# GENERAL PROCEDURE OF DRUG DEVELOPE-MENT

We found Lead Compound (Which Show Pharmacological Action)

↓

Starts drug developement process

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Non-Clinical / Pre Clinical trials (on animals)

↓

All application INDA [Investigational New drug Application] to permission for clinical trials

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Rieview of FOA (food & drug Administration)

- Approved
- Not approve
- Approvable

↓

Clinical trials (Phase-I, 2, 3, 4)

↓

Pharmacovigilance

(When a drug introduced in a market then drug is under pharmacovigilance to check side-effect, reactions to ensure saffety and Quality)

# DRUG DEVELOPEMENT TEAMS

Drug developement is the process of introducing a new drug to the market once a lead compound has been identified through the process of drug discovery.

## 1. Drug discovery Project Team

→ The primary responsibility of this group is to identify lead compounds.

→ One a lead compound identified, the discovery team further includes bioanalytical chemists, pharmacokinetics, and toxicology experts for the developement of the drug candidate.

## 2. Pre - Clinical drug developement project team

The responsibilities of this group is;

→ to start the pre-clinical developement

→ to prepare an IND and to submit the mandatory documents to the FDA.

### Faculty Included

- Monggement - assigned project team leader
- Coordinator
- RA and QA professionals
- Clinical trial team
- Analytical Chemists
- Manufacturing and marketing analysts.

## Clinical Drug developement project team

This team includes;

- Physicians
- Clinical Pharmacokinetics
- Clinical Research associates
- Marketing team
- Drug product production
- QA Statisticians

## 4. Marketing Team

This team provide stategies to introduce a New drug in a market and determines whether a drug has potential ~~to~~ in comparison to other company's product.

## 5. Regulatory Affair team

The main responsibility of this team is to maintain rule and regulations establish by federal food drug and Cosmetic Act.

# NON CLINICAL DRUG DEVELOPEMENT

These are the labortary test, which is performed on the animals while developing a New drug.

## Types of Non- Clinical trials

### 1. In Silico

These are performed on compute or via computer simulation by using chemical structures.

In Vivo

These trials are performed on a whole living organism. eg. animals, humans and plants.

3. In-Vitro

These are performed in a controlled environment outside of a living organism.

eg. use of hepatocyte (cells from the liver) cultures for metabolism studies.

The main aims of Pre-Clinical trials are;

→ Assesment of Efficacy

→ Toxicology

→ Safety

→ To check how drug is delivered in the body

→ To check how will the body react

## PHARMACOLOGICAL STUDIES

1. Pharmacokinetic Profile Study

It deals with Study of ADME. Generally, ADME Studies are conducted in two species, usually rats and dogs, repeated with different dose levels in male & females.

The main task of Pharmacokinetic Studies is to find an optimal dose level and to provide information about the dose effect relationship.

Metabolism Study → The drug metabolism Studies needed to characterize the fate (whether the compound is changed

id to what) of a lead or drug candidate in the body.

Metabolism Study carried out by both;

In-vitro

In-vivo

2) Pharmacodynamic Profile Study

a) Primary Pharmacodynamic Study → Study Physiological effects of the drug.

b) Secondary Pharmacodynamic Study → Study Mechanism of drug Action

c) Safety Pharmacodynamic Studies → They are conducted to identify possible undesirable pharmacodynamic effects (Adverse effects) of a compound.

There are three types of Safety Pharmacological Studies;

→ Core battery Study

The core battery studies is mandatory in order to investigate before first administration in humans. The core battery means organ systems which are important in life-supporting functions (includes cardiovascular, respiratory, and Central Nervous System).

→ follow Up Studies

The follow up studies provide a deeper insite into kinetic conditions and potential repeat dose administrations on a suitable animal species.

Supplemental Studies → In Supplemental Studies organs system which are not addressed in the core battery are investigated. This is done with other major organ systems such as gastrointestinal, renal or the immune system.

## TOXICOLOGICAL STUDIES

### I.) Acute Toxicity (Single dose) and Chronic toxicity (Repeated -dose) Study

Acute toxicity is usually occur by administration of a single high dose of test drug to rodents. Both rat and mice (male and female) are usually employed.

Repeated-dose toxicity studies should be carried out in at least two species, out of which one should be a non-rodent.

### 2) Reproductive Toxicity Study

These studies evaluate male and female fertility, embryo and fetal death, Newborn, the lactation process, care of young. These reproductive paromeders have been evaluated in three segments:

Segment I → evaluates fertility and general performance in rats.

Segment II → Commonly conducted in rats and rabbits, determines the embryo toxicity or teretogenic effect of drug candidate.

Segment III → Normally conducted only in rats, evaluate the effects of drugs candidate on late fetal developement, labor and delivery, lactation and growth of the Newborn.

### 3) Genotoxicity / Mutagenecity Study

Mutagenecity study aim to determine whether the drug candidate is capable of inducing DNA damage, either by

inducing alterations in chromosomal Structures. These studies are carried out by both in vitro and in vivo methods.

4) Carcinogenicity Study

Long-term carcinogenecity study is carried out, if the drug is used for administration over prolonged period (more than 6 months). In such type of study animal is observed for the developement of tumours.

Two types of dose is used for the study;

1. Maximum tolerated dose (MTD)
2. 25-fold AUC

5) Immunotoxicity Study

In this, ability of drug compound to induce immune response is studied. Immunotoxicity which may be investigated during repeated dose toxicity studies. It identifies adverse effects of drugs on the immune system as immunosupression which can lead to infectious disease.

6) Toxicokinetic Studies

Toxicokinetic studies may be conducted as separate or supportive studies. Toxicokinetic Studies should be performed according to GLP.

# INVESTIGATIONAL NEW DRUG

IND ( Investigational New drug ) is a document submitted to the FDA (food and drug Administration) in the united States to request permission to start human clinical trials for a New drug.

The purpose of an IND is to;

→ ensure the safety of the drug product.

→ Gather data on the effectiveness of drug product.

→ Meet the FDA's requirements for conducting human clinical trials.

## Classification of IND

1. Commercial

Permits sponser to collect data clinical safety and effectiveness needed for the marketing in the form of NDA.

2. Research ( Non - Commercial)

Permits the sponser to use drug in research to obtained advance scientific knowledge of new drug. No plan to market the drug.

## Types of IND Applications

1. Investigator IND application

In this an application is submitted by an physician, who both initiates and conduct an investigation

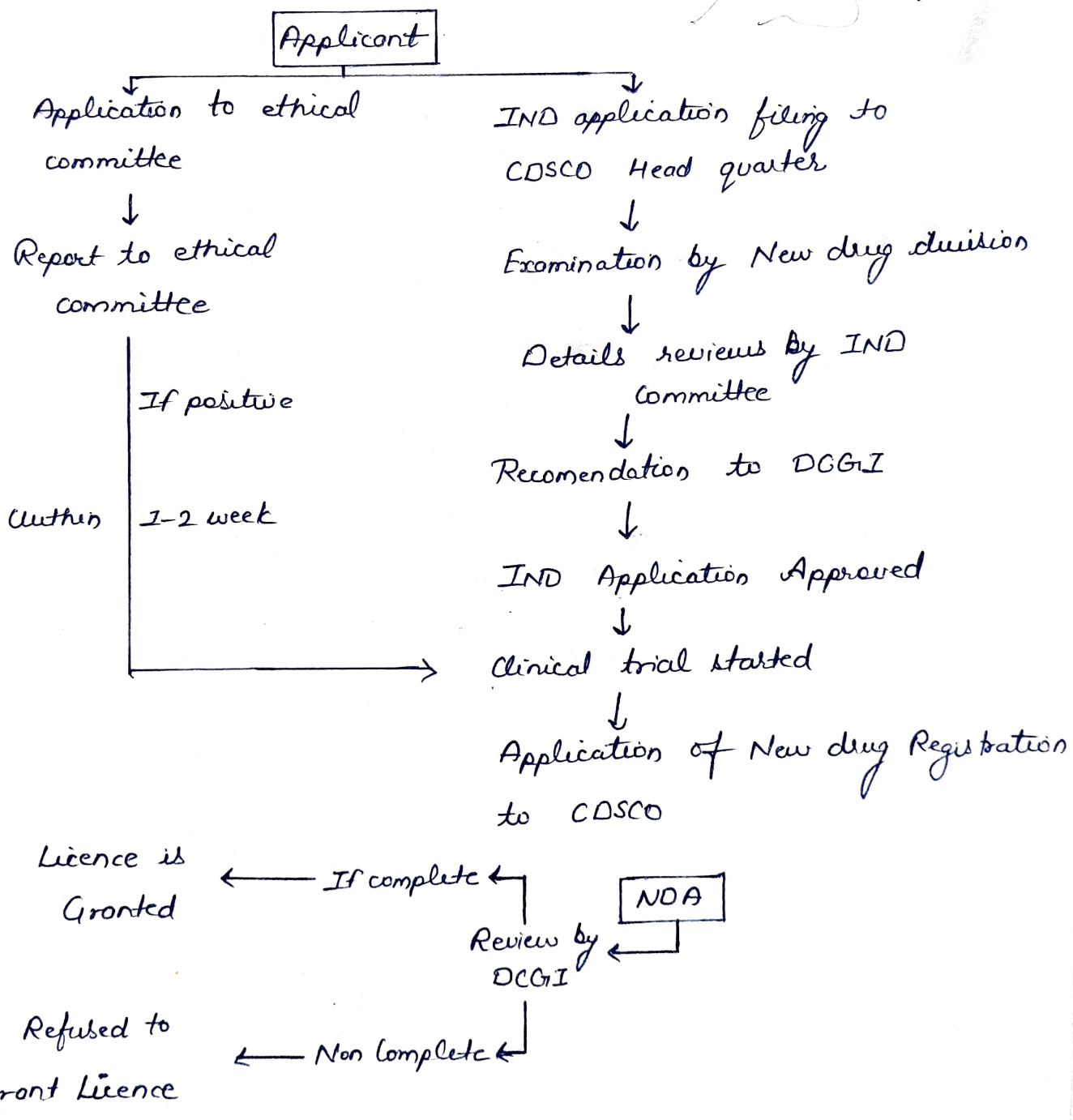
2. Emergency Use IND Application

This application allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of IND application

3. Treatment IND Application

This application is submitted for experimental drugs showing promise in clinical testing for serious life-threatening conditions.

- Procedure for approval



# INVESTIGATOR'S BROCHURE (IB)

An investigator's brochure (IB) is a document that provide information about a drug to investigators conducting clinical trials. It includes;

→ Product description
→ Pharmacology & toxicology data
→ Clinical experience and trial results
→ Safety information
→ Dosage and administration instructions
→ Precaution & warning for vulnerable populations
→ Regulatory status and approvels

## Contents of IB

1. Table of Contents
2. Summary - not exceeding 2 Pages, highliting the significant physical, chemical, Pharmaceutical, pharmacological, toxicological, pharmacokinetic and clinical information available of IP
3. Introduction - Chemical Name, Active ingredient, Pharmacological class, Therapeutic Indication.
4. Description of IP - Physical, chemical and Pharmaceutical properties of IP, Storage and handling of IP
5. Non Clinical Studies - The results of all relavent non-clinical pharmacology, toxicology, pharmacokinetic and investigational product metabolism studies should be provided in summary form.

→ Non Clinical Pharmacology

A summary of the pharmacological aspects of the

vestigational product studied in animals should be included.

→ Pharmacokinetic and Product Metabolism in Animals

A summary of the pharmacokinetic (ADME) and biotransformation study should be given.

→ Toxicology

A summary of adverse effects found in developement of drug should be given.

6. Effects in humans → known effects of the investigational ~~know~~ products in human should be provided, including information on pharmacokinetics, metabolism, Pharmacodynamics, dose response, safety and efficacy.

7. Summary of data and Guidance for Investigator: This Section should contain non-clinical and clinical data of IP - IB provides the investigator a clear understanding of possible risk, adverse reaction, observation and precautions needed for clinical trial.

# NEW DRUG APPLICATION

The New drug Application (NDA) is an application submitted to FDA for permission to market a new drug product in the united states.

Aims of NDA

→ Safety and effectiveness of drug

→ Benifits overweigh risks

→ Is the drug's proposed labelling appropriate and what should it contain.

## NDA Contains :

Introduction : Brief description of the drug and the therapeutic class to which it belongs.

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Chemical and pharmaceutical information

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Animal Pharmacology

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Animal Toxicology

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Human Clinical Pharmacology (Phase I)

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Therapeutic exploratory trials (Phase II)

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Therapeutic confirmatory trials (Phase III)

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Special Studies of geriatrics, pediatrics, pregnant or nursing women

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Regulatory Status in other countries

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Prescribing information

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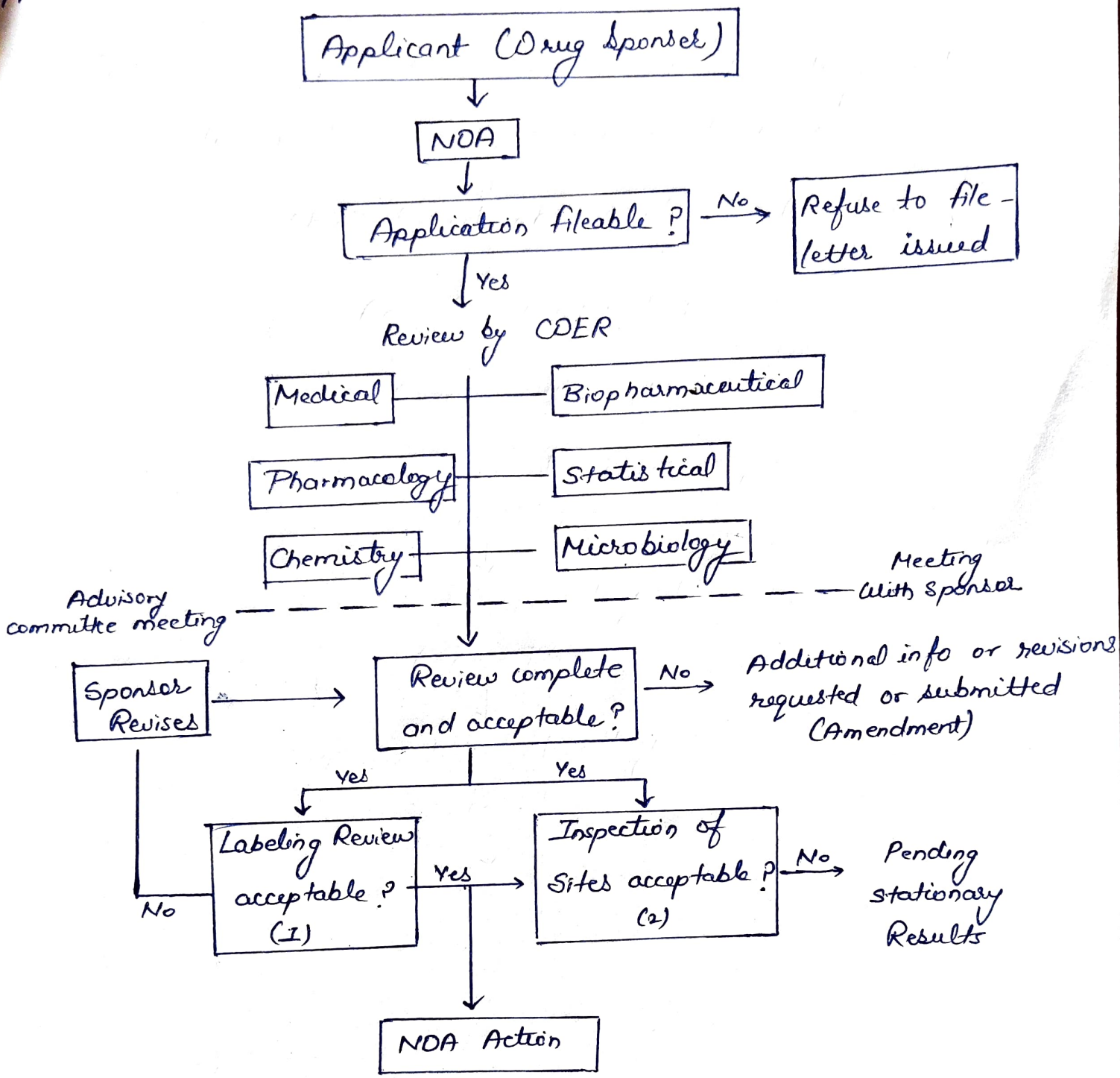
Samples and Testing Protocols

## NDA Review Process :

Once the application is submitted, the FDA has 60 days to conduct a preliminary review. If everything is found to be acceptable and they communicate the acceptance of the

application .



