

IND Application

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 investigation 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.

Criteria for application:

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

① New indication

① change in the approved route of administration or dosage level

① change in the approved patient population (eg paediatric) or in a population at greater or increase of risk

① Significant change in the proportion 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.

Application categories: Commercial and 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) and 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.

there are three types of IND →

1. Regular IND →

① 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 drugs in an emergency situation that does not allow time for submission of an IND in accordance with 21 CFR, 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 immediately 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, manufacturing, 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.

IND CHART

Applicant (Drug sponsor)

IND

Review by CDER

Medical Chemistry pharmacology / Toxicology Statistical

Safety Review Sponsor submits new data

Safety acceptable for study to proceed No Clinical Hold decision

Complete Reviews

Notify sponsor

Reviews complete No Sponsor notified of deficiencies

No deficiencies Study ongoing

IND application contents:

1. Cover sheet / application form
2. Table of contents.
3. Introductory statement.
4. General investigational plan.
5. Investigator brochure.
6. protocols.
7. chemistry manufacturing and control info
8. pharmacology and toxicology info.
9. Previous human experience with drug.
10. Additional information as required by FDA.

1) Application form:

- ① Required for initial IND and all subsequent submissions.
- ① Provides basic info about sponsor and submission contents.
- ① Must be signed and dated.

2) Introductory statement:

- ① Drug name, structure, pharmacological class, development history, foreign testing.

3) General investigational plan:

- ① Summary of studies anticipated in first year.
- ① Study rationale.

4) Investigator brochure:

- ① package insert.
- ① Early versions contain more pre-clinical data.
- ① Later versions more heavily weighted with clinical data.

5) Protocols:

- ① Must include at least initial protocol.
- ① No subjects planned.
- ① Eligibility requirements.

6) Chemistry, manufacturing and control info:

- ① Manufacturing process
- ① Raw materials and finished product

① May refer to drug master file on previous application.

7) Pharmacology and toxicology 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.

① Other relevant info

① Copies of referenced materials.

① Address issues and possible drug abuse.

Dependence, radioactivity etc.

IND Amendments:

1. New protocol introduced

2. Changes made to protocol that may affected -

① Scientific soundness of study

① Rights safety or welfare of study

Subjects

3. Addition of new study investigations (FDA Form 1572)

4. New/ revised information not related to protocol

① New pharmacology, toxicology, chemistry clinical info

① Discontinuance of a study.

Clinical trials phases

Why do Research studies:

- To collect data on usual and unusual events conditions and populations group.
- 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:

Observational studies:

Groups are studied and contrasts made b/w groups.

The observed data collected are analyzed.

Analytic studies:

- ① Also called experimental.
- ② Study the impact of a certain therapy.
- ③ Ultimately the investigator controls factors being studied.

Principle

Clinical trial:

- ① Considered the 'true' experimental study - Gold standard of clinical research.
- ② Often a prospective study that compares the effect and value of an intervention against a control in human subjects.

Important

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Steps involved in clinical trial:

New chemical entity

- ① Organic Synthesis
- ① Isolation from plants

Preclinical studies

- ① Chemistry
- ① physical properties
- ① Biological
- ① Preformulation

Investigational new drug application

- ① Submission
- ① FDA review

Clinical trial:

- ① phase 1
- ① phase 2
- ① phase 3

Preclinical studies:

- ① Long term animal toxicity
- ① Product formulation
- ① Manufacturing, control
- ① Package, label design

New drug application

- ① Submission
- ① FDA review
- ① Pre approval plant inspection
- ① FDA action

Post marketing

- ① phase and clinical studies
- ① adverse reaction reporting
- ① Product life extension

Phase zero

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 porcine are also used.

The choice of species is based on which will give the best correlation to human trial. Difference in the 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 upto 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.

Types of animal testing:

① pharmacological profile.

- ① Teratogens.
- ② mutagenesis
- ③ carcinogenesis.

Types of clinical trials:

The US 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 trials:

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 drug 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 chronic illness.

Abbreviated New Drug Application (ANDA)

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An abbreviated New drug application (ANDA) is specific designed for an approval of a generic drug product.

When data within an ANDA are submitted to the food and drug administrations 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.

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.

OGD → office of generic drugs
CDER → center for drug evaluation
and research.

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ANDA Review Process

Applicant

↓
ANDA

↓
Acceptable and complete

↓
Review by OGD/CDER

Bioequivalence Review

Chemistry/Micro review

Request for plant
inspection

Labeling Review

↓
Bioequivalence Review
acceptable

Chemistry/micro/labeling
Review acceptable

No

↓
Bioequivalence
deficiency letter

No

↓
Not approvable
letter

↓
preapproval Inspection

acceptable

↓
ANDA approved

↓
Approval of
deferred pending
satisfactory
results

The guidelines to assist in preparing ANDA include :

1. Format and Content for:

a. application Summary.

b. Chemistry, manufacturing and control Section

c. Non clinical 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 documentