical review committees should ensure that prospective subjects who are pregnant are adequately informed about the risk and benefits to themselves, their pregnancy, the foetus and their subsequent offspring, and to their fertility.

Research in this population should be performed only if it is relevant to particular health needs of a pregnant woman or her foetus. And if it is supported by reliable evidence from animal experiments, particularly as to risks of teratogenicity and mutagenicity.

Guideline 18: Safeguarding confidentiality

The investigators must establish secure safeguards of confidentiality of subject's research data. Subjects should be told the limits, legal or other to the investigator's ability to safeguard.

Guideline 19: right of injured subjects to treatment and compensation

Investigators should ensure that research subjects who suffer injury as a result of their participation are entitled to free medical treatment for such injury and to such financial or other assistance as would compensate them equitably for any resultant impairment, disability and handicap.

- In case of death as a result of their participation their dependants are entitled to compensation. Subjects must not be asking to waive the right to compensation

Guideline 20: Strengthening the capacity for

ethical and scientific review and biomedical research:

Many countries lack the capacity to asses or ensure the scientific quality or ethical acceptability of biomedical research carried out in their jurisdiction.

- In externally sponsored collaborative research, sponsors and investigators have an ethical obligation to ensure that biomedical research projects for which they are responsible in each countries contribute effectively to national or local capacity to design and conduct biomedical research and to provide scientific and ethical review and monitoring of such research.

Guideline 21: ethical obligation of external sponsors to provide health-care services:

External sponsors are ethically obligated to ensure the availability of:

Health care services that are essential to

the safe conduct of the research; treatment for subjects who suffering injury as a consequence of research interventions; and beneficial intervention or product developed as a result of the research reasonably available to the population or community concerned).

Composition, Responsibilities, Procedures of IRB/IEC

Definition:

- An institutional review board (IRB), also known as an independent ethics committee (IEC) or ethical review board (ERB), is a committee that has been formally designated to approve, monitor, and review biomedical and behavioral research involving humans with the aim to protect the rights and welfare of the research subjects.

Composition, functions and operations:

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

→ An IRB/IEC may invite non-members with expertise in special areas for assistance.

o Responsibilities:

- An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects.

o 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), available safety

information, information about payments, and compensation available to subjects, the investigator's current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the IRB/IEC may need to fulfil 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 / Favourable opinion
- Modifications required prior to its approval/favourable opinion
- Disapproval / Negative opinion
- Termination / Suspension of any prior approval/favourable opinion
- 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.

When a non-therapeutic trial is to be carried out with the consent of the subject's 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.

- 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 subjects 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/favourable opinion of an appropriate amendment.

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

i- Deviations from, or changes of, the protocol to eliminate immediate hazards to the trial subjects

ii- Changes increasing the risk to subjects and/or

affecting significantly the conduct of the trial.
iii. All adverse drug reactions (ADRs) that are both serious and unexpected.
iv. 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:
i- Its trial-related decisions/opinions
ii- The reasons for its decisions/opinions
iii- 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.

Clinical research regulation in USA-food and drug administration:

The US food and drug administration is a scientific, regulatory and public health agency. It is responsible for most food products, human and animal drugs, therapeutic agents and biological origin, medical devices, radiation emitting products for consume, medical and occupational use, cosmetics and animal feed.

The current staffs approximately 9100 employees are composed of chemist, pharmacist, physician, microbiologists, veterinarians, pharmacologist and laboratories. Agency scientists evaluate applications for new human drugs and biologics, complex medical devices, food and colour additives, infant's formula and animal drugs.

. The FDA monitors the manufacture, import, transport, storage and sale of about $1 trillion worth of products annually.

The FDA visits more than 16000 facilities a year

including manufacturing plants and clinical study sites.

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

- The first GXP REGULATIONS (GXP is a general team for good practice quality guidelines and regulations.

GXP encompasses good manufacturing practice (GMP), good laboratory practice (GLP) and good clinical practice (GCP).

We will focus on GCP, since that is the most applicable clinical trials

- In the past, the GCP regulations varied significantly from country to country, but after international conference on harmonization issued guidelines, the differences have largely been resolved.

- Although united States, European union, Japan are the members of ICH, the most countries

have now adapted the output from conference.

• Specify: تعیین کردن

GCP specifies how a clinical trial is performed.

The purpose of GCP is to:

• Protect patient safety and rights

• Ensure data integrity

• Specifically, GCP is meant to prevent careless errors, violations, fraud, and ethical issues.

GCP are required and important Because of the following:

→ Clinical trials usually involve exposing patients to risk, by administering drugs of unknown efficacy and safety.

→ The risk can be very severe and include death

→ Decision (such as approval decisions) will be made on the basis of data from clinical trials there will affect health and safety of future patients who will receive the drug.

□ Where to find GCP Regulations:

GCP can be found in several places:
The main sources are ICH guidelines that have been published.
The ICH guidelines are adapted in to law or regulations by individual countries. by their law making bodies.

•In the United states they are found in:
21 CFR (Code of federal regulations) part 11: electronic records/electronic signatures
21 CRF part 50: protection of human subjects ---
21 CRF part 54: financial disclosures by investigators
21 CRF part 56: institutional review boards
21 CRF part 312: investigational new drug applications
21 CRF part 314: Application for FDA approval to market a new drug.

Other Regulation:
Health insurance portability and Accountability (مسؤولية) Act Guidelines:
In addition to GCP, there are many regulations for

example; there are strict privacy laws in many countries. In the United State they are HIPAA regulations. -These were passed in 1996 and have very stringent requirements and penalties including criminal penalties HIPAA apply to covered entities which are health care providers health plan, health care clearinghouses. -A pharmaceutical company typically is not covered entirely. However, it can become a hybrid or a covered entity by doing certain things, such as, for example, collecting information from patients in an outreach or patient support programs.

Protected Health Information (PHI):

- Created or received by Health care provider, health plan, health care clearinghouses or employer
- Relates to physical or mental health or conditions provision of health care or payment of provision of health care.
- Identifies could be reasonably used to identify individuals.

- Includes demographics: data collected from an individual.

HIPAA applies to person for 2 years after death as well.

The penalties for negligent disclosures are $100 $25000/person/year. For wrongful disclosures, the fine can be up to $250,000 and 1-10 years in Rison.

- For clinical research, HIPAA disclosures are required from the covered entity (e.g the investigator) to --- Sponsor.

European Union Clinical Trial Directive

- The EU directive was first published by the EMEA (European Medicine Agency) in 2001.
- The purpose was to harmonize the initiation and conduct of clinical trials in European Union. Among other thing it was also designed to:
  - Protect patients, especially incapacitated and minors patients;
  - Standardize applications for starting trials;
  - Standardize EC process
  - Standardize pharmacoviligance data handling
  - Allow information exchange between European Union countries;
  - Mandate GCP inspection

The European medicine agency (EMEA) is a European agency for the evaluation of medicinal product. Until 2004, the European Medicines Agency was known as the European agency for the evaluation of medicinal products.

Roughly parallel to the U.S. FDA, but without

FDA-style centralization: the EMEA was set up in 1995 with funding from the European Union and the pharmaceutical industries, as well as indirect subside from member. State, in an attempt to harmonize the work of existing national medicine regulatory bodies.

The scientific opinions of the agency are prepared by three committees responsible for medicines for human use:

- Committee for Medicinal Product for Human use (CMPH)
- Committee for Medicinal Product for Veterinary use (CMPV)
- Committee for Orphan Medicinal products (COMP)
- Committee on Herbal Medicinal product (HMPC)

Committee for Medicinal product for Human use (CMPH):

- A chairman
- One member nominated by each of the 25 EU

member state.

- One member nominated by each of the EEA-EFTA State Iceland and Norway.
- Up to five co-opted members, chosen among experts nominated by member states or the EMEA the recruited, when necessary, to gain additional expertise in particular scientific area.
- CHMP members and alternates are nominated by member state in consultation with the EMEA Management Board.

Responsibilities:

The CHMP plays a vital role in the marketing procedures for medicines in European Union.

Conducting the initial assessment of medicinal product for which a community-wide marketing authorization is sought.

- The CHMP is also responsible for several post authorization and maintenance activities.
- Assessment of any medication or extension to

existing marketing authorization.

- In the mutual-recognition and decentralized procedures, the CHMP arbitrates in cases where there is a disagreement b/w member states concerning the marketing authorization of a particular medicinal product.
- The CHMP also acts in referral cases, initiated when there are concerns relating to the protection of public health.

Other important activities of the CHMP and its working parties include:

- The provision of assistance to companies researching and developing new medicines
- The preparation of scientific and regulatory guidelines for pharmaceutical industries
- Co-operation with international partners on harmonization of regulatory requirements for medicines.

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

The directive does not automatically become effective across European Union. Each country must implement it by passing laws enacting them.

They can add more detail during the implementation.

• Now, there are five detailed guidance documents associated with directives:

1. European clinical trial database (EudraCT) ---
2. The request for authorization of clinical trial on medicinal products for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial
3. The application, format and documentation to be submitted in an application for an EC opinion.
4. The European database of SUSARS (Eudravigilance)
5. The collection, verification, and presentation of adverse reaction reports.

EudraCT

European regulatory authorities need a database in order to provide each of them with an overview of clinical trials being conducted in the community. This database is needed to facilitate communication on these clinical trials b/w the authorities, to enable each to undertake better the oversight of clinical trial and investigational medicinal product development, and to provide the enhanced protection of clinical trial subjects and patients-- receiving investigational medicinal products.

EudraCT Number

The unique EudraCT number for clinical trial has the format

YYYY-NNNNNN-CC

YYYY- is the year in which the number is issued

NNNNNN- is a six sequential number

CC- is check digit

The directive requires that for a clinical trial application, the following must be submitted to a competent authority:

- Application form with the Eudract number
- Protocol
- Investigator's brochure(IB)
- Investigational Medicinal product number
- Country Specific Information.

Regulatory Authorities In India

- Clinical trials in India are regulated by schedule Y of the drug and cosmetics rules.
- The rules are enforced by the office of the DCGI (Drug control general of India) who is also responsible for monitoring all clinical trials submitted to that office for approval.
- Today India is considered as the most favored destination for conduct of the clinical trials, sponsored by both international and Indian companies. Apart from the unique criteria possessed by India to attract global players, the main criteria which given the advantage to India, is the momentum at which ICMR and DCGI has adopted themselves to the Global Regulatory Guidelines. All this scope and improvement has been well recognized and appreciated considering the fact that India's involvement in Global GCP is only a decade old.

List of regulatory bodies in India

DCGI	Drugs Control General of India
ICMR	Indian Council of Medical Research
GEAC	Genetic Engineering Approval Committee
DBT	Department of Biotechnology
AERB	Atomic Energy Review Board
DTAB	Drug Technical Advisory Board
DGFT	Director General of Foreign Trade

Drug Control General of India (DCGI)

DCGI is a regulatory apex body under government of India, which oversees all clinical trial undergoing in India. This agency reviews the clinical study protocol and associated relevant documents. It is mandatory to obtain its approval before starting trials on human in India.

It is governed by rules in amended schedule Y in addition to the experts at DCGI's office. They also avail the external experts and other government agencies like ICMR, GEAC, DBT, AERB, DTAB and DGFT.

DCGI heads the Central Drug Standard Control Organization (CDSCO) and discharge the functions attached to the central government.

The DCGI also has the responsibility of laying down regulatory measures and amendment of Act and rules, laying standards for drugs, cosmetics, diagnostics, devices and updating the Indian pharmacopeia.

Indian Council of Medicinal Research (ICMR)

The Indian council of medical research, New Delhi, the apex body in India for the formulation, co-ordination and promotion of biomedical research, is one of the oldest medical research bodies in the world.

The council promotes biomedical research in the country through intramural as well as extramural research.

Intramural research is carried out currently through the council's 21 permanent research institutes/centers which are mission-oriented national institutes located in different parts of India.

Genetic engineering approval committee (GEAC)

The GEAD consists of experts in the field of genetic engineering and molecular biology, experts drawn from Indian council of agricultural research, (ICAR, ICMR, Drug controller of India, Department of Atomic energy Ministry of science and technology. Ministry of central pollution control Board.)

Clinical trials involving use of genetic engineered

products would be referred by DCGI to GEAC for recommendations. Based on recommendations received DCGI provides approval for conduct of clinical trials involving genetically engineered products.

Department of Biotechnology (DBT)

Department of Biotechnology set up under the ministry of science and technology in 1986, gave a impetus to the development of field of modern biology and biotechnology in India.

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

Atomic Energy Review Board (AERB)

The regulatory authority of AERB derived from

the rules and notification promulgated under the Atomic Energy Act and Environmental Act, 1986. The mission of the board is to ensure that use of ionizing radiation and nuclear energy in India does not cause undue risk to health and environment. Currently, the Board consists of full time Chairman, an ex-office member and secretary.

□ Drug Technical Advisory Board (DTAB)

The Drug Technical Advisory Board, is a highest technical body under the drug and cosmetic Act, has endorsed the adoption of GCP guidelines for clinical trial in India.

□ Director General of Foreign Trade (DGFT)

DGFT overseas import and export of all biological samples from/to overseas countries. This apex body is responsible for issuance of import and export license.

• Parallel submission can be made to DCGI and

DGFT on obtaining approval from DCGI to conduct the trial, DGFT gives permission to import drugs there by reducing the timelines for study start up.

Sponsor:

An individual, company, institution or organization which takes responsibility for the initiation, management and/or financing of a clinical trial.

Responsibilities:

1. Quality Assurance and Quality control
2. Contract Research Organization (CRO)
3. Medical Expertise
4. Trial design
5. Trial management, data handling and record keeping
6. Investigator selection
7. Allocation of Responsibilities
8. Compensation to subjects and investigators
9. Financing
10. Notification/Submission to Regulatory Authority
11. Confirmation of review by IRB/IEC
12. Information on investigational products
13. Manufacturing, packaging, labeling and coding investigational product(s)

14. Supplying and Handling investigational Product(s)
15. Record Access

1- 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 requirement(s).

2. 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.

3. Medical Expertise:

برگزیدن، معین کردن

- The Sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial related medical questions or problems.

4. 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.

5. 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.

6. Investigator selection:

- The sponsor is responsible for selecting the investigator(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.

7. Allocation of responsibilities:

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

8. Compensation to subjects and investigators:

- If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should identify (legal and financial coverage) the investigator the institution against

claims arising from the trial, except for claims that arise from malpractice and/or negligence.

9. Financing:

- The financial aspects of the trial should be documented in an agreement b/w the sponsor and the investigator.

10. Notification / Submission to regulatory Authority:

- 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).

11. Information on investigational Product(s)

- When planning trials, the sponsor should ensure that sufficient safety and efficacy data from

nonclinical studies and/or clinical trials are available to support human exposure by the route at the dosage for the duration and in the trial population to be studied.

12. Manufacturing, Packaging, labeling 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 labeled in a manner that protects the blinding, if applicable.
- In addition, the labeling should comply with applicable regulatory requirement(s).

13. Supplying and Handling investigational Product(s)

- The sponsor is responsible for supplying the investigator(s) with the investigational product(s).

□ Investigator:

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

- Sponsor-investigator:

An individual who both initiates and conducts alone or with others a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject.

- Sub investigator:

Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g. associates, residents, research fellows).

□ Investigators' Responsibilities:

1. investigators Qualifications

2. Adequacy of Resources
3. Medical care of study participants
4. Communication with the IRB/IEC
5. Compliance with the Protocol
6. Investigational Product care
7. Randomization and unblinding proceed (2M)
8. The informed consent
9. Records and Reports
10. Progress reports
11. Safety reporting
12. Stopping or suspending a study
13. Final report

1. Investigators Qualifications:

- Properly qualified to assume the responsibilities for conduct of the study.
- Very familiar with the drug under investigation
- Will comply with regulations and be prepared for audits and monitoring
- Has available detailed list of all to whom responsibility is delegated.

2. Adequacy of resources:

- Can recruit SP in sufficient numbers and on time
- There is enough time to complete the study
- There are enough qualified staff and adequate facilities to complete the study.
- The staff are well informed about the Test Agent and the Protocol.

3. Medical Care of Study SP Participants:

- All medical decisions are made by qualified physicians
- All medical acts are performed by qualified physicians.
- The investigator is responsible for care of SP when there are "Adverse Events"
- The primary physician of the SP is notified regarding the participation of their patient on the study.
- The Study Physician knows when and why a Study Participant leaves a study accounting for all SP.

4. Communication with the IRB/IEC:

- Written approval is obtained before the study begins

- informed consent is in the language of the SP
- The IRB has a current investigators Brochure
- The IRB has all documents when needed
- Protocol amendments are submitted on time
- The IRB/IEC gets an annual report of each study

5. Compliance with the Protocol:

- Has signed Protocol confirming agreement to comply with it to the letter
- Has not deviated from the Protocol without written agreement from the Sponsor and the IRB/IEC.
- Has documented each and every deviation (for subject safety reasons) from the protocol when it occurs.
- Implements deviations to avoid risk but immediately submits amendments to IRB, Sponsor and the FDA.

6. Investigational Product care:

- Accepts responsibility for the products, its usage and its

Storage according to the Protocol.

- Only a Pharmacist involved under PI's supervision
- Explains to SP, and uses test agent, properly only
- Detailed records of test agents use kept throughout the study
- Retained unused test agent and destroy only under the written instruction from the Sponsor

7. Randomization and unblinding procedure:

- The study randomization procedures (documented in the protocol) are followed exactly.
- The randomization code is only broken in accordance with the protocol
- If the study was blinded, any unblinding was documented and Sponsor notified in writing.

8. The informed consent

- Insure that the declaration of Helsinki and the principles of GCP are adhered to
- Insure that there is no coercion of subjects to

be on, or stay on, a study at any time

- Insure SP understanding of the information they are presented by you or your designees
- Insure that the informed consent is signed and dated by the SP or SP's legal representative.

9. Records and Reports:

- Data is ALCOA (accurate, legible (خوانا، روشن), contemporaneous (هم‌زمان), original and attributable (نسبت دادن)) and complete
- Data on the CRF's is consistent with (exactly the same as) that of the source documents (raw data)
- All changes to a CRF are dated and signed such that the original data is not obscured (مبهم کردن)
- Essential documents are retained (نگاه داشتن) at least 2 years after the last approval of the test agent for market.

10- Progress Reports:

- A written report is submitted to the IRB/IEC at least annually is required but
  - Low Risk - yearly is ok
  - Moderate Risk - twice a year
  - High Risk - monthly to quarterly as needed...

- A written report is submitted to the IRB/IEC if the PI notes any change that might significantly change the conduct of the trial.

11. Safety Reporting

- All SAE's are immediately reported to the Sponsor and followed up by a written report forthwith. = immediately
- Study Participants are not to be identified to anyone
- All AE's critical to the safety evaluation are reported to the Sponsor per protocol.
- The Sponsor and the IRB are given all details in the event of a death of a SP while on study.

12. Premature Stopping or Suspending a Study:

- All SP are informed if a study is terminated or even suspended.
- The institution, the Sponsor and the IRB are informed in writting if the PI terminates the study.
- The institution and the IRB are informed in

writting if the sponsor terminates the study
- The institution and the sponsor are informed in writting if the IRB terminates the study.

13. Final Report(s) by investigator:

- The Principal investigator is expected to file a written report at the conclusion (انتهاء/انتهاء) of a study.

Final Report:

- Upon completion of the study the investigator must notify the IRB and the sponsor.
- The final report should contain the introduction, description of the methods, results and discussion of the finding.

□ Definitions:

◦ Sponsor:

An individual, company, institution, or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial.

◦ Contract Research Organisation:

An individual or organisation which are contracted by the sponsor to conduct one or several of the sponsor's trial related duties and functions. The ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor (GCP).

□ Contract Research Services:

◦ Product development

◦ Clinical research management (pre-clinical-phase IV)

- Clinical, medical, security monitoring
- Toxicology
- laboratory services
- Data management
- Bio Statistics
- Consulting services associated with Goverment agencies
- licensing procedures
- Medicine management (production, packaging, labeling, storage, distribution, collection)
- Researchers and central services choice etc.

CRO choice:

- Clinical research, must be done basing on the written rules of: ICH-GCP, Declaration of Helsinki, GMP, GDP, local regulations and guidelines.

According to ICH-GCP related to the CRO;

5.2.1 The sponsor may transfer all or a portion of duties and functions associated with its own to the Contract Research Organizations. However, the ultimate responsibility of the quality and accuracy of research data always belongs to the sponsor. Contract Research Organization has to apply quality control and quality assurance system.

5.2.2 Any task or function transferred or taken over from the Contract Research Organizations has to be specified in writing.

5.2.3 The responsibility of any task or function specially not transferred or taken over from the Contract Research Organizations belongs to the sponsor.

. 5.2.4 Refers made to the sponsor in the user guide, to the extent of task or function transferred or taken over from the Contract Research Organizations also does include the Contract Research.

. The sponsor has to be sure of the quality of service received and having required experience and knowledge of the duties, that are transferred from SAK. For this reason, many sponsors have created criteria to work with CRO who have these competencies.

. Some of these criteria are:

→ experience from similar projects of the CRO
→ experience with similar sponsors of the CRO
→ For how much years the CRO is working in this area.

→ training and experience of staff with clinical research

→ Compliance and information with local regulations

→ Software used

- Making a contract with the CRO:

The sponsor after primarily determining needs of its own research has to make a contract with the CRO for the transfer of tasks related to these services.

This contract has also to contain:

legal issues such as contract work directive, the service time, time of payment, amount etc (obligations, insurance, termination, choice of law etc).

• CRO responsibilities:

• CRO training programs should be created for new joining organizations.

• If services should be taken from outside, assessment process should be available.

• CRO training programs should be created for service taken from people/organizations from outside.

• It should have appropriate personnel, infrastructure and facilities to meet the requirements of the project.

• It should have the necessary software to monitors and measure Project management and performance.

• It should be made sure that the insurance made by the sponsor is appropriate.

• The application file provided by the sponsor

should be careful reviewed and compliance must be ensured.

- It should be made sure that Medicines process is managed well (place and conditions of the place where drugs are being manufactured, in which conditions they are stored, how the distribution is made, shelf life, tags, etc).
- For Protocol or research brochure revision, process must be defined.
- If there is transfer of the task, it must be well documented.
- Routine quality control of the system must be created.

Contract: قرارداد، قرارداد بستن

Contract Research Organisation (CRO)

A person or an organisation contracted by sponsor to perform sponsor's trial related duties and functions.

- FDA definition: CRO is a person, an independent contractor (پیمانکار) of sponsor

-One or more obligations (وظایف) of sponsor such as:

→ design of Protocol
→ Selection of research site
→ Monitoring of investigators
→ Evaluation of study data
→ Preparation of materials to be filled ē FDA.

Services: Protocol development

-Site/investigator recruitment and selection
-Personal training
-Clinical trial management
-Quality assurance and site monitoring
-Data analysis
-medical writing
-Processing and preparing regulatory filling and liaison ē regulatory bodies

Contract Research Organization

#Responsibilites of CRO:

- CRO work in a team under direct supervision of principal investigators.

A- General Responsibilities:

a- Capacity building
b- training new CROs

a- Capacity building:

Work of CRO begins the day he joins employment whether or not sponsor has selected an investigator site for any particular trial.
They conduct an indep survey of new sites. to assess:

- Manpower presence or competence
- Support staff
- Infra structure
- Presence of functional ethics committee
- Compatible management
- Major disease - incidence + prevalence rate

b- Training new CROs:

Experienced CRO → train new CROs

training conducting
- Feasibility studies
- designing trial document
- Setting up of Sites
- Conduct of trial
- Trial close out

B- Trial-related Responsibilities: P_2PST

a- Site identification

b- Pre trial documentation

c- Financial Responsibilities

D- Training the Site Staff

E- Post trial activities

a- Site identification

. To identify right site for trial → Fulfil all criteria by protocol.

- CRC understand { needs, Expectations, Potential of the site

b- Pretrial documentation:

CRC collect updated and signed resume of each member of site ...

Pretrial documents:
1- Form 1572
2- Financial disclosure form
3- undertaking from principal investigator
4- Confidentiality non-disclosure agreement
5- Coordinating c IRB

CRC must ensure that pretrial documents are completed within specified timeline.

c- Financial responsibilities:

Senior CRC negotiate (گفت وگو کردن، با پول نقد تبدیل کردن) the trial budgets at the site. includes: ◦investigators fees
- IRB fees
- Site adminstration fees
- lab cost
- Study subject travel

(D) training site staff:

CRC train the site staff

Can highlight on → inclusion criteria
→ Exculsion criteria
→ schedule of visits
→ window period
→ visit specific activites
→ Safety guidlines and reporting timeline as per protocol.

(E) Post trial activities:

Once hospital phase of trial is over. completely study documentation will become important

They do { final check CRFs (case report forms)
maintain an archival inventory of records

□ Potential advantages of CROs:

- Reduce time needed to develop a new drug
- Reduce Sponsor's fixed cost associated with personnel, equipment and facilities
- Provide knowledge of regulatory climate in foreign markets.

Clinical Research Associate (CRA):

-Also called a clinical monitor or trial monitor, is a health-care professional who performs many activities related to medical research, particularly clinical trials.

- Clinical research associates collect and organize data obtained during studies and trials conducted in fields, such as biotechnology and pharmaceuticals.

- CRA
  - ensures compliance ē protocol
  - check clinical site activities
  - make on-site visits
  - reviews CRFs
  - Communicates ē investigators

□ As per ICH-GCP guidline:

-Monitors should be appointed by sponsor.
-Monitors should be trained, have scientific and clinical knowledge.

- A monitor's qualifications should be documented.
- Monitors should be familiar c̄ { Investigational products, Protocol, written informed consent form }

□ Monitor's Responsibilities:

1- Acting as main line communication b/w sponsor and investigator.

2. Verifying that investigator has adequate qualification and resources facilities including { laboratories, equipment, staff, adequate safety ---

3- Investigational product: that storage time and condition are acceptable.

4. that investigational products are supplied only to subjects who are eligible to recieve it and at protocol specified dose.

5- Subjects are provided c̄ necessary instruction on using, handling, storing.

6. Disposition of unused investigated products at trial sites. complies c applicable regulatory and is in accordance c sponsor.

7. Verifying that investigator follows approved protocol and all approved amendment.

8. Verifying that written informed consent was obtained before each subject's participation in trial

9. Ensuring that investigator recieves (current investigator brochure.

10- Ensuring that investigators trial staff are performing.

11- Verifying the investigator is enrolling only eligible subjects

12. Reporting the subject recruitment rate.

13. Verify: documents and trial records are accurate, complete and up to date.

14. Verify that investigators provides all required reports, notification, application and these documents are accurate, complete

15. Checking the accuracy and completeness of CRF entries, source documents and related records.

16. Any dose and therapy modifications are well documented for each trial subject.

17. Adverse event, contamitant medication and intercurrent illnesses are reported ε protocol on CRFs.

Auditors:

Audit:

A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirements

Audit Certificate

A declaration of confirmation by the auditor that an audit has taken place.

Audit Report

A written evaluation by the sponsor's auditor of the results of the audit.

Audit Trail

Documentation that allows reconstruction of the course of events.

Auditors

• Selection and Qualification of Auditors

a- The sponsor should appoint individuals, who are independent of the clinical trials/systems to conduct audits.

b- The sponsor should ensure that the auditors are qualified by training and experience to conduct audits properly. An auditor's qualifications should be documented.

□ Responsibilities of Auditors:

The sponsor should specify the roles and responsibilities of the auditor before starting to conduct an audit so as to ensure fair and smooth performance of the audit. The auditor is responsible for maintaining the confidentiality of information obtained during an audit, planning (designing and updating) and conducting the audit, and reporting the audit results.

□ Purpose of Audit:

To evaluate the trial conduct and compliance with:

i. Quality Systems

ii. SOPs

iii. Protocol

iv. Good clinical practice and

V. Other applicable regulatory requirements

□ What to audit?

- Organization and personnel responsibilities and functions.
- Qualification, training and adequacy of staff list of monitors, List of all investigators
- Drug supply agreement, clinical trial (site) agreement, other services agreement and material transfer agreement.

- Quality management System
- Investigational drug
  - → Manufacturing
  - → Packaging
  - → labeling and coding of the IP (including placebo and active comparator where applicable) in accordance with applicable GMP standards Labeling requirements.
- Drug product Accountability
- IRB/IEC
  - responsibility
  - composition
  - functions
  - operations
  - Procedures
  - Records

- Essential documents:
  - → Investigator's brochure
  - → Signed protocol and amendments (How are changes and deviations to the protocol handled?)
  - → Advertisements for subject recruitment
  - → Informed consent forms, Approved by IRB/IEC? (All been signed off according to requirements
  - → Financial aspects of the trial
  - → Case report forms
  - → Serious adverse events reporting
  - → instructions for handling
  - → Shipping records
- Bio-analytical laboratories
- computerized systems
- Statistical components

- How to execute an audit?

→ The execution of audit process is divided into three steps:

i- Before the audit

ii- During the audit

iii- After the audit

□ Before the audit process:

- Auditor contacts the site to arrange for a mutually acceptable date and time for an audit to be conducted.

- A detailed agenda of an audit is informed to the CRC and also about the documents to be checked during an audit.

- Auditor previews the protocol, CRF, local regulations and guidelines, project

specific guidelines, relevant SOPs to be aware of the trial.

□ During the audit process:

- Opening meeting
  - → An introductory meeting between the auditor and the site team.
  - → Auditor briefs the scope and procedures to be followed during the audit.
  - → An opportunity for trial team members to communicate with the auditor.

- Reviewing documents and collating information
- Audit observations (documents all observations)

□ After the audit process:

- Auditor should issue the audit report within 28 days of the final audit activity.
- He makes clinical research personnel

aware of the findings relevant to their activities, and findings are classified as critical, major and minor.

- Prevention / corrective action list should accompany the report.
- A formal audit response should be prepared and submitted by the trial team to the concerned personnel after the corrective measures have been taken.
- Following the satisfactory responses to the audit, auditor issues an audit certificate confirming that audit has taken place and filed in clinical trial report and also submitted to regulatory authorities.

Clinical Research Coordinator (CRC)

- The clinical Research Coordinator (CRC) is responsible for conducting clinical trials using Good Clinical Practice (GCP) under the auspices (بِشتبان) of the Principal Investigator (PI).
- Good Clinical Practices Principles have been defined by Madelene Ottosen, RN, MSN, of The University of Texas Health Science Center at Houston as:
  - All trials are conducted etically, as defined by the Declaration of Helsinki, rigorously (بدقة), as defined by the International Conference on Harmonization Guidelines (ICH).
  - Benefits outweigh risks for each patient.
  - Rights, safety and well-being of patients prevail (يسود) over science.
  - All available non-clinical and clinical information on any investigational agent can

Support the trial as designed.

- All trials are scientifically sound and clearly described.
- All clinical trials have current Institutional Review Board approval.
- Medical decisions and care are the responsibility of qualified health care professionals, specifically physicians and, if applicable, dentists.
- Everyone involved in the clinical trial is qualified by training, education and experience.
- Informed consent is given freely by every participant.
- All study documentation is recorded, handled and stored to allow accurate reporting, interpretation and verification.
- Confidentiality of subjects is respected

and protected.

- Investigational products maintain Good Manufacturing Practice in storage, manufacturing and handling.
- Systems to ensure quality are implemented in all aspects of the trial.

- Although the PI is responsible for the conduct of the trial, "it has been said that the CRC is the heart and soul of the research study and that, ultimately, it is the CRC who carries forward the research goals, thereby playing a significant role in the success of the research study. Most importantly, CRCs are often involved in essential duties that have been traditionally performed by the PI, such as conducting the informed consent process

and ensuring compliance with the protocol".

.The CRC's primary responsibility, as with all clinical research professionals, is the protection of human subjects, but the CRC has many other responsibilities.

.Although not inclusive, some of the CRC responsibilities include preparing the Institutional Review Board submission, writting the informed consent document, working with the institutional official in contract negotiations, developing a detailed cost analysis, negotiating the budget with the sponsor (i.e. pharmaceutical company or granting agency), subject recruitment, patient care, adverse event reporting, preparing the case report form (CRF), submitting CRFs and other data to the Sponsor as necessary and study close-out.

Responsibilities:

1. Institutional Review Board Submissions
2. Informed consent
   - Basic elements
   - Additional elements
3. Contracting with pharmaceutical companies
4. Cost analysis and budget negotiations
5. Subject recruitment
6. Patient care
7. Adverse events
8. Case report forms
9. Study close

1. Institutional Review Board submissions:

All research involving human subjects must be approved by an Institutional Review Board. Each IRB has requirements for protocol submi-

ssions which usually require the preparation of an IRB application and informed consent document. A study cannot begin unless IRB approval is obtained.

2. Informed consent:

The IRB must approve the informed consent prior to study initiation and often the CRC is liaison b/w the IRB and the Sponsor. The Sponsor will have set requirements of the informed consent as does the IRB.

Each local IRB is responsible for the review and approval of the informed consent, but the CRC is responsible for the communication b/w the IRB and the Sponsor.

• § 46.116 of the code of Federal Regulations outlines the elements of informed consent as:

•Basic elements:

1. A statement that the study involves research, an explanation of the purpose of the research and the expected duration of the subject's participation; a description of the procedures to be followed, and identification of any procedures which are experimental;

2. A description of any reasonably foreseeable risks or discomforts to the subject;

3. A description of any benefits to the subject or to others which may reasonably be expected from the research.

4. A disclosure of appropriate alternative procedures or courses of treatment, if any,

that might be advantageous to the subject;

5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

6. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

7. An explanation of whom to contact for answers to pertinent questions about the research and research subject's rights, and whom to contact in the event of a research

related injury to the subject; and

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

- Additional elements:

When appropriate, one or more of the following elements of information shall also be provided to each subject:

1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is

or may become pregnant) which are currently (در حال حاضر)
unforeseeable. (پیش بینی نشده)

anticipate: (انتظار داشتن)

2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;

3. Any additional costs to the subject that may result from participation in the research;

4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

5. A statement that significant new findings

developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject; and

6. The approximate number of subjects involved in the study.

3. Contracting with pharmaceutical companies:

The Site conducting the clinical trial will negotiate (تفاوض کردن) the clinical trial management (CTA) to conform to its policies and procedures.

The resolution of many contractual issues requires coordination b/w the Sponsor, the PI and the Site, which is usually the responsibility of the CRC.

The involvement of each party is essential to a successful CTA with mutually acceptable terms.

•The CTA should include terms for indemnification, confidentiality, publication, intellectual property, insurance, data safety and monitoring boards, subject injury, governing law and termination clauses.

negotiation: داد و ستد

4. Cost analysis and budget negotiations:

•To develop a cost analysis, the CRC will review the protocol schema and determine which procedures are standard of care versus research. The research charges will be included in the budget along with personnel effort, site initiation costs, IRB fees throughout the life of the clinical trial, pharmacy costs, travel costs for the PI and CRC to attend Investigator meetings, equipment, dedicated fax and computer lines, supplies, screen failures, subject Stipends,

Subject travel costs, and any other items that are defined as a direct cost to the clinical trial.

In addition, if the clinical trial is conducted at an Academic Medical Center (AMC) there will be an indirect cost rate that will be applied to the direct costs of the study. The indirect rate is approximately 30% for pharmaceutical trials and can be upwards of 50% for federal trials, depending on the AMC's federally negotiated indirect costs rate.

5. Subject recruitment:

Prior to agreeing to conduct the clinical trial, the CRC (and the PI) will determine if they have the appropriate patient population. The CRC is responsible for subject recruitment

once the trial begins or establishing the research team that will recruit subjects. It is important that viable subject recruitment occurs beforehand as the clinical trial agreement will stipulate the number of subjects the site is required to recruit.

6. Patient Care:

- The CRC will coordinate and conduct patient care visits and assure all procedures are conducted in compliance with the protocol.

The CRC will interact with the PI to assure patient receives appropriate medical evaluation and care when needed and will alert the PI of any serious adverse events that may occur throughout the course of the study.

7. Adverse events:

An adverse event is described as "any adverse change in health or "side-effect" that occurs in a person who participates in a clinical trial while the patient is receiving the treatment (study medication, application of the study device, etc.) or within a pre-specified period of time after their treatment has been completed". The CRC must report all adverse events to the sponsor and all serious adverse events to the IRB and sponsor.

8. Case report forms:

The purpose of the case report form (CRF) is to collect relevant data in accordance with the protocol and in compliance with regulatory requirements.

The CRC will collect the data on the CRF and submit to the Sponsor either electronically or paper format.

9. Study close:

In accordance with the local IRB, the CRC will complete IRB Study close documentation and make any appropriate notifications to the Study Subjects, research team, and pharmacies.

- The CRC will work with the Sponsor's clinical monitor in completing outstanding monitoring findings and queries.

In addition, the CRC is responsible for complying with the record retention policies of the FDA, the ICH, and the clinical trial agreement.

authority: اولیای امور (در جمع)

269

Introduction:

National regulatory authorities oversee (سرکشی کردن) and monitor the development of new drugs.

1. In USA FDA oversees new drug development
2. In Europe European Agency for the Evaluation of Medicinal products (EAEM)
3. In Japan the Ministry of Health, Labour and Welfare
4. In China the State Drug Administration (SDA)
5. In India DCGI, CDSCO, SLA, NPAC, CDA

Objective:

The overall objective of a Drug Regulatory Authority (DRA) is to ensure that:

1. Medicinal products are of acceptable quality, safety and efficacy.

2. Manufactured and distributed in ways which ensure their quality until they reach the patient/consumer, and their commercial promotion is accurate.

Regulatory Authority

Roles and Responsibilities:

1. Regulatory affairs officers ensure the appropriate licensing, marketing and legal compliance of pharmaceutical and medical products in order to control the safety and efficacy of products.

2. They combine their knowledge of scientific, legal and business issues to ensure products, which are developed, manufactured or distributed by a wide range of companies, meet the required legislation.

3. They advise on and coordinate the approval and registration of pharmaceuticals, veterinary medicines, complementary medicines, chemicals, pesticides, therapeutic devices and other products.

4. Regulatory affairs officers are the crucial link b/w their company, its products and regulatory authorities.

Responsibilities:

1. Ensuring that a company's products comply with the regulations.

2. keeping abreast (همسو) of international legislation (قانون), guidelines and customer practices.

Collate: جفت‌یابی و تطبیق کردن

3. Collecting and collating a wide range of information

4. Keeping up to date with a company's product range

5. Developing and writing clear arguments (استدلال) and explanations for new product licenses and license renewals.

6. Preparing submissions of license variations and renewals to strict deadlines.

7. Monitoring and setting timelines for license

variations and renewals approvals

8. Working with specialist computer software and resources

9. Writing clear, accessible product labels and patient information leaflets

10. planning and developing product trials and interpreting trial data.

11. Advising scientists and manufacturers on regulatory requirements

12. Project managing teams of colleagues involved with the development of new products.

undertake: بعده گرفتن

13. Undertaking and managing regulatory inspections

14. Reviewing company practices and providing

advice on changes to systems;

liaise: رابطه داشتن

15. liaising with, and making presentations to, regulatory authorities

16. Negotiating with regulatory authorities for marketing authorization

17. Specifying storage, labeling and packaging requirements

Protocol

Protocol:

Written detailed procedure for conducting the research study and collecting data.

- The contents of a trial protocol should generally include the following topics. However, site specific information may be provided on separate protocol page(s), or addressed in a separate agreement, and some of the information listed below may be contained in other protocol referenced documents, such as Investigator's Brochure.

GBOT SET SS REFAQ

1- General information:

1. Protocol title, protocol identifying number, and date.

Any amendment(s) should also bear the amendment number(s) and date(s).

2. Name and address of the sponsor and monitor (if other than the sponsor).

3. Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.

4. Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial.

5. Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).

6. Name, title, address and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).

7. Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

2. Background information:

i - Name and description of the investigational product(s)

ii. A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.

iii. Summary of the known and potential risks and benefits, if any, to human subjects.

iv. Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).

v. A Statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

vi. Description of the population to be Studied.

vii. References to literature and data that are relevant to the trial, and that provide background for the trial.

3. Trial objectives and purpose:

A detailed description of the objectives and the purpose of the trial.

4. Trial design:

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design.

A description of the trial design, should include:

i. A specific statement of the primary endpoints and secondary endpoints, if any, to be measured during the trial.

ii- A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.

iii- A description of the measures taken to minimize/avoid bias, including a- randomization

b- Blinding

iv. A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).

v. The expected duration of subject participation, and a description of the sequence and duration

of all trial periods, including follow-up, if any.

vi. A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.

vii. Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

viii. Maintenance of trial treatment randomization codes and procedures for breaking codes.

ix. The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be Source data.

5. Selection and withdrawal of subjects:

i. Subject inclusion criteria

ii. Subject exclusion criteria

iii- Subject withdrawal criteria (i.e terminating investigational product treatment / trial treatment) and procedures specifying:

a) When and how to withdraw subjects from the trial/ investigational product treatment.

b) The type and timing of the data to be collected for withdrawn subjects

c) Whether and how subjects are to be replaced.

d) The follow-up for subjects withdrawn from investigational product treatment/ trial treatment.

6. Treatment of Subjects:

i- The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects

for each investigational product treatment /trial treatment group/arm of the trial.

ii- Medication(s)/ treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

iii- Procedures for monitoring Subject compliance.

7. Assessment of efficacy:

i- Specification of the efficacy parameters.

ii- Methods and timing for assessing, recording and analysing of efficacy parameters.

8. Assessment of Safety:

i- Specification of safety parameters

ii- The methods and timing for assessing, recording and analysing safety parameters.

iii- Procedures for eliciting reports of and for

recording and reporting adverse event and intercurrent illnesses.

iv. The type and duration of the follow-up of subjects after adverse events.

9. Statistics:

i. A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).

ii- The number of subjects planned to be enrolled In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on(or calculations of) the lower of the trial and clinical justification.

iii- The level of significance to be used.

iv- Criteria for the termination of the trial.

v. Procedure for accounting for missing, unused, and spurious data.

vi. Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate)

7. The selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects)

10. Direct Access to Source Data/documents:

The Sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC reviews and regulatory inspection(s), providing direct

access to source data/documents.

11. Quality Control and Quality Assurance:

12. Ethics:

Description of ethical considerations relating to the trial.

13. Data handling and record keeping

14. Financing and insurance

Financing and insurance if not addressed in a separate agreement.

15. Publication policy:

Publication policy, if not addressed in a separate agreement.

16. Supplements

RAJIV GANDHI UNIVERSITY OF HEALTH SCIENCES,
BANGALORE, KARNATAKA

ANNEXURE- II

PROFORMA OF REGISTRATION OF SUBJECT FOR DISSERTATION

1)	NAME OF THE CANDIDATE AND ADDRESS	HEDIEH FAROKHI KOUROSH ALLAHDINI HESAROEYEH REZA RAHIMI(PB)
2)	NAME OF THE INSTITUTION	VISVESWARAPURA INSTITUTE OF PHARMACEUTICAL SCIENCES, BANASHANKARI-II STAGE, BANGALORE-70
3)	COURSE OF THE STUDY AND SUBJECT	PHARM D
4)	DATE OF ADMISSION TO THE COURSE	NOVEMBER-2011 SEPTEMBER-2014(PB)
5)	TITLE OF THE TOPIC	ASSESSMENT OF RISK FACTORS AND DRUG THERAPY FOR SURGICAL SITE INFECTIONS

287

6.0	BRIEF RESUME OF THE INTENDED WORK

6.1) Need for the study

Surgical site infection is a type of healthcare-associated infection in which a wound infection occurs after an invasive (surgical) procedure. Surgical site infections have been shown to compose up to 20% of all of healthcare-associated infections. At least 5% of patients undergoing a surgical procedure develop a surgical site infection. Most surgical site infections are caused by contamination of an incision with microorganisms from the patient's own body during surgery.

Surgical site infections can have a significant effect on quality of life for the patient. They are associated with considerable morbidity and extended hospital stay. In addition, surgical site infections result in a considerable financial burden to healthcare providers. Advances in surgery and anaesthesia have resulted in patients who are at greater risk of surgical site infections being considered for surgery.[1]

CLASSIFICATION:

There are 3 different types of surgical site infection defined by the Centers for Disease Control and Prevention (CDC). In the criteria put forth by the CDC, SSIs are classified as either incisional or organ/space, with incisional SSIs being further sub classified as superficial (involving only skin and subcutaneous tissue) versus deep (involving underlying soft tissue) Centers for Disease

1)Superficial Incisional SSI

Infection occurs within 30 days after the operation and infection involves only skin or subcutaneous tissue of the incision.

2)Deep Incisional SSI

Infection occurs within 30 days after the operation if no implant is left in place or within 1 year if implant is in place and the infection appears to be related to the operation and infection involves deep soft tissues (eg. fascial and muscle layers).

3)Organ/Space SSI

Infection occurs within 30 days after the operation if no implant is left in place or within 1 year if implant is in place and the infection appears to be related to the operation and infection involves any part of the anatomy (eg. organs or spaces), other than the incision, which was opened or manipulated during an operation[2].

SYMPTOMS:

An SSI may cause:

- Fever more than 100.5°F 48 hours or more after surgery
- Chills
- Fast heart rate
- Chest pain

- Symptoms in the area where the surgery took place:
  - Redness
  - Drainage
  - Pus
  - Pain
  - Swelling
  - Bad odour [3]

RISK FACTORS:

The risk of SSI is increased by factors that:

- increase the risk of endogenous contamination (for example, procedures that involve parts of the body with a high concentration of normal flora such as the bowel)
- increase the risk of exogenous contamination (for example, prolonged operations that increase the length of time that tissues are exposed)
- diminish the efficacy of the general immune response (for example, diabetes, malnutrition, or immunosuppressive therapy with radiotherapy, chemotherapy or steroids) or local immune response (for example, foreign bodies, damaged tissue or formation of a haematoma).[4]

The degree of risk for an SSI is linked to the type of surgical wound you have. Surgical wounds can be classified in this way:

- Clean wounds. These are not inflamed or contaminated and do not involve operating on an internal organ; the risk for an SSI in this type of wound is less than 2 percent.
- Clean-contaminated wounds. These have no evidence of infection at the time of surgery, but do involve operating on an internal organ; the risk for SSI is less than 10 percent.
- Contaminated wounds. These involve operating on an internal organ with a spilling of contents from the organ into the wound; the risk for SSI is 13 to 20 percent.
- Dirty wounds. These are wounds in which a known infection is present at the time of the surgery; the risk for SSI is about 40 percent.[5]

TREATMENT:

Medicines:

The following medicines are commonly administered:

- Antibiotics: This medicine is given to help treat or prevent an infection caused by bacteria. Antibiotics are warranted when local cellulitis or wound necrosis is present[6]

- Medicines to treat pain, swelling, or fever: These medicines are safe for most people to use. However, they can cause serious problems when used by people with certain medical conditions. Treatment options:
- Cleansing: Cleansing may be done by rinsing the wound with sterile (clean) water.
- Debridement: This is done to clean and remove objects, dirt, or dead skin and tissues from the wound area. Caregivers may cut out the damaged areas in or around the wound.
- Hyperbaric oxygen therapy: This is also called HBO. HBO is used to get more oxygen into your body. The oxygen is given under pressure to help it get into your tissues and blood.
- Negative pressure therapy: This is also called vacuum-assisted closure (VAC). A special foam dressing with an attached tube is placed inside the wound cavity and tightly covered.
- Wound dressings: Dressings (bandages) are used to protect the wound from further injury and infection. They may also help provide pressure to decrease swelling. [7]

6.2) REVIEW OF LITERATURE:

- A study was conducted by Cheng K et al to determine risk factors for surgical site infection in a teaching hospital which included 1138 patients. The study included patients who underwent breast, hernia, esophagus, stomach, appendix, colon or rectal surgery in range of 2-92 years old. Risk factors assessed were type of operation, wound classification, volume of blood loss, blood transfusion, risk index, duration of surgery, diabetes, cancer, gastrointestinal catheter, urinary catheter, post operative drainage and pre-procedural WBC count could be regarded as potential indicators of SSI and that relevant preventive measures should be taken to reduce SSI and improve patient outcome [8]
- A study was conducted by Justin E Richards et al to determine Stress-Induced Hyperglycemia as a risk factor for surgical-site infection in non-diabetic Orthopaedic trauma patients admitted to the intensive Care Unit. This study included one hundred and eighty-seven consecutive trauma patients with isolated orthopaedic injuries. Blood glucose values during initial hospitalization were recorded. The admission blood glucose (BG) and hyperglycemic Index (HGI) were determined for each patient. Perioperative infectious complications found were pneumonia, urinary tract infection (UTI), surgical-site infection (SSI), sepsis. Stress-induced hyperglycemia demonstrated a significant independent association with SSI's in non-diabetic orthopedics trauma patients who were admitted to the ICU.[9]
- A study was carried out by Margaret A Olsen et.al to determine risk factors for surgical site infection following major breast surgery. A retrospective case control study design was used to determine independent risk factors for surgical site infection in subjects selected from a cohort of patients who had undergone mastectomy, breast reconstruction or reduction surgery

between January 1998 and June 2002 at a tertiary care university affiliated hospital. The medical records of 57 patients with breast SSI and 268 randomly selected uninfected were taken as case selected for control were reviewed. Suboptimal prophylactic antibiotic dosing is a potentially modifiable risk factor for SSI following breast surgery. Risk of SSI was increased in patients undergoing mastectomy and in patients who had an implant or tissue expander placed during surgery. Knowledge of these risk factors can be used to develop a specific risk stratification index to predict SSI in breast surgery and infection preventive strategies tailored for breast surgery patients[10].

- A study was conducted by Albert F Pullter Gunne et al to determine incidence of surgical site infection following adult spinal deformity surgery. This study was retrospectively performed on a large case cohort of all adult patients who underwent surgery for kyphosis or scoliosis. Preoperative patient characteristics including age, gender, weight, Presence of obesity , co morbidities, use of non steroidal anti inflammatory drugs, serum albumin level, serum protein level and serum white blood cells count were recorded. In this retrospective cohort analysis, 830 adult patients underwent surgery for a spinal deformity (kyphosis/scoliosis), 46 patients (5.5%) developed a SSI, out of which 17 patients (2.0%) had an isolated superficial SSI, and 29 patients (3.5%) had a deep SSI. Obese patients were found to have an increased risk for all types of SSI, while patients who had a prior SSI were at increased risk for recurrent SSI. An anterior/posterior procedure on the same day has a tendency to increase the risk for SSI. By understanding these findings, protocols can be developed to decrease the rate of SSI in this high risk population[11].
- A study was conducted by Tingting Ren et al to determine risk factors for surgical site infection of pilon fractures. The medical records of all pilon fracture patients who underwent surgical fixation from January 2010 to October 2012 were reviewed to identify those who developed a surgical site infection. A total of 519 patients were enrolled in the study from January 2010 toOctober 2012. This study included patients aged above 18 years who underwent surgical fixation of a pilon fracture during the study period; and at least 12 months of clinical and radiographic follow-up. Patients exhibiting the risk factors identified in this study were counseled regarding the possible surgical site infection that may develop after surgical fixation.[12]
- A study was conducted by AeuMuro G.Lake et al to determine surgical site infection following cases during the hysterectomy. They conducted a cross sectional analysis of the 2005-09 American College of Surgeons National Surgical Quality Improvement Program used the data files to analyze case of hysterectomies. A total of 13,822 women were included in their final analysis. Their finding of the decreased occurrence of superficial SSI after vaginal approach for hysterectomy reaffirms the role for vaginal hysterectomy as the route of choice for hysterectomy.[13]
- A study was conducted by Jadranka Maksimovic et al to determine surgical site infections in orthopedic patients. A 6-month prospective cohort study on 227 patients, with 30 days of patient follow-up after surgery, was conducted at the teaching hospital in Belgrade. They collected patients' basic demographic data and data on underlying disease status, surgical procedures, preoperative preparation of patients, and antibiotic prophylaxis. It was found that

	there is a high incidence of surgical site infections in orthopedic patients in Serbia in comparison with developed countries and some developing countries. Points for intervention could be reduction of personnel during surgery, better treatment of wounds, decreasing ASA score and reduction of the time between surgical site shaving and the intervention.[14] ➢ A study was conducted by Francois Durand et al to determine whether smoking was a risk factor for organ/space surgical site infection in orthopaedic surgery with implant materials. This study included a prospective cohort of 3,908 patients from June 2003 to December 2006. Smoking was found to be a significant risk factor for organ/space SSI. A significant difference between smokers and non-smokers for surgical wound complications (hematoma, discharge or wound dehiscence) during the period between surgical procedure and discharge from hospital.[15] ➢ A study was conducted by Demisew Amenu et al to determine surgical site infection rate and risk factors among obstetric cases of Jimma university specialized hospital in southwest Ethiopia. It was seen that surgical site infections rates are higher than acceptable standards indicating the need for improving antenatal care, increasing the number of skilled birth attendants at the local clinics, increasing basic and comprehensive emergency obstetric care services, applying improved surgical techniques and improving infection prevention practices to decrease infection rate to acceptable standard.[16] ➢ A study was conducted by Keith S.Kaya et al to determine the impact of surgical site infection on older operative patient. Retrospective matched outcomes study was used in eight hospitals including Duke University Medical Center and 7 community hospitals. On the Patients ≥ 65 years old undergoing surgery from 1991-2003. Cases were defined as patients who developed deep incisional or organ/space SSI and controls were operative patients who did not develop SSI. Controls were frequency matched to cases by type and year of operative procedure and by hospital in a 1:1 ratio. In this study they measured mortality, duration of hospitalization (including re-admissions) and hospital charges for the 90 days following surgery.1,337 patients were enrolled in the study: 561 cases with SSI and 576 control patients without SSI. Among elderly operative patients, SSI was associated with an almost 4-fold increase in mortality, a mean attributable duration of hospitalization after surgery of 15.7 days (95% CI 13.9, 17.6) and mean attributable hospital charges of $43,970 (95% CI $31,881, $56,060). [17]
	6.3) OBJECTIVES OF THE STUDY : 1. To identify the risk factors associated with surgical site infection (SSI) 2. To study drug therapy given during the SSI
7.0)	MATERIALS AND METHODS :-
	7.1) Source of Data : 1. Treatment chart/case sheet, lab report.

7.2) INCLUSION CRITERIA:

Hospitalised in-patients undergoing surgery in the department of surgery at Kims hospital and research center

7.3) EXCLUSION CRITERIA

OPD procedure and other types of healthcare infection that mainly affect surgical patients are postoperative respiratory and urinary tract infections, bacteraemias(including methicillin-resistant Staphylococcus aureus infections and intravascular cannula infection) and antibiotic-related diarrhoeas(particularly clostridium difficle enteritis).

7.4) METHOD AND COLLECTION OF DATA:

Data will be collected from in-patients who are undergoing emergency and elective surgeries.
Direct observation of wound health professional from the department of Surgery.

Identification of potential risk factors:

- Age
- Sex
- Obesity
- Chronic disease
- Days spend preoperative/Number of days
- Previous hospitalization within past 2 weeks
- Intra-operative finding of infection
- Duration of surgery/Less than 60 min or greater than 60 min
- Drain or inserted
- Antibiotics administration if yes, details of antibiotic
- Wound classification (clean/clean contaminated/contaminated/dirty)
- Days spend at hospital postoperatively
- Nature of surgery (elective or emergency)
- Preoperative shower

Drug therapy:

Drug given

First dose

- previous days
- inward >120 min before incision
- inward <60 min
- inward between 60 to 120 min
- in OT
- after incision

	Intraoperative dose(Yes/No) Last dose
	7.5) Duration of the study: The study will be conducted for a period of 6 months.
	7.6) Place of Study: Surgery department ,KIMS hospital Bangalore
	7.7) Does the study require any investigation or intervention to be conducted on patient or other humans or animals if so, please describe briefly -No-
	7.8) Has ethical clearance been obtained from your Institution? Applied for ethics committee for the approval.

8.0)	LIST OF REFERENCES

1) Surgical site infection: Prevention and treatment of surgical site infection NICE guidelines [CG74] Published date: October 2008

2) Reducing Surgical Site Infections by David E Reichman published in2009

3) Surgical Site Infection(SSI; Surgical Wound Infection)by Patricia Griffin Kellicker, BSN

4) Surgical Site Infection:Prevention and Treatment of Surgical Site Infection *NICE Clinical Guidelines, No. 74* National Collaborating Centre for Women's and Children's Health (UK). London: RCOG Press; 2008 Oct.

5)www.hopkinsmedicine.org/healthlibrary/conditions/surgical_care/surgical_site_infections_134,144/

6) Perspectives in Prevention and Treatment of Surgical Site Infection – A Narrative Review of the Literature by David Leaper November 2013

7) www.drugs.com/cg/surgical-site-infections-inpatient-care.html

8) Cheng K, Li J, Kong Q, Wang C, Ye N, Xia G Risk factors for surgical site infection in a teaching hospital: a prospective study of 1,138 patients.2015 Aug 14;9:1171-7. doi: 10.2147/PPA.S86153. eCollection 2015.

9) Richards JE, Kauffmann RM, Obremskey WT, May AK. J Orthop Trauma. Stress-induced hyperglycemia as a risk factor for surgical-site infection in nondiabetic orthopedic trauma patients admitted to the intensive care unit.2013 Jan;27(1):16-21. doi: 10.1097/BOT.0b013e31825d60e5.

10) Margaret A. Olsen, PhD, MPH, Mellani Lefta, BS, Jill R. Dietz, MD, Keith E. Brandt, MD, Rebecca Aft, MD,Ryan Matthews, BS, Jennie Mayfield, BSN, MPH, CIC, and Victoria J. Fraser, MD Risk Factors for Surgical Site Infection Following Major Breast Surgery.J Am Coll Surg. 2008 Sep; 207(3): 326–335.Published online 2008 Jun 26. doi: 10.1016/j.jamcollsurg.2008.04.021

11) Albert F. Pull ter Gunne,[✉] C. J. H. M. van Laarhoven, and David B. Cohen Incidence of surgical site infection following adult spinal deformity surgery: an analysis of patient risk.Eur Spine J. 2010 Jun; 19(6): 982–988.Published online 2010 Jan 12. doi: 10.1007/s00586-009-1269-1

12) Tingting Ren,[I] Liang Ding,[II,*] Feng Xue,[II,**] Zhimin He,[II] and Haijun Xiao[II] Risk factors for surgical site infection of pilon fracturesClinics (Sao Paulo). 2015 Jun; 70(6): 419–422.Published online 2015 Jun. doi: 10.6061/clinics/2015(06)06

13) AeuMuro G. Lake, MD, Alexandra M. McPencow, MD, Madeline A. Dick-Biascoechea, MD, Deanna K. Martin, MPH, and Elisabeth A. Erekson, MD MPH Surgical site infection after hysterectomy.Am J Obstet Gynecol. Author manuscript; available in PMC 2013 Nov 12.

14) Jadranka Maksimović, Ljiljana Marković-Denić,[1] Marko Bumbaširević,[2] Jelena Marinković, and Hristina Vlajinac[1]Croat Surgical Site Infections in Orthopedic Patients: Prospective Cohort StudyMed J. 2008 Feb; 49(1): 58–65.doi: 10.3325/cmj.2008.1.58

15) François Durand, Philippe Berthelot, Celine Cazorla, Frederic Farizon, and Frederic Lucht Smoking is a risk factor of organ/space surgical site infection in orthopaedic surgery with implant materials.nt Orthop. 2013 Apr; 37(4): 723–727..Published online 2013 Feb 27. doi: 10.1007/s00264-013-1814-8

16) Demisew Amenu,[1] Tefera Belachew,[2] and Fitsum Araya Surgical Site Infection Rate and Risk Factors Among Obstetric Cases of Jimma University Specialized Hospital, Southwest Ethiopia.Ethiop J Health Sci. 2011 Jul; 21(2): 91–100.

17) Keith S. Kaye, MD, MPH,[1] Deverick J. Anderson, MD, MPH,[1] Richard Sloane, MS,[1] Luke F. Chen, MBBS, FRACP,[1] Yong Choi, RN,[1] Katherine Link, RN,[1] Daniel J. Sexton, MD,[1] and Kenneth E. Schmader, MD .The Impact of Surgical Site Infection on Older Operative PatientsJ Am Geriatr Soc. 2009 Jan; 57(1): 46–54..doi: 10.1111/j.1532-5415.2008.02053.x

18) Manuela Buonanno,[1] Gerhard Randers-Pehrson,[1] Alan W. Bigelow,[1] Sheetal Trivedi,[2] Franklin D. Lowy,[2] Henry M. Spotnitz,[3] Scott M. Hammer,[2] and David J. Brenner[1]207-nm UV Light - A Promising Tool for Safe Low-Cost Reduction of Surgical Site Infections. I: *In Vitro* Studies.PLoS One. 2013; 8(10): e76968.

19) Dane K. Wukich, MD,[1] Brandon E. Crim, DPM,[1] Robert G. Frykberg, DPM, MPH,[2] and Bedda L. Rosario Neuropathy and Poorly Controlled Diabetes Increase the Rate of Surgical Site Infection After Foot and Ankle SurgeryJ Bone Joint Surg Am. 2014 May 21; 96(10): 832–839.Published online 2014 May 21. doi: 10.2106/JBJS.L.01302

20) Belinda M. Maher,[a] Michelle E. Mulcahy,[a] Alison G. Murphy,[a] Mieszko Wilk,[a] Kate M. O'Keeffe,[a] Joan A. Geoghegan,[c] Ed C. Lavelle,[b] and Rachel M. McLoughlin[a] Nlrp-3-Driven Interleukin 17 Production by γδT Cells Controls Infection Outcomes during *Staphylococcus aureus* Surgical Site Infection.Infect Immun. 2013 Dec; 81(12): 4478–4489.

21) Alyssa J. Reiffel,[1] Philip S. Barie,[1,2] and Jason A. Spector A Multi-Disciplinary Review of the Potential Association between Closed-Suction Drains and Surgical Site InfectionSurg Infect (Larchmt). 2013 Jun; 14(3): 244–269.doi: 10.1089/sur.2011.126

22) Emily S Petherick,[1] Jane E Dalton,[2] Peter J Moore,[3] and Nicky Cullum Methods for identifying surgical wound infection after discharge from hospital: a systematic review.BMC Infect Dis. 2006; 6: 170.Published online 2006 Nov 27. doi: 10.1186/1471-2334-6-170[1]

23) Donald E. Fry The Prevention of Surgical Site Infection in Elective Colon Surgery.Scientifica (Cairo). 2013; 2013: 896297.Published online 2013 Dec 19. doi: 10.1155/2013/896297

24) Thomas D Pinkney,[1] David C Bartlett,[1,2] William Hawkins,[1] Tony Mak,[1] Haney Youssef,[1] Kaori Futaba,[1] Gareth Harrison,[1] Adrian Gheorghe,[3] Jennifer M Bradbury,[4] Melanie J Calvert,[3] George Dowswell,[3] Laura Magill,[5] Val Redman,[3] Sue Wilson,[3] David Leaper,[6] and Dion G Morton Reduction of surgical site infection using a novel intervention (ROSSINI): study protocol for a randomised

controlled trial. Published online 2011 Oct 4. doi: 10.1186/1745-6215-12-217

25Thomas D Pinkney, ,[1,2] Melanie Calvert, ,[1,3]David C Bartlett, ,[1] Adrian Gheorghe, [3] Val Redman, ,[3] George Dowswell, ,[1,3] William Hawkins, ,[1] Tony Mak, ,[1] Haney Youssef, [1] Caroline Richardson, ,[1] Steven Hornby, ,[1] Laura Magill, ,[1,4] Richard Haslop, ,[3] Sue Wilson, [3] and Dion Morton, Impact of wound edge protection devices on surgical site infection after laparotomy: multicentre randomised controlled trial (ROSSINI Trial).BMJ. 2013; 347: f4305.Published online 2013 Jul 31. doi: 10.1136/bmj.f4305

26) Motoi Uchino,[1] Hiroki Ikeuchi,[1] Hiroki Matsuoka,[1] Yoshiko Takahashi,[2] Naohiro Tomita,[1] and Yoshio Takesue[2] Surgical Site Infection and Validity of Staged Surgical Procedure in Emergent/Urgent Surgery for Ulcerative Colitis.Int Surg. 2013 Jan-Mar; 98(1): 24–32.doi: 10.9738/CC83.1

27) Samuel C Smith,[1] Clare F Heal,[2] and Petra G Buttner Prevention of surgical site infection in lower limb skin lesion excisions with single dose oral antibiotic prophylaxis: a prospective randomised placebo-controlled double-blind trial.BMJ Open. 2014; 4(7): e005270.Published online 2014 Jul 30. doi: 10.1136/bmjopen-2014-005270

9.0	NAME & SIGNATURE OF THE CANDIDATE	Hedieh Farokhi Kouroush Allahdini hesaroeyeh Reza Rahimi
10.0	REGISTRATION NUMBER	
11.0	NAME AND DESIGNATION OF THE GUIDE	Dr.Vanaja K Assistant Professor VIPS, Bangalore.
11.1	REMARKS OF THE GUIDE	
11.2	SIGNATURE OF THE GUIDE	
12.0	NAME OF THE HEAD OF THE DEPARTMENT	Dr.Githa Kishore Professor, VIPS, Bangalore.
12.1	SIGNATURE OF THE HEAD OF THE DEPARTMENT	
13.0	NAME AND DESIGNATION OF CO-GUIDE	Dr. Lakshmi.S Assistant Professor Department of Surgery KIMS Hospital and Research Centre, Bangalore
13.1	SIGNATURE OF THE CO-GUIDE	
14.0	NAME OF THE PRINCIPAL	Dr. G.Y Narmada
14.1	REMARKS OF THE PRINCIPAL	
14.2	SIGNATURE OF PRINCIPAL WITH SEAL	

Case Report Form (CRF)

Definitions:

Case Report Forms are the research instruments or tools designed to collect the data that are necessary to answer the research questions of a specific protocol.

• The Good Clinical Practice (GCP) standard developed by the International Conference on Harmonization, defines CRF as "the printed, optical or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject."

• Generally, data recorded on a CRF include basic subject-specific sociodemographic information such as birth date, ethnicity, race, education level; data from study specific examinations, measurements or specialty tests, data abstracted from the subject's medical record or other source

documents such as ambulatory and in-patient records, laboratory results, other tests and special procedures. Design of research surveys and questionnaires require special considerations that are addressed in the "CRC Research Practice Guideline for Developing Surveys".

□ Purpose of CRFs:

i- Capturing all protocol-required information

ii- Facilitates data collection and entry

iii- Benefits data management

iv- Benefits statistical analysis

v. Simplifies database design and data validation processes as well as manipulation of data during statistical analysis.

CREs Development Process:

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. Because of the significance of the CRF in the

successful completion of the clinical trail, and the importance of its design to the different contributors to that endeavour, a team-based approach to CRF design and review is highly recommended.

Ideally, this team would, as a minimum include:

- CRF designer
- Medical advisor
- Clinical monitor
- Data entry leader
- Data manager
- Statistician

- Prior to designing the CRF, the investigator and study team should carefully review the study protocol and do the following:

1. Develop the list of variables that need to

be collected. Use the research questions specified in the IRB-approved protocol to guide development of the variable list. For each research question, make a list of the specific, measurable variables that are needed to answer that question.

2. Identify the best source for the data to be collected. For each variable listed, identify where the data will come from, i.e. the data source.

3. Determine the timing and availability of the data to be collected. Data points that will be collected at the same time (e.g. same study visit) or from the same location (e.g. lab results from Power Chart), or available at the same time (e.g. lab results from batched runs from central labs) should be grouped together

(e.g one CRF for local lab data available within 24 hours of the visits and another CRF for central lab data available twice per year)

4. Determine the data management system. Early in the planning stage, the Principal Investigator should determine the data management system that will be employed for the study. CRF design may be significantly affected by the functionality of the data management application used.

5. Determine the regulatory requirements for the study. There are CRF content and formatting conventions that will support compliance with FDA regulations if the research study is FDA regulated.

• Well designed CRFs will support the goal of accuracy and completeness in data collection and compliance with human subject's protection regulations. Whenever possible, Investigators should use already existing CRFs as templates and modify as needed to create study specific CRFs.

1. Content Standards:

• Include a data field for the unique, confidential subject identification (ID) number on each page of every form.

• NEVER use the subject's name, medical record number, or social security number as a study identifier, and never include such identifiers on the same CRF that includes other research data.

• Include a standard section at the beginning

of each form and include key variables that identify the subject and the research event. The CRC (cyclic Redundancy Check) routinely labels this as "Section A. General Information" and includes the subject's unique study ID number, date of study visit or event, an event or visit code, and ID/initials of person completing the form.

- Dated signatures by a PI or their IRB approved designee on the study are necessary on some CRFs according to FDA regulations and to support best practices.

- Include a header on the first page and include the name of the study, the form name, the assigned form number and version date of every approved CRF that was used to collect data.

- Include a standard footer on every page

and include the form name, form number and page number in the footer.

- Provide variable definitions and abbreviated instructions on the CRF for proper form completion wherever applicable.

- When possible, use closed-ended questions and assign numeric codes to each of the response categories. Avoid open-ended open text questions.

- List all parts of a question series on the same page.

2. Formating Standards:

- To minimize data recording and data entry errors, consider who the end users will be when deciding about design issues such as formatting and font size.

- For paper CRFs, use adequate font size for readability. The CRC routinely uses 11-point font as a default font size.
- Use adequate line spacing for easy readability to minimize data recording and data entry errors. The CRC commonly uses 1.5 line spacing.
- Assign a number to each question and sub-question to provide a clear reference to every item on paper.
- Use subsections to divide the form and organize it by topic. For example, Section A: General information; Section B: Demographic data etc.
- Document "dates" consistently following a standard format: MM/DD/YYYY.
- Use a table format when there is a series of questions that have the same response categories, and organize the questions in rows and responses

in columns.

3. CRF version control:

. When drafting CRFs, always save the most recent version of the document with a unique version date added as an extension to the MS Word document name. Then update the version in the header and standard footer on each page of the CRF.

. For example, to revise a CRF in development, open the document named, "Form 1-version 10-01-15.doc" and save it.

4. Quality control review for programmability:

A CRC Project Manager/ Research Coordinator should complete a critical review of the CRFs prior to pre-testing to evaluate the form for

programmability. The Project Manager/Research Coordinator will evaluate variables and coding schemes for compatibility with the selected database application.

5. Pre-Testing:

CRFs should be pre-tested prior to study start up to evaluate the logic, wording and general construction of the CRFs as well as the overall feasibility of the data collection plan and procedures. A pre-test should be completed by experienced study staff with a small number of subjects or volunteers. Ideally, those responsible for data collection will assist with pre-testing data forms.

6. Review and approval of final CRFs:

- The last step in the CRF development process is to incorporate all the changes that resulted from the pre-test and obtain official "Sign-off" from the Principal Investigator and the Study Biostatistician prior to sending CRF for database programming.

- The Study Principal Investigator and Biostatistician should provide an official "Sign-off" of each CRF to certify each is final and includes all variables required to answer the protocol research questions. This sign off should be provided in writing via a hard copy or electronic method. The official "Sign-off" should be maintained in the study research files.

Frequently, the PI will ask all co-Investigators, Biostatistician, the Study Project Director and/or Study Coordinator to review and "Sign-off" on all or a sub-set of the CRFs

prior to providing his/her own final "sign-off".

7. Convert CRFs to PDF document for use in the field:

- If the study uses hard copy CRFs, always convert the study CRF documents to PDF documents prior to distribution to data collectors.

Do not distribute the final approved CRFs as Word documents to data collectors to avoid inadvertent or intentional alterations to the approved master CRFs.

- Changes to CRFs should be made only by authorized persons with PI approval

Paper Case Report Form V.S. Electronic CRF:

- There are two types of CRFs used in clinical research, that is, traditional paper CRF and

improvised electronic CRF (eCRF). Paper CRF is the traditional way of data capture and a better option if studies are small or vary in design, whereas eCRFs are considered if studies are large with similar designs.

- In the current global scenario, eCRFs are preferred over paper CRFs as they are less time consuming, and also encourage the sponsor/ pharmaceutical company to carry out large multicentric studies at the same time due to the ease of administration. It is designed in such a way that data entry can be done with zero/ minimal errors.

Moreover, the regulatory authorities are readily accepting submissions in which validated electronic data capture (EDC) systems are used.

• While designing an eCRF, repetitive data such as protocol ID, site code, subject ID, and patient initials will be generated by the system automatically from the first page to all others, thus ensuring no duplication of CRF pages. In eCRF, linking the data between two related pages of CRFs becomes easy and quick.

• Designing a paper CRF is a tedious job that could result in data errors and wrong conclusions, requiring more attention to minimize duplication of CRF pages. Chances of error during data transfer from the source document to paper CRF are common. However, this method may not require user training and system validation as in the case of EDC systems.

• Despite their many advantages, eCRFs have not

been accepted widely. Main reasons behind this are lack of available on-site technology, investigators' lack of motivation, complexity of installation, and maintenance of the software and high investment cost.

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CASE REPORT FORM

Trial Title

Short Title/Acronym

Chief Investigator:
Sponsor Number: XX/XXXX
EudraCT Number: XXXX-XXXXXX-XXX
Name of site:
CRF Version Number: X, XX/XXX/XXXX

Patient Initials	☐☐☐	Subject No.	☐☐☐
Screening No.	☐☐☐	Centre No.	☐☐☐

315

VISIT 1 (SCREENING) DEMOGRAPHIC DATA

Date of Assessment: ___/___/_____

(DD / MMM / YYYY)

Informed Consent:	
Date participant/relative signed written consent form: ___/___/_____ (DD / MMM / YYYY)	**Date of first trial-related procedure:** ___/___/_____ (DD / MMM / YYYY)
Name of person taking informed consent: _____	

Demographic Data:							
Date of Birth: ___/___/_____ (DD / MMM / YYYY)							
Ethinicity:							
White	White British ☐		White Irish ☐		White Other ☐		
Mixed race	White & Black Caribbean ☐		White & Black African ☐		White & Asian ☐	Other mixed background ☐	
Asian or Asian British	Indian ☐		Bangladeshi ☐		Pakistani ☐	Other Asian background ☐	
Black or Black British	Caribbean ☐		African ☐		Black Other ☐		
Chinese or other ethnicity	Chinese ☐		Other ☐ (please specify)				
Sex: ☐ Male ☐ Female							

Completed by: _____

Name Signature Date

* Record the comment on the protocol deviation/violation log.

< Short Title/Acronym>

Sponsor No. X X / X X X X

Subject/Screening No. ___ ___ ___

Patient Initials ___ ___ ___

Site Name

VISIT 1 (SCREENING) MEDICAL HISTORY

Date of Assessment: ___/___/_____

(DD / MMM / YYYY)

Has the patient had any relevant medical history?	☐ No ☐ Yes, Complete below		
Condition / illness /surgical procedure	**Start date** (DD/MMM/YYYY)	**Stop date** (DD/MMM/YYYY)	Or tick if ongoing at Screening Visit?
	___/___/___	___/___/___	☐
	___/___/___	___/___/___	☐
	___/___/___	___/___/___	☐
	___/___/___	___/___/___	☐
	___/___/___	___/___/___	☐
	___/___/___	___/___/___	☐
	___/___/___	___/___/___	☐
	___/___/___	___/___/___	☐
	___/___/___	___/___/___	☐
	___/___/___	___/___/___	☐
	___/___/___	___/___/___	☐
	___/___/___	___/___/___	☐

Completed by: _____

Name Signature Date

* Record the comment on the protocol deviation/violation log.

< Short Title/Acronym>

Sponsor No. X X / X X X X

Subject/Screening No. [ ] [ ] [ ]

Patient Initials [ ] [ ] [ ]

Site Name

VISIT 1 (SCREENING) PHYSICAL EXAM

Date of Assessment: ___ / _____ / _____

(DD / MMM / YYYY)

Was Physical Examination performed? ☐ No ☐ Yes, Complete below				
System	*Abnormal	Normal	Not done	*If noted ABNORMAL, please provide brief description and comment if clinically significant or not (CS/NCS)
General Appearance	☐	☐	☐	
Skin	☐	☐	☐	
Eyes, Ears, Nose & Throat	☐	☐	☐	
Head, Neck & Thyroid	☐	☐	☐	
Cardiovascular	☐	☐	☐	
Respiratory	☐	☐	☐	
Abdomen	☐	☐	☐	
Extremities	☐	☐	☐	
Genitalia	☐	☐	☐	
Anorectal	☐	☐	☐	
Lymph Nodes	☐	☐	☐	
Muscular-Skeletal	☐	☐	☐	
Neurological	☐	☐	☐	
Others (please specify)	☐	☐	☐	

Completed by: _____

Name Signature Date

* Record the comment on the protocol deviation/violation log.

318

< Short Title/Acronym>

Sponsor No. X X / X X X X

Subject/Screening No. ___ ___ ___

Patient Initials ___ ___ ___

Site Name

VISIT 1 (SCREENING) VITAL SIGNS & ECG

Were Vital Signs performed?	☐ No (comment below) ☐ Yes, Complete below Comment*:
Date of Vital Signs:	___/___/_____ (DD / MMM / YYYY)
Time of Vital Signs:	____:____ HH:MM
Blood Pressure supine/standing/seating :	___ ___ ___ / ___ ___ ___ mmHg
Pulse:	___ ___ ___ beats/min
Weight: ___ ___ ___ . ___ kg	Height: ___ . ___ ___ m
Oral/ Tympanic Temperature:	___ ___ . ___ °C

Was an ECG performed?	☐ No (comment below) ☐ Yes, Complete below Comment*:
Date & Time of ECG:	___/___/_____ ____:____ (DD / MMM / YYYY) HH:MM
The ECG is:	☐ Within normal limits ☐ Abnormal, NOT clinically significant ☐ Abnormal, clinically significant, please specify: _____

Completed by: _____
Name Signature Date

* Record the comment on the protocol deviation/violation log.

< Short Title/Acronym>

Sponsor No. X X / X X X X

Subject/Screening No. ☐☐☐ Patient Initials ☐☐☐ Site Name

VISIT 1 (SCREENING) HAEMATOLOGY

Clinical Haematology Laboratory tests performed?	☐ No (comment below) ☐ Yes, Complete below Comment: _____
Date of Sample:	___/___/____ (DD / MMM / YYYY)
Time of Sample	____:____ HH:MM
Was laboratory sample taken at different hospital to <insert investigator's site lab name>?	☐ No ☐ Yes, Complete below Laboratory name / Location: _____

HAEMATOLOGY Laboratory Parameter	Value	Unit (site to pre-complete prior to the finalization of the template)	If parameter indicated as out of normal range on report, please check if clinically significant:
WBC			☐ No ☐ Yes
RBC			☐ No ☐ Yes
Hb			☐ No ☐ Yes
HCT			☐ No ☐ Yes
MCV			☐ No ☐ Yes
MCH			☐ No ☐ Yes
PLT			☐ No ☐ Yes
NEUTROPHILS			☐ No ☐ Yes
LYMPHOCYTES			☐ No ☐ Yes

Completed by: _____
Name Signature Date

* Record the comment on the protocol deviation/violation log.

320

MONOCYTES			☐ No ☐ Yes
EOSINOPHILS			☐ No ☐ Yes
BASOPHILS			☐ No ☐ Yes
RETICULOCYTES			☐ No ☐ Yes

VISIT 1 (SCREENING) BIOCHEMISTRY

Clinical Biochemistry Laboratory tests performed?	☐ No (comment below) ☐ Yes, Complete below Comment: _____
Date of Sample:	__ __ / __ __ __ / __ __ __ __ (DD / MMM / YYYY)
Time of Sample	_____ : _____ HH:MM
Were laboratory samples taken at different hospital other than <insert investigator's site lab name>?	☐ No ☐ Yes, Complete below Laboratory name / Location: _____

BIOCHEMISTRY Laboratory Parameter	Value	Unit (site to pre-complete prior to the finalization of the template)	If parameter indicated as out of normal range on report, please check if clinically significant:
SODIUM			☐ No ☐ Yes
POTASSIUM			☐ No ☐ Yes
CHLORIDE			☐ No ☐ Yes
BICARBONATE			☐ No ☐ Yes

Completed by: _____
Name Signature Date

* Record the comment on the protocol deviation/violation log.

UREA			☐ No ☐ Yes
CREATININE			☐ No ☐ Yes
TOTAL PROTEIN			☐ No ☐ Yes
TOTAL BILIRUBIN			☐ No ☐ Yes
ALBUMIN			☐ No ☐ Yes
ALK PHOS			☐ No ☐ Yes
ALT			☐ No ☐ Yes
AST			☐ No ☐ Yes
CALCIUM			☐ No ☐ Yes

VISIT 1 (SCREENING) < INSERT ASSESSMENT>

Clinical <insert assessment> Laboratory tests performed?	☐ No (comment below) ☐ Yes, Complete below Comment *: _____
Date of Sample:	___/___/_____ (DD / MMM / YYYY)
Time of Sample	_____:_____ HH:MM
Was laboratory sample taken at different hospital to <insert investigator's site lab name>?	☐ No ☐ Yes, Complete below Laboratory name / Location: _____

Completed by: _____
Name Signature Date

* Record the comment on the protocol deviation/violation log.

Sponsor No. X X / X X X X

Subject/Screening No. ___ ___ ___

Patient Initials ___ ___ ___

Site Name

<INSERT ASSESSMENT> Laboratory Parameter	Value	Unit (site to pre-complete prior to the finalization of the template)	If parameter indicated as out of normal range on report, please check if clinically significant:
			☐ No ☐ Yes
			☐ No ☐ Yes
			☐ No ☐ Yes
			☐ No ☐ Yes
			☐ No ☐ Yes
			☐ No ☐ Yes
			☐ No ☐ Yes
			☐ No ☐ Yes
			☐ No ☐ Yes
			☐ No ☐ Yes
			☐ No ☐ Yes
			☐ No ☐ Yes
			☐ No ☐ Yes

Completed by: _____

Name Signature Date

* Record the comment on the protocol deviation/violation log.

< Short Title/Acronym>

Sponsor No. | X | X | / | X | X | X | X |

Subject/Screening No. | | | | Patient Initials | | | | Site: Name

VISIT 1 (SCREENING) SCREENING CONCOMITANT MEDICATIONS

Date of Assessment: ___/___/_____

(DD / MMM / YYYY)

Is the participant taken any concomitant medications at screening or <insert time frame as specified in protocol>					☐ No ☐ Yes, Complete below		
Medication (Record Generic or trade name)	Reason for use (Medical History diagnosis or other reason, e.g. Prophylaxis)	Dose and units	Frequency	Route	Start Date (DD/MMM/YYYY)	Stop Date (DD//MMM/YYY)	Or tick if ongoing at Screening Visit
1.					___/___/___	___/___/___	☐
2.					___/___/___	___/___/___	☐
3.					___/___/___	___/___/___	☐
4.					___/___/___	___/___/___	☐
5.					___/___/___	___/___/___	☐
6.					___/___/___	___/___/___	☐
7.					___/___/___	___/___/___	☐
8.					___/___/___	___/___/___	☐
9.					___/___/___	___/___/___	☐
10.					___/___/___	___/___/___	☐

Completed by: _____

Name Signature Date

* Record the comment on the protocol deviation/violation log.

< Short Title/Acronym>

Sponsor No. | X | X | / | X | X | X | X |

Subject/Screening No. | | | |

Patient Initials | | | |

Site: Name

VISIT 1 (SCREENING) SMOKING / ALCOHOL STATUS

Date of Assessment: ___/_____/_____

(DD / MMM / YYYY)

Has the participant ever smoked? ☐ **No** ☐ **Yes,** Complete below

☐ **Current Smoker**

Participant's average daily use:
- Number of cigarettes : ___ ___
- Number of cigars : ___ ___
- Number of pipes : ___ ___

Smoked for ___ ___ **months/years**

☐ **Former smoker**

Smoked for ___ ___ **months/years**

Date when smoking ceased: ___/_____/_____
(DD / MMM / YYYY)

When smoking, participant's average daily use:
- Number of cigarettes : ___ ___
- Number of cigars : ___ ___
- Number of pipes : ___ ___

Participant's alcohol consumption

Participant's average consumption per <insert time frame stated in protocol>:
- Number of units of wine : ___ ___
- Number of units of beer : ___ ___
- Number of units of spirits : ___ ___

(see protocol for definition of units)

Completed by: _____
Name Signature Date

* Record the comment on the protocol deviation/violation log.

< Short Title/Acronym>

Sponsor No. | X | X | / | X | X | X | X |

Subject/Screening No. | | | |

Patient Initials | | | |

Site: Name

VISIT 1 (SCREENING) INCLUSION CRITERIA

Date of Assessment: ___ / ____ / _____

(DD / MMM / YYYY)

The following criteria MUST be answered YES for participant to be included in the trial (except where NA is appropriate):		Yes	No	N/A
1.		☐	☐	☐
2.		☐	☐	☐
3.		☐	☐	☐
4.		☐	☐	☐
5.		☐	☐	☐
6.		☐	☐	☐
7.		☐	☐	☐
8.		☐	☐	☐
9.		☐	☐	☐
10.		☐	☐	☐
If any of the above criteria is answered NO, the participant is NOT eligible for the trial and must not be included in the study. Please list reason(s) for ineligibility for screen failure on Participant Eligibility Review page.				

Completed by: _____

Name Signature Date

* Record the comment on the protocol deviation/violation log.

Sponsor No. | X | X | / | X | X | X | X |

Subject/Screening No. | | | |

Patient Initials | | | |

Site | Name |

VISIT 1 (SCREENING) EXCLUSION CRITERIA

Date of Assessment: __/____/_____

(DD / MMM / YYYY)

The following criteria MUST be answered NO for the participant to be included in the trial:		Yes	No
1.		☐	☐
2.		☐	☐
3.		☐	☐
4.		☐	☐
5.		☐	☐
6.		☐	☐
7.		☐	☐
8.		☐	☐
9.		☐	☐
10.		☐	☐

If any of the above criteria is answered YES, the participant is NOT eligible for the trial and must not be included in the study. Please list reason(s) for ineligibility for screen failure on Participant Eligibility Review page.

Completed by: _____

Name Signature Date

* Record the comment on the protocol deviation/violation log.

< Short Title/Acronym>

Sponsor No. | X | X | / | X | X | X | X |

Subject/Screening No. | | | |

Patient Initials | | | |

Site: Name

VISIT 1 (SCREENING) PARTICIPANT ELIGIBILITY REVIEW

End of Screening Visit Checklist:			
		Yes	No
1.	Does the participant satisfy the inclusion and exclusion criteria to date?	☐	☐
2.	Have all Screening Visit procedures been completed?	☐	☐
3.	Have the Medical History and Concomitant Medication pages been completed?	☐	☐
4.	Is the participant still willing to proceed in the trial?	☐	☐

Participant's eligibility Investigator Sign-Off:	
Is the participant eligible to take part in the Clinical Trial?	☐ Yes ☐ No, Please give reason for screen failure below
Investigator's Signature: _____ Date : __ __ / __ __ __ / __ __ __ __ (DD / MMM / YYYY)	
Investigator's Name: _____	
Reason(s) for screen failure:	
1.	
2.	
3.	

Completed by: _____
Name Signature Date

* Record the comment on the protocol deviation/violation log.

< Short Title/Acronym>

Sponsor No. | X | X | / | X | X | X | X |

Subject No. | | | |

Patient Initials | | | |

Site: Name

VISIT <INSERT VISIT No.> / NAME>

Participant Randomisation/Enrolment	
Participant study Number allocated:	___ ___ ___
Date of Randomisation/Enrolment:	___/___ ___/___ ___ ___ (DD / MMM / YYYY)

Completed by: _____

Name Signature Date

* Record the comment on the protocol deviation/violation log.

< Short Title/Acronym>

Sponsor No. | X | X | / | X | X | X | X |

Subject No. | | | |

Patient Initials | | | |

Site | Name |

VISIT X <INSERT VISIT NAME> CHECKLIST

Date of Visit: ___/___/_____

(DD / MMM / YYYY)

Visit Checklist:

		Yes	No
1.	**Have there been any new Adverse Events?** (If yes, please record in Adverse Events page)	☐	☐
2.	**Have there been any changes in Concomitant Medications?** (If yes, please record in Concomitant Medications Log)	☐	☐
3.	**Add further assessments required at each visit, amend the following pages to fit your requirements**	☐	☐
4.		☐	☐

Completed by: _____

Name Signature Date

* Record the comment on the protocol deviation/violation log.

< Short Title/Acronym>

Sponsor No. X X / X X X X

Subject No. ☐☐☐ Patient Initials ☐☐☐ Site Name

VISIT X <INSERT VISIT NAME> PHYSICAL EXAM

Date of Assessment: ___/_____/_____

(DD / MMM / YYYY)

Was Physical Examination performed? ☐ No (comment Below) ☐ Yes, Complete below

Comment*:_____

System	*Changed	Not Changed	Not done	*If CHANGED from previous examination or new abnormality noted, please provide brief description and comment if clinically significant or not (CS/NCS). IF CS consider if it is an AE and add to log (if appropriate)
General Appearance	☐	☐	☐	
Skin	☐	☐	☐	
Eyes, Ears, Nose & Throat	☐	☐	☐	
Head, Neck & Thyroid	☐	☐	☐	
Cardiovascular	☐	☐	☐	
Respiratory	☐	☐	☐	
Abdomen	☐	☐	☐	
Extremities	☐	☐	☐	
Genitalia	☐	☐	☐	
Anorectal	☐	☐	☐	
Lymph Nodes	☐	☐	☐	
Muscular-Skeletal	☐	☐	☐	
Neurological	☐	☐	☐	
Others (please specify)	☐	☐	☐	

Completed by: _____

Name Signature Date

* Record the comment on the protocol deviation/violation log.

< Short Title/Acronym>

Sponsor No. X X / X X X X

Subject No. ☐☐☐ Patient Initials ☐☐☐ Site Name

VISIT X <INSERT VISIT NAME> BIOCHEMISTRY

Clinical Biochemistry Laboratory tests performed?	☐ No (Comment Below) ☐ Yes, Complete below Comment*:_____
Date & Time of Sample:	___/___/_____ (DD / MMM / YYYY) _____:_____ HH:MM
Was laboratory sample taken at different hospital to <insert investigator's site lab name>?	☐ No ☐ Yes, Complete below Laboratory name / Location: _____

BIOCHEMISTRY Laboratory Parameter	Value	Unit (site to pre-complete prior to the finalization of the template)	If parameter indicated as out of normal range on report, please check if clinically significant IF - CS consider if it is an AE and add to log (if appropriate)::
SODIUM			☐ No ☐ Yes
POTASSIUM			☐ No ☐ Yes
CHLORIDE			☐ No ☐ Yes
BICARBONATE			☐ No ☐ Yes
UREA			☐ No ☐ Yes
CREATININE			☐ No ☐ Yes
TOTAL PROTEIN			☐ No ☐ Yes
TOTAL BILIRUBIN			☐ No ☐ Yes
ALBUMIN			☐ No ☐ Yes
ALK PHOS			☐ No ☐ Yes
ALT			☐ No ☐ Yes
AST			☐ No ☐ Yes
CALCIUM			☐ No ☐ Yes

Completed by:_____

Name Signature Date

* Record the comment on the protocol deviation/violation log.

< Short Title/Acronym>

Sponsor No. | X | X | / | X | X | X | X |

Subject No. | | | | Patient Initials | | | | Site | Name |

VISIT X <INSERT VISIT NAME> <INSERT ASSESSMENT>

Clinical <insert assessment> Laboratory tests performed?	☐ No (Comment Below) ☐ Yes, Complete below Comment*:_____
Date & Time of Sample:	___/___/_____ (DD / MMM / YYYY) _____:_____ HH:MM
Was laboratory sample taken at different hospital to <insert investigator's site lab name>?	☐ No ☐ Yes, Complete below Laboratory name / Location: _____

<INSERT ASSESSMENT> Laboratory Parameter	Value	Unit	If parameter indicated as out of normal range on report, please check if clinically significant IF CS consider if it is an AE and add to log (if appropriate)::
			☐ No ☐ Yes
			☐ No ☐ Yes
			☐ No ☐ Yes
			☐ No ☐ Yes
			☐ No ☐ Yes
			☐ No ☐ Yes
			☐ No ☐ Yes
			☐ No ☐ Yes
			☐ No ☐ Yes
			☐ No ☐ Yes

Completed by: _____
Name Signature Date

* Record the comment on the protocol deviation/violation log.

< Short Title/Acronym>

Sponsor No. | X | X | / | X | X | X | X |

Subject No. | | | |

Patient Initials | | | |

Site | Name |

VISIT X <INSERT VISIT NAME>< ASSESSMENT PERFORMED>

<Insert other assessments>

Completed by: _____

Name Signature Date

* Record the comment on the protocol deviation/violation log.

< Short Title/Acronym>

Sponsor No. | X | X | / | X | X | X | X |

Subject No. | | | | Patient Initials | | | | Site: Name

VISIT X <INSERT VISIT NAME> TRIAL MEDICATION ADIMINSTRATION

<Insert name of trial medication> Administration

CHOOSE APPROPRIATE DOSING/DISPENSING TABLE FOR YOUR PROTOCOL AND MODIFY AS REQUIRED

Date of Dosing (DD/MMM/YYYY)	Time of Dosing (24 hr)	Dose (including units)	Comment ONLY if dose delayed, interrupted, reduced or altered
__/__/____	__:__		
__/__/____	__:__		

Start date of dosing (DD/MMM/YYYY)	Stop date of dosing (DD/MMM/YYYY)	Dose (including units)	Comment ONLY if dose delayed, interrupted, reduced or altered
__/__/____	__/__/____		
__/__/____	__/__/____		

INFUSION

Date of Infusion (DD/MMM/YYYY)	Start time of infusion	Stop time of infusion	Dose (including units)	Comment ONLY if dose delayed, interrupted, reduced or altered
__/__/____	__:__	__:__		
__/__/____	__:__	__:__		

Completed by: _____
Name Signature Date

* Record the comment on the protocol deviation/violation log.

< Short Title/Acronym>

Sponsor No. | X | X | / | X | X | X | X |

Subject No. | | | |

Patient Initials | | | |

Site | Name |

VISIT X <INSERT VISIT NAME> TRIAL MEDICATION DISPENSING

DISPENSING

Date of Dispensing IMP (DD/MMM/YYYY)	Quantity Dispensed (no. tablets/ pens/patches)	<Daily> Dose (including units)	Comment ONLY if dose delayed, reduced or altered
____/____/____			

Note: add more rows depending on how IMP is dispensed and Returned

RETURNS (add to subsequent visit)

Date of Returning IMP (DD/MMM/YYYY)	Quantity Returned (no. tablets/ pens/patches)	Comment on compliance
____/____/____		

Completed by: _____

Name Signature Date

* Record the comment on the protocol deviation/violation log.

TRIAL COMPLETION

Did participant complete the trial?	☐ **Yes,** Please provide date of last visit: ___/___/20___ (DD / MMM / YYYY) ☐ **No,** Please provide date of withdrawal and complete below: ___/___/20___ (DD / MMM / YYYY)

Early Withdrawal: please tick most appropriate reason for participant not completing the trial:

- ☐ **Adverse Events related:** please state related AE: _____ (add details to AE page)
- ☐ **Participant's decision, specify:** _____
- ☐ **Investigator's decision, specify:** _____
- ☐ **Sponsor's decision**
- ☐ **Lost to follow up**
- ☐ **Patient deceased**
- ☐ **Other, specify:** _____

Completed by: _____

Name Signature Date

* Record the comment on the protocol deviation/violation log.

< Short Title/Acronym>

Sponsor No. X X / X X X X

Subject No. ☐☐☐ Patient Initials ☐☐☐ Site Name

ADVERSE EVENTS PAGE

AE No	Event Name (Please give Diagnosis if known)	Start date (DD/MMM/YYYY)	Stop date (DD/MMM/YYYY)	Serious? If serious, please complete a JRO SAE form	Con-comitant Medication given	Severity 0 - Mild 1- Mode-rate 2 - Severe	Study Drug Action 0 - None 1 - Temporarily Interrupted 2 - permanently withdrawn	Outcome 0 - Resolved 1- Resolved with sequelea 2 - Not resolved	Relationship to Study Drug 0 - Definitely 1 - Probably 2 - Possibly 3 - Unlikely 4 - Not related 5 - Not assessable
1		___/___/___	___/___/___	☐ No ☐ Yes	☐ No ☐ Yes				
2		___/___/___	___/___/___	☐ No ☐ Yes	☐ No ☐ Yes				
3		___/___/___	___/___/___	☐ No ☐ Yes	☐ No ☐ Yes				
4		___/___/___	___/___/___	☐ No ☐ Yes	☐ No ☐ Yes				
5		___/___/___	___/___/___	☐ No ☐ Yes	☐ No ☐ Yes				
6		___/___/___	___/___/___	☐ No ☐ Yes	☐ No ☐ Yes				

I have reviewed the AEs on this page and have assessed them for seriousness, causality, severity and outcome and confirm that, to the best of my knowledge, it accurately reflects the study information obtained for this participant

PI signature _____ **Date:** _____ ☐ **Please check box if this is the last page used**

Completed by: _____ _____

Name Signature Date

< Short Title/Acronym>

Sponsor No. | X | X | / | X | X | X | X |

Subject No. | | | | Patient Initials | | | | Site: Name

ADVERSE EVENTS PAGE (CONTINUATION PAGE)

AE No	Event Name (Please give Diagnosis if known)	Start date (DD/MMM/YYYY)	Stop date (DD/MMM/YYYY)	Serious? If serious, please complete a JRO SAE form	Concomitant Medication given	Severity 0 - Mild 1- Moderate 2 - Severe	Study Drug Action 0 - None 1 - Temporarily Interrupted 2 - permanently withdrawn	Outcome 0 - Resolved 1- Resolved with sequelea 2 - Not resolved	Relationship to Study Drug 0 - Definitely 1 - Probably 2 - Possibly 3 - Unlikely 4 - Not related 5 - Not assessable
__		__/__/__	__/__/__	☐ No ☐ Yes	☐ No ☐ Yes				
__		__/__/__	__/__/__	☐ No ☐ Yes	☐ No ☐ Yes				
__		__/__/__	__/__/__	☐ No ☐ Yes	☐ No ☐ Yes				
__		__/__/__	__/__/__	☐ No ☐ Yes	☐ No ☐ Yes				
__		__/__/__	__/__/__	☐ No ☐ Yes	☐ No ☐ Yes				
__		__/__/__	__/__/__	☐ No ☐ Yes	☐ No ☐ Yes				

I have reviewed the AEs on this page and have assessed them for seriousness, causality, severity and outcome and confirm that, to the best of my knowledge, it accurately reflects the study information obtained for this participant

PI signature________________ Date:________________ ☐ **Please check box if this is the last page used**

341

Completed by: ____
Name Signature Date

< Short Title/Acronym>

Sponsor No. | X | X | / | X | X | X | X |

Subject No. | | | | Patient Initials | | | | Site | Name |

CONCOMITANT MEDICATIONS LOG

Has the participant used any Concomitant Medications? ☐ No ☐ Yes, Complete below

CM No.	Medication name (Record <specify Generic or Brand> name)	Start date (DD/MMM/YYYY)	Stop date (DD/MMM/YYYY)	Or tick if ongoing at end of study?	Reason for use (Enter related AE diagnosis, or other reasons for use, e.g. Prophylaxis)	Dose (Units)	Route	Frequency
1.		___/___/___	___/___/___	☐				
2.		___/___/___	___/___/___	☐				
3.		___/___/___	___/___/___	☐				
4.		___/___/___	___/___/___	☐				
5.		___/___/___	___/___/___	☐				
6.		___/___/___	___/___/___	☐				
7.		___/___/___	___/___/___	☐				

☐ Please check box if this is the last page used

Note: Use the Concomittent log to record Non-IMPs

349

Completed by: _____ _____ _____

Name Signature Date

< Short Title/Acronym>

Sponsor No. | X | X | / | X | X | X | X |

Subject | | | | Site | | | |

CONCOMITANT MEDICATIONS LOG (CONTINUATION PAGE)

CM No.	Medication name (Record Generic name)	Start date (DD/MMM/YYYY)	Stop date (DD/MMM/YYYY)	Or tick if ongoing at end of study?	Reason for use (Enter related AE diagnosis, or other reasons for use, e.g. Prophylaxis)	Dose (Units)	Route	Frequency
—.		___/___/____	___/___/____	☐				
—.		___/___/____	___/___/____	☐				
—.		___/___/____	___/___/____	☐				
—.		___/___/____	___/___/____	☐				
—.		___/___/____	___/___/____	☐				
—.		___/___/____	___/___/____	☐				
—.		___/___/____	___/___/____	☐				
—.		___/___/____	___/___/____	☐				

☐ Please check box if this is the last page used

343

Completed by: _____ | _____ | _____

Name | Signature | Date

< Short Title/Acronym>

Sponsor No. | X | X | / | X | X | X | X |

Subject No. | | | |

Patient Initials | | | |

Site: Name

PRINICIPAL INVESTIGATOR'S SIGN OFF

Principal Investigator's Signature Statement:

I have reviewed this CRF and confirm that, to the best of my knowledge, it accurately reflects the study information obtained for this participant. All entries were made either by me or by a person under my supervision who has signed the Delegation and Signature Log.

Principal Investigator's Signature:

_____

Principal Investigator's Name:

_____

Date of Signature: __ __ / _ _ _ / __ __ __ __
(DD / MMM / YYYY)

ONCE SIGNED, NO FURTHER CHANGES CAN BE MADE TO THIS CRF WITHOUT A SIGNED DATA QUERY FORM.

4.8 Informed Consent of Trial Subjects:

ICH GCP definition:

"A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form".

4.8.1 In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/

favourable opinion of the written informed consent form and any other written information to be provided to subjects.

4.8.2 The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favourable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication

of this information should be documented.

4.8.3 Neither the investigator, no the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

4.8.4 None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

4.8.5 The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information and the approval/favourable opinion by the IRB/IEC.

4.8.6 The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.

4.8.7 Before informed consent may be obtained,

the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

4.8.8 Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

4.8.9 If a subject is unable to read or if a

legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. 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 legally

acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

4.8.10 Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

a) That the trial involves research

b) The purpose of the trial

c) The trial treatment(s) and the probability for random assignment to each treatment.

d) The trial procedures to be followed, including all invasive procedures.

e) The subject's responsibilities

f) Those aspects of the trial that are experimental.

g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.

h- The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.

i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.

j) The compensation and/or treatment available to the subject in the event of trial-related injury.

k) The anticipated prorated payment, if any, to the subject for participating in the trial.

l) The anticipated expenses, if any, to the subject for participating in the trial.

m) That the subject's participation in the trial

is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority (ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

o) That records identifying the subject will be kept confidential and, to the extent permitted by

dated consent form updates and a copy of any amendments to the written information provided to subjects.

4.8.12 When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g. minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.

4.8.13 Except as described in 4.8.14, a non-therapeutic trial (i.e. a trial in which

there is no anticipated direct clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

4.8.14 Non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:

a) The objectives of the trial can not be met by means of a trial in subjects who can give informed consent personally.

b) The foreseeable risks to the subjects are low.

c) The negative impact on the subject's well-being is minimized and low.

d) The trial is not prohibited by law.

e) The approval / favourable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval / favourable opinion covers this aspect.

Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

4.8.15 In emergency situations, when prior consent of the subject is not possible, the

consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favourable opinion by the IRB/IEC, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see 4.8.10) should be requested.

Informed Consent Form Template for Clinical Studies

(This template is for either clinical trials or clinical research)
(language used throughout form should be at the level of a local student of class 6th/8th)

Notes to Researchers:

1. Please note that this is a template developed by the WHO ERC to assist the Principal Investigator in the design of their informed consent forms (ICF). It is important that Principal Investigators adapt their own ICFs to the outline and requirements of their particular study. **The logo of the Institution must be used on the ICF and not the WHO logo.**

2. The informed consent form consists of two parts: the information sheet and the consent certificate.

3. Do not be concerned by the length of this template. It is long only because it contains guidance and explanations which are for you and which you will not include in the informed consent forms that you develop and provide to participants in your research.

4. This template includes examples of key questions that may be asked at the end of each section, that could ensure the understanding of the information being provided, especially if the research study is complex. These are just examples, and suggestions, and the investigators will have to modify the questions depending upon their study.

5. In this template:
   - square brackets indicate where specific information is to be inserted
   - bold lettering indicates sections or wording which should be included
   - standard lettering is used for explanations to researchers only and must not be included in your consent forms. The explanation is provided in black, and examples are provided in red in italics. Suggested questions to elucidate understanding are given in black in italics.

TEMPLATE ON FOLLOWING PAGE

[YOUR INSTITUTIONAL LETTERHEAD]
Please do not submit consent forms on the WHO letter head

[Informed Consent form for _____]

Name the group of individuals for whom this informed consent form is written.Because research for a single project is often carried out with a number of different groups of individuals - for example healthcare workers, patients, and parents of patients - it is important that you identify which group this particular consent is for.

(Example: This Informed Consent Form is for men and women who attend clinic Z, and who we are inviting to participate in research on X. The title of our research project is "……")

You may provide the following information either as a running paragraph or under headings as shown below.

[Name of Principal Investigator]
[Name of Organization]
[Name of Sponsor]
[Name of Proposal and version]

This Informed Consent Form has two parts:

- **Information Sheet (to share information about the research with you)**
- **Certificate of Consent (for signatures if you agree to take part)**

You will be given a copy of the full Informed Consent Form

PART I: Information Sheet

Introduction

Briefly state who you are and explain that you are inviting them to participate in the research you are doing. Inform them that they may talk to anyone they feel comfortable talking with about the research and that they can take time to reflect on whether they want to participate or not. Assure the participant that if they do not understand some of the words or concepts, that you will take time to explain them as you go along and that they can ask questions now or later.

(Example: I am X, working for the Y Research Institute. We are doing research on Z disease, which is very common in this country. I am going to give you information and invite you to be part of this research. You do not have to decide today whether or not you will participate in the research. Before you decide, you can talk to anyone you feel comfortable with about the research.

There may be some words that you do not understand. Please ask me to stop as we go through the information and I will take time to explain. If you have questions later, you can ask them of me, the study doctor or the staff.)

Purpose of the research

Explain in lay terms why you are doing the research. The language used should clarify rather than confuse. Use local and simplified terms for a disease, e.g. local name of disease instead of malaria, mosquito instead of anopheles, "mosquitoes help in spreading the disease" rather than "mosquitoes are the vectors". Avoid using terms like pathogenesis, indicators, determinants, equitable etc. There are guides on the internet to help you find substitutes for words which are overly scientific or are professional jargon.

(Example: Malaria is one of the most common and dangerous diseases in this region. The drugs that are currently used to help people with malaria are not as good as we would like them to be. In fact, only 40 out of every 100 people given the malaria drug XYZ are completely cured. There is a new drug which may work better. The reason we are doing this research is to find out if the new drug ABX is better than drug XYZ which is currently being used.)

Type of Research Intervention

Briefly state the type of intervention that will be undertaken. This will be expanded upon in the procedures section but it may be helpful and less confusing to the participant if they know from the very beginning whether, for example, the research involves a vaccine, an interview, a biopsy or a series of finger pricks.

(Example: This research will involve a single injection in your arm as well as four follow-up visits to the clinic.)

Participant selection

State why this participant has been chosen for this research. People often wonder why they have been chosen to participate and may be fearful, confused or concerned.

(Example: We are inviting all adults with malaria who attend clinic Z to participate in the research on the new malaria drug.)

- ***Example of question to elucidate understanding:*** *Do you know why we are asking you to take part in this study? Do you know what the study is about?*

Voluntary Participation

Indicate clearly that they can choose to participate or not. State, what the alternative - in terms of the treatment offered by the clinic - will be, if they decide not to participate. State, only if it is applicable, that they will still receive all the services they usually do whether they choose to participate or not. This can be repeated and expanded upon later in the form as well, but it is important to state clearly at the beginning of the form that participation is voluntary so that the other information can be heard in this context.

(Example: Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive at this clinic will continue and nothing will change. If you choose not to participate in this research project, you will offered the treatment that is routinely offered in this clinic/hospital for disease Z, and we will tell you more about it later. You may change your mind later and stop participating even if you agreed earlier.)

- ***Examples of question to elucidate understanding:*** *If you decide not to take part in this research study, do you know what your options are? Do you know that you do not have to take part in this research study, if you do not wish to? Do you have any questions?*

Include the following section only if the protocol is for a clinical trial:

Information on the Trial Drug [Name of Drug]
1) give the phase of the trial and explain what that means. Explain to the participant why you are comparing or testing the drugs.
2) provide as much information as is appropriate and understandable about the drug such as its manufacturer or location of manufacture and the reason for its development.
3) explain the known experience with this drug
4) explain comprehensively all the known side-effects/toxicity of this drug, as well as the adverse effects of all the other medicines that are being used in the trial

(Example: The drug we are testing in this research is called ABX. It has been tested before with people who do not have malaria but who live in areas where malaria is common. We now want to test the drug on people who have malaria. This second research is called a "phase 2" trial.

The drug ABX is made by Company C. You should know that it has a few side effects. One of the side effects, or problems, is that you may feel tired for the first day after being given the drug. Also, 20% of the people who tried the drug in previous research experienced temporary swelling where the injection entered the skin. We know of no other problem or risks.

Some participants in the research will not be given the drug which we are testing. Instead, they will be given the drug XYZ, the drug which is most commonly used in this region to treat malaria. There is no risk associated with that drug and no known problems. It does not, however, cure malaria as often as we would like.)

Procedures and Protocol
Describe or explain the exact procedures that will be followed on a step-by-step basis, the tests that will be done, and any drugs that will be given. Explain from the outset what some of the more unfamiliar procedures involve (placebo, randomization, biopsy, etc.) Indicate which procedure is routine and which is experimental or research.Participants should know what to expect and what is expected of them. Use active, rather than conditional, language. Write "we will ask you to...." instead of "we would like to ask you to....".

In this template, this section has been divided into two: firstly, an explanation of unfamiliar procedures and, secondly, a description of process.

A. Unfamiliar Procedures
This section should be included if there may be procedures which are not familiar to the participant.

If the protocol is for a clinical trial:
1) involving randomization or blinding, the participants should be told what that means and what chance they have of getting which drug (i.e. one in four chances of getting the test drug).

(Example:. Because we do not know if the new malaria drug is better than the currently available drug for treating malaria, we need to compare the two. To do this, we will put people taking part in this research into two groups. The groups are selected by chance, as if by tossing a coin.

Participants in one group will be given the test drug while participants in the other group will be given the drug that is currently being used for malaria. It is important that neither you nor we know which of the two drugs you are given. This information will be in our files, but we will not look at these files until

after the research is finished. This is the best way we have for testing without being influenced by what we think or hope might happen. We will then compare which of the two has the best results.

The healthcare workers will be looking after you and the other participants very carefully during the study. If we are concerned about what the drug is doing, we will find out which drug you are getting and make changes. If there is anything you are concerned about or that is bothering you about the research please talk to me or one of the other researchers)

2) involving an inactive drug or placebo, it is important to ensure that the participants understand what is meant by a placebo or inactive drug.

(Example: A placebo or inactive medicine looks like real medicine but it is not. It is a dummy or pretend medicine. It has no effect on a person because it has no real medicine in it. Sometimes when we want to know whether a new medicine is good, we give some people the new medicine and some people the pretend or dummy medicine. For the research to be good, it is important that you do not know whether you have been given the real medicine or the pretend or dummy medicine. This is one of the best ways we have for knowing what the medicine we are testing really does.)

3) which may necessitate a rescue medicine, then provide information about the rescue medicine or treatment such as what it is and the criterion for its use. For example, in pain trials, if the test drug does not control pain, then intravenous morphine may be used as a rescue medicine.

(Example:. If we find that the medicine that is being used does not have the desired effect, or not to the extent that we wish it to have, we will use what is called a "rescue medicine." The medicine that we will use is called QRS and it has been proven to control pain. If you find that the drug we are testing does not stop your pain and it is very uncomfortable for you, we can use the rescue medicine to make you more comfortable.)

If the protocol is for clinical research:
Firstly, explain that there are standards/guidelines that will be followed for the treatment of their condition. Secondly, if as part of the research a biopsy will be taken, then explain whether it will be under local anesthesia, sedation or general anesthesia, and what sort of symptoms and side effects the participant should expect under each category.

(Example: You will receive the treatment of your condition according to national guidelines. This means that you will be (explain the treatment). To confirm the cause of your swelling, a small sample of your skin will be taken. The guidelines say that the sample must be taken using a local anesthesia which means that we will give you an injection close to the area where we will take the sample from. This will make the area numb so that you will not feel any pain when we take the sample.)

For any clinical study (if relevant):
If blood samples are to be taken explain how many times and how much in a language that the person understands. It may, for example, be inappropriate to tell a tribal villager that blood equal to a wine-glass full will be taken but it may be very appropriate to use pictures or other props to illustrate the procedure if it is unfamiliar.

If the samples are to be used only for this research, then explicitly mention here that the biological samples obtained during this research procedure will be used only for this research, and will be destroyed after _____ years, when the research is completed. If the tissues/blood samples or any other human biological material will be stored for a duration longer than the research purpose, or is likely to be used for a purpose other than mentioned in the research proposal, then provide information about this and

- ***Examples of question to elucidate understanding:*** *Can you tell me if you have understood correctly the benefits that you will have if you take part in the study? Do you know if the study will pay for your travel costs and time lost, and do you know how much you will be re-imbursed? Do you have any other questions?*

Confidentiality

Explain how the research team will maintain the confidentiality of data, especially with respect to the information about the participant which would otherwise be known only to the physician but would now be available to the entire research team. Note that because something out of the ordinary is being done through research, any individual taking part in the research is likely to be more easily identified by members of the community and is therefore more likely to be stigmatized.

(Example: With this research, something out of the ordinary is being done in your community. It is possible that if others in the community are aware that you are participating, they may ask you questions. We will not be sharing the identity of those participating in the research.

The information that we collect from this research project will be kept confidential. Information about you that will be collected during the research will be put away and no-one but the researchers will be able to see it. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is and we will lock that information up with a lock and key. It will not be shared with or given to anyone except [name who will have access to the information, such as research sponsors, DSMB board, your clinician, etc].)

- ***Example of question to elucidate understanding:*** *Did you understand the procedures that we will be using to make sure that any information that we as researchers collect about you will remain confidential? Do you have any questions about them?*

Sharing the Results

Where it is relevant, your plan for sharing the information with the participants should be provided. If you have a plan and a timeline for the sharing of information, include the details. You should also inform the participant that the research findings will be shared more broadly, for example, through publications and conferences.

(Example: The knowledge that we get from doing this research will be shared with you through community meetings before it is made widely available to the public. Confidential information will not be shared. There will be small meetings in the community and these will be announced. After these meetings, we will publish the results in order that other interested people may learn from our research.)

Right to Refuse or Withdraw

This is a reconfirmation that participation is voluntary and includes the right to withdraw. Tailor this section to ensure that it fits for the group for whom you are seeking consent. The example used here is for a patient at a clinic.

(Example: You do not have to take part in this research if you do not wish to do so and refusing to participate will not affect your treatment at this clinic in any way. You will still have all the benefits that you would otherwise have at this clinic. You may stop participating in the research at any time that you wish without losing any of your rights as a patient here. Your treatment at this clinic will not be affected in any way.)
OR

(Example: You do not have to take part in this research if you do not wish to do so. You may also stop participating in the research at any time you choose. It is your choice and all of your rights will still be respected.)

Alternatives to Participating
Include this section only if the study involves administration of investigational drugs or use of new therapeutic procedures. It is important to explain and describe the established standard treatment.

(Example: If you do not wish to take part in the research, you will be provided with the established standard treatment available at the centre/institute/hospital. People who have malaria are given....)

Who to Contact
Provide the name and contact information of someone who is involved, informed and accessible (a local person who can actually be contacted. State also that the proposal has been approved and how.

(Example: If you have any questions you may ask them now or later, even after the study has started. If you wish to ask questions later, you may contact any of the following: [name, address/telephone number/e-mail])

This proposal has been reviewed and approved by [name of the local IRB], which is a committee whose task it is to make sure that research participants are protected from harm. If you wish to find about more about the IRB, contact [name, address, telephone number.]). It has also been reviewed by the Ethics Review Committee of the World Health Organization (WHO), which is funding/sponsoring/supporting the study.

- *Example of question to elucidate understanding: Do you know that you do not have to take part in this study if you do not wish to? You can say No if you wish to? Do you know that you can ask me questions later, if you wish to? Do you know that I have given the contact details of the person who can give you more information about the study? Etc.*

You can ask me any more questions about any part of the research study, if you wish to. Do you have any questions?

PART II: Certificate of Consent
This section should be written in the first person and have a statement similar to the one in bold below. If the participant is illiterate but gives oral consent, a witness must sign. A researcher or the person going over the informed consent must sign each consent. The certificate of consent should avoid statements that have "I understand...." phrases. The understanding should perhaps be better tested through targeted questions during the reading of the information sheet (some examples of questions are given above), or through the questions being asked at the end of the reading of the information sheet, if the potential participant is reading the information sheet him/herself.

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Print Name of Participant_____

Signature of Participant _____

Date _____
Day/month/year

If illiterate
A literate witness must sign (if possible, this person should be selected by the participant and should have no connection to the research team). Participants who are illiterate should include their thumb-print as well.

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness_____ AND Thumb print of participant

Signature of witness _____

Date _____
Day/month/year

Statement by the researcher/person taking consent
I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:
1.
2.
3.
I confirm that the participant was given an opportunity to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

Print Name of Researcher/person taking the consent_____

Signature of Researcher /person taking the consent_____

Date _____
Day/month/year

Informed Consent Process

- Consent in the content of medical profession implies to permission by the patient to perform an act on his body either for diagnosis or therapeutic procedure.
- It is a process of information exchange that may include reading and signing the informed consent document.
- Institutional Review Boards (IRB), clinical investigators, and research sponsors all share responsibility for ensuring that the informed consent process is adequate.
- The clinical investigator is responsible for ensuring that informed consent is obtained from each research subject before that subject participates in the research study.
- FDA does not require the investigator to personally conduct the consent interview.
- In addition to signing the consent, the subject/representative should enter the date of signature on the consent document, to permit verification that consent was actually obtained before the subject began participation in the study

- A copy of the consent document must be provided to the subject and the original signed consent document should be retained in the study records.
- The IRB should be aware of who will conduct the consent interview.

Goals:

The goal of the informed consent process is to provide people with sufficient information so they can make informed choices about whether to begin or continue participation in clinical research.

Types of ICF:

There are three principal forms of (informed) consent:

i- Presumed consent: in which participants are presumed to have consented to participation in the research unless they indicate otherwise.

ii- Verbal consent: in which the researcher verbally informs participants and receives oral confirmation of consent.

- Written consent: in which the researcher provides written information regarding the research project to participants and retains a signed copy of this consent form.

Components of ICF:

- Informed consent should involve the provision (تقدیم، تدارک) or collection of information on:
  - Name and contact details of researcher
  - Name and contact details of participant
  - Aims and objectives of the research project
  - Role of the participant in the research project
  - Treatment of material/information collected
  - Potential risks to the participant
  - Sources of advice/help/support/treatment
  - Voluntary participation and freedom to withdraw
  - Signature and date of researcher and participant

Basic Elements of ICF: 5M

- The following elements are required in all consent

forms as per FDA:

- A statement that the study involves research
- An explanation of the purposes of the research
- The expected duration of the subject's participation
- A description of the procedures to be followed and identification of those being done for research purposes
- Identification of any experimental procedures
- A description of any reasonably risks or discomforts to the subject.
- A description of any benefits to the subject or to others
- A statement describing the extent to which confidentiality of records identifying the subject will be maintained
- A statement that the FDA may inspect the records.
- For research involving more than minimal risk, an explanation as to whether any compensation exists if injury occurs.

- For research involving more than minimal risk, an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist.
- An explanation of whom to contact for answers to pertinent questions about research and research subject's rights. At least one contact's name and phone number must be other than the investigator's or study personnel.
- A statement that participation is voluntary.
- A statement that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled.
- A statement that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
- Eligibility for medical care is based upon the usual eligibility policy and is not guaranteed by participation in a research study.
- A copy of this consent form will be placed in your medical record.

- Your records may be reviewed by quality assurance and federal regulatory authorities as well as the Institutional Review Board.

General Requirement:

- No investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative.

- The information that is given to the subject or the representative shall be in language understandable to the subject or the representative.

- No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's rights.

- The IRB should ensure that technical and scientific terms are adequately explained or that common terms are substituted.

- The IRB should ensure that the informed consent document properly translates complex scientific concepts into simple concepts that the typical subject can read.

Example: Format of informed consent form subjects participating in clinical trial:

Study title: ..... Study number: .....

Subject's initial: ..... Subject's name: .....

Date of birth/age: ..

1. I confirm that I have read and understand the information sheet dated ..... for the above study and have had the opportunity to ask questions.

2. I understand that my participation in the study is voluntary and I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

3. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose.

4. I agree to take apart in the above study:---

Signature of the Subject: Date:

Signature of investigator: Date:

Study investigator's name: Date:

Signature of witness:

Name of witness:

Introduction:

- Data management includes all aspects of data planning, handling, analysis, documentation and storage and takes place during all stage of a study.
- The objective is to create a reliable database containing high quality data.
- Data management is a too often neglected part of study design, and includes:
  - Planning the data needs of the study
  - Data collection
  - Data entry
  - Data validation and checking
  - Data manipulation
  - Data files backup
  - Data documentation

- Each of these processes requires thought (تفكر، تمركز) and time, each requires pains taking attention to detail.
- The main element of data management are

database files.

Database files contain text, numerical, images and other data in machine readable form. Such files should be viewed as part of a database management systems.

- DBMS (System) which allows for a board range of data functions, including data entry, checking, updating, documentation, and analysis.

1. Data collection:

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

→ Existing systems

→ Import lab results

- Scan results
- And other digital data

2. Data Management Software (Data analysis):

- Many DBMS's are available for personal computers. Options include:

i- Spread sheet (e.g. Excel, SPSS data sheet)

ii- Commercial database program (e.g. Access)

iii- Specialty data entry program (e.g. Epi Data)

i- Spreads sheet are to be avoided for all but the smallest data systems, since they are unreliable and easily corrupted.

ii- Commercially database programs are expensive, tend to be large and slow and often lack controlled data-entry facilities

iii- Specialty data entry programs are ideal for data entry and storage. For example using

Epi Data because it is fast, reliable, allows for controlled data-entry, and is open-source.

- Epi Data refers to a group of applications used in combination for creating documented data structures and analysis of quantitative data.

The Epi Data Association, which created the software was created in 1999 and is based in Denmark.

3. Data Entry and Validation:

- Data processing errors are errors that occur after data have been collected.
- This is distinct from measurement errors, which are differences b/w the true state of affairs and what appears on the data collection form.
- Examples of data processing errors

- Transpositions (e.g. 19 becomes 91 during data entry)
- Copying errors (e.g. 0 (zero) becomes "O" during data entry)

- Coding errors (e.g. a racial group gets improperly coded because of changes in the coding scheme)
- Routing errors (e.g. the interviewer asks the wrong question or asks questions in the wrong order)
- Consistency errors (contradictory responses, such as the reporting of a hysterectomy after the respondent has identified himself as a male)
- Rang errors (responses outside of the range of plausible answers, such as a reported age of 290)
- To prevent such errors, you must identify the stage at which they occur and correct the problem.

- Methods to prevent data entry errors include:
1. Manual checks during data collection (e.g. checks for completeness, handwriting legibility)

2. Range and consistency checking during data entry (e.g. preventing impossible results, such as ages greater than 110).

3. Double entry and validation following data entry.

4. Data backup and storage:

There are two kinds of computer users.

i- Those that have lost a major chunk of data, and

ii- those who are going to lose a major chunk of data.

- Data loss can be due to natural disasters, human error and computer failure.
- You've worked to hard to collect and enter data, and you must now take care of it.
- The most common loss of data among students is due to loss of data somewhere on the computer. The best way to prevent such loss is to know the physical allocation of your data (local drive, removable media, network) and to use logical filenames. All too often students save files to unknown locations (usually the default set up by the program).
- But never find saved files or have the saved

files deleted by the local area network as a part of routine data clean up.

- Always Be Aware Of The Location And Path "Folder" To Which Files Are Being Written.
- In addition, it is essential to back-up all data (e.g data files, code books, software setting, computer programs, word processing documents).
- Back up System Sentail manual or automated copying of files to removable media (e.g. floopy disks, Zip disks, tape) or to network storage.
- Back up procedures should be thoroughly tested to ensure archived files remain uncorrupted and can be restored.
- Procedures should be written up so that personnel unfamiliar with back up and restore methods could follow them from scratch.
- Health researcher must be aware of confidentiality and ethical requirements when working with research files.
- This is especially important when data contain

personal identifiers and medical information.
- It is each researcher's duty to make him or herself aware of local, national, and international laws governing use of health data.

5. Documentation:

Documentation should include:

i- The objectives and methods of the study.

ii. detailed of events and activities

iii- For each data collection activity, a record of the detailed procedures used and an accounting of the number of subjects in scope, the number selected for data collection, and the disposition for all subjects (by category, e.g. could not contact, refusal). This material should have cross references to original sources (e.g. computer runs) tenable verification when necessary.

iv- Lists and descriptions of all interventions applied and materials used (e.g. intervention materials, training materials)

V. Documentation on all computerized data and final analyses (information on data sets, variables, computer runs).

□ Safety Monitoring in clinical trials: [5,10]

- Definition:

- Can be defined as a planned, ongoing process of reviewing data collected in a clinical trial with the primary purpose of protecting the safety of trial participants, the credibility of the trial, and the validity of trial results.

- As appropriate, monitoring might be conducted by the investigator the sponsor (e.g, medical monitor) or by an independent monitoring board.

- Persons affected:

1. Principal investigators
2. Institutional Review Board
3. Other oversight committees charged with evaluating the integrity and safety of data collected during human subjects research.

- Data and safety monitoring is required for all types of clinical trials, including physiologic,

toxicity and dose-finding studies (phase I); efficacy studies (phase II); efficacy, effectiveness, and comparative trials (phase III).

- Monitoring should be commensurate (متناسب) with risks and a variety of types of monitoring may be anticipated (پیش بینی کردن).

- Depending on the nature, size and complexity of the clinical trial in many cases, the principal investigator would be expected to perform the monitoring function.

- It is recommended that all clinical trials, even those that pose little likelihood of harm, should consider an external monitoring body.

Purpose:

To establish guidelines for protecting the safety of participants in human subjects research and ensuring validity, integrity of

data collected by appropriate DSM.

□ Policy:

This policy is to ensure that human subjects research includes provisions for monitoring data to ensure the safety of participants and that the IRB has criteria by which to evaluate whether research submitted for review adequately protects human subjects.

The level and formality of monitoring should increase as the level of risk increases.

Data and Safety Monitoring Board (DSMB):

- A DSMB is an independent group of individuals with pertinent (= skill) expertise that reviews on a regular basis.
- Unblinded data from protocols involving human subjects research to assure the continuing safety of research subjects, relevance of the study question, appropriateness of the study, and integrity of the accumulating data.

- The DSMB reviews data independently from the investigator(s) and IRB to:

i: Determine whether the accumulating data support continuing the trial, whether

ii- Study procedures should be changed, or whether the trial should be halted for reasons relating to the safety of the subjects, the efficacy of the treatment under study, or adequate study performance (e.g. poor recruitment of subjects).

- Human subjects research that require a Data Safety Monitoring Board include:

1. Procedures that involve Blinding
2. Research that involves multiple sites, research that targets vulnerable subjects, or
3. Employs high-risk interventions
4. The data and safety monitoring functions and oversight of such activities are distinct from the requirement of study review and approval by the IRB.

Responsibilities:

1. Principal Investigators: MR. PES

i- Ensuring the IRB is provided sufficient information to evaluate the appropriateness of a data and safety plan to ensure participants are appropriately protected.

ii- And responsible for developing and presenting to the IRB a plan to monitor the data to ensure participant's welfare and safety are adequately protected.

iii - Setting intervals at which the data will be evaluated are timely and effective.

iv- Identifying a mechanism for reporting the finding (including DSMB reports) in a timely fashion to the IRB, the sponsor and as appropriate federal agencies.

v. Reporting findings to the participants, if applicable to allow them opportunity to re-affirm their willingness to continue participation.

MRRP 4

2. Data and Safety Monitoring Board:

i- All investigators involved in the research, is responsible for providing impartial (بطريقة نزيهة) evaluation of the data at pre-determined intervals and reporting in a timely fashion the outcome of those evaluations to:

- Sponsors
- Institutional Review Board (IRB)

ii- Review the research protocol and plans for data and safety monitoring.

iii- Evaluate the progress (تقدم) of interventional trials), including periodic assessments of data quality and timeliness, participant recruitment (تعيين), accrual and retention.

- Participant risk versus benefit, performance of trial sites, and other factors that can affect study outcome.

iv. Monitoring should also consider factors external to the study when interpreting the data, such as scientific or therapeutic developments that may have an impact (اثر) on the safety of the participants or the ethics of the study.

v. Make recommendations to the IRB, and investigators concerning continuation or conclusion (تابان) of the trial (s).

3- Sponsors:

i- Reporting to the IRB any findings that could affect the safety of participants which could influence the conduct of the study within the time frame outlined in the clinical trial agreement with the institution.

ii- Reporting to the IRB any findings that could impact subject safety with two years of study closure.

4. The IRB:

i. Modifications to that plan.

-is responsible for reviewing the plan to ensure Subject safety.

ii. Require a third party to implement data and safety monitoring

iii. - Approve these plan.

iv. They can have the authority to stop a research study in progress, remove individual subjects from a study, and take what ever steps are necessary to protect the safety and well-being of research subjects.

400

GLOSSARY

1. Adverse drug reaction (ADR): In the preapproval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established, all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. Regarding marketed medicinal products: A response to a drug that is noxious and unintended and that occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (see the ICH guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

2. Adverse event (AE): An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

3. Amendment (to the protocol): See Protocol Amendment.

4. Applicable regulatory requirement(s): Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products of the jurisdiction where trial is conducted.

5. Approval (in relation to institutional review boards (IRBs)): The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, good clinical practice (GCP), and the applicable regulatory requirements.

6 .Audit: A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).

7.Audit certificate: A declaration of confirmation by the auditor that an audit has taken place.

8. Audit report: A written evaluation by the sponsor's auditor of the results of the audit.

9. Audit trail: Documentation that allows reconstruction of the course of events.

10. Blinding/masking: A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single blinding usually refers to the subject(s) being unaware, and double blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

11. Case report form (CRF): A printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each trial subject.

12.Clinical trial/study: Any investigation in human subjects intended to discover or verify the clinical, pharmacological, and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

13.Clinical Trial/Study Report: A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the ICH Guidance for Structure and Content of Clinical Study Reports).

14.Comparator (Product): An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.

15.Compliance (in relation to trials): Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.

16.Confidentiality: Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity.

17.Contract: A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

18.Coordinating Committee: A committee that a sponsor may organize to coordinate the conduct of a multicenter trial.

19.Coordinating Investigator: An investigator assigned the responsibility for the coordination of investigators at different centers participating in a multicenter trial.

20.Contract Research Organization (CRO): A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

21.Direct Access: Permission to examine, analyze, verify, and reproduce any records

and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsors, monitors, and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information.

22.Documentation: All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records; and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

23.Essential Documents: Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (see section 8. "Essential Documents for the Conduct of a Clinical Trial").

24.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.

25.Independent Data Monitoring Committee (IDMC) (Data and Safety Monitoring Board, Monitoring Committee, Data Monitoring Committee): An independent data monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

26.Impartial Witness: A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

27.Independent Ethics Committee (IEC): An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical/scientific professionals and nonmedical/nonscientific members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favorable opinion on the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.
The legal status, composition, function, operations, and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in this guidance.

28.Informed Consent: A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.

29.Inspection: The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CROs) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

30.Institution (medical): Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

31.Institutional Review Board (IRB): An independent body constituted of medical, scientific, and nonscientific members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trials, of protocols and amendments, and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

32.Interim Clinical Trial/Study Report: A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

33.Investigational Product: A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

34.Investigator: A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. See also Subinvestigator.

35.Investigator/Institution: An expression meaning "the investigator and/or institution, where required by the applicable regulatory requirements."

36.Investigator's Brochure: A compilation of the clinical and nonclinical data on the investigational product(s) that is relevant to the study of the investigational product(s) in human subjects.

37.Legally Acceptable Representative: An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

38.Monitoring: The act of overseeing the progress of a clinical trial, and of ensuring

that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), GCP, and the applicable regulatory requirement(s).

39.Monitoring Report: A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor's SOPs.

40.Multicenter Trial: A clinical trial conducted according to a single protocol but at more than one site, and, therefore, carried out by more than one investigator.

41.Nonclinical Study: Biomedical studies not performed on human subjects.

42.Opinion (in relation to Independent Ethics Committee): The judgment and/or the advice provided by an Independent Ethics Committee (IEC).

43.Original Medical Record: See Source Documents.

44.Protocol: A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guidance, the term protocol refers to protocol and protocol amendments.

45.Protocol Amendment: A written description of a change(s) to or formal clarification of a protocol.

46.Quality Assurance (QA): All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded). and reported in compliance with GCP and the applicable regulatory requirement(s).

47.Quality Control (QC): The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trialrelated activities have been fulfilled.

48.Randomization: The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

49.Regulatory Authorities: Bodies having the power to regulate. In the ICH GCP guidance, the expression "Regulatory Authorities" includes the authorities that review submitted clinical data and those that conduct inspections (see section 1.29). These bodies are sometimes referred to as competent authorities.

50.Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR): 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, or
! Is a congenital anomaly/birth defect.
(See the ICH guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.)

51.Source Data: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

52.Source Documents: Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).

53.Sponsor: An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical trial.

54.Sponsor-Investigator: An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

55.Standard Operating Procedures (SOPs): Detailed, written instructions to achieve uniformity of the performance of a specific function.

56.Subinvestigator: Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). See also Investigator.

57.Subject/Trial Subject: An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

58.Subject Identification Code: A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial-related data.

59.Trial Site: The location(s) where trial-related activities are actually conducted.

60.Unexpected Adverse Drug Reaction: An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product). (See the ICH Guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.)

61.Vulnerable Subjects: Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

62.Well-being (of the trial subjects): The physical and mental integrity of the subjects participating in a clinical trial.