# BIOEQUIVALENCE STUDIES

Bioequivalence Studies are special type of Studies where two drugs or two sets of formulation of the same drug are compared to show that they have nearly equal bioavalability and Pharmacokinetic / Pharmacodynamic parameters.

Bioavailability → It means the rate and time to which the active ingredient is absorbs froms drug and reaches to the site of Action.

Equivalance → It is a relative term that compares drug products with respect to a specific characteristic or function.

Types of Equivalences

1. Chemical Equivalence

Two or more drug contain some active ingredient (API) in the same amount, called chemical equivalence.

2. Pharmaceutical Equivalence

Comparison of two or more drugs that have same strength, quality, purity, content uniformity but containing different excipients.

3. Bioequivalance

This term denotes that drug substance in two or more identical dosage forms, reaches in systemic circulation at (same) same rate and time.

4. Therapeutic Equivalence

Comparison of two or more drug products that contain the same active ingredient and same pharmacological effect and can control the disease to the same extent & time.

# CLINICAL RESEARCH PROTOCOLS

A clinical trial protocol is detailed document that outlines the plan for a clinical trial. It is document that states the background, objectives, rationale, design, methodology and statistical considerations of the study.

The protocol means;

- To clarify the research question
- To compile existing knowledge
- To formulate a hypothesis and objectives
- To decide about a study design
- To clarify ethical considerations
- To apply for funding
- To have a guideline and tool for research team.

Parts of the protocol:

1. Title page

Title page introduces the document, its title precise number, sponsor and author to reader

2. Signature page

Significance page of all healthcare proffesionals in the trial must be given.

3. Content Page

This help navigation through the document.

4. List of Abbreviations

All abbreviations used should be listed and defined.

5. Introduction / Summary

The summary should be only one to two pages long. It should give the reader sufficient information.

6. Objectives

Each objective mentioned in protocal, should have a corresponding discuss in the Statistical Section.

7. Background / Rationale

All protocals requires a section in which background is detally mentioned.

8. Eligibility Criteria

Eligibility Creteria must be mentioned.

9. Study Design / Methods

The study design section should contain a stepwise description of all procedures required by the study.

10. Adverse effects

These are the terms commonly associated with drugs. They are used by Nurses and doctors.

# DATA PRESENTATION FOR FDA SUB-MISSIONS

Study data standards describe a standard way to exchange clinical and non clinical study data. These standards provide a consistent framework for orgaxing study data, including templates for datasets, standard name for variables. When preparing data for FDA submission, it's essential to present in a clear, concise and well organised manner. Here are some points make better data presentation;

1. Follow FDA Guidelines

Learn the FDA regulations, such as 21 CFR part 11, and guidance documents like the 'FDA data standards catalog'.

2. Use standardized formats

Utilize standardized formats like CDISC (Clinical data interchange standards Consortium) for data submission.

3. Organize data logically

Present data in a logical and easy-to-follow order, using clear headings and labels.

4. Include Relevant information

Provide all Necessary data, including;

- Study protocol
- Study results
- Adverse event data
- Labortary data

5. Use Visual aids

Use visual aids like tables, figures and graphs for better understanding.

6. Ensure data quality

Verify data accuracy, completeness and consistency.

7. Use electronic submissions

Submit data electronically, using formats like PDF, XML, or SAS transport files.

8. Validate data

Validate data to ensure it meets FDA requirements.

Some Common data presentation formats for FDA Submission:

1. NDAs (New drug Application) → for new drug approvals
2. BLAs (Biological License Applications) → for biological product approvals
3. ANDAs (Abbreviated New drug Applications) → for generic drug approvals
4. Periodic Safety update reports → for post-marketing safety updates

# MANAGEMENT OF CLINICAL STUDIES

Clinical trials management is most simply defined as the process that an organisation follow to ensure that quality is delivered efficiently and punctually.

It refers to a standards-driven process that a

a project manager initiates and follows in order to succesfully manage clinical trials.

It is possible to reduce the total cost of a clinical trial by 60-90%. without compromising the scintific validity of the results.

## Life cycle of Clinical Trial project

A more accurate control, is ensured by breaking down the life cycle of each clinical trial project into 4 phases;

- Conceptual
- Planning
- Implementation
- Analysis

## Clinical Trial Protocol

Already covered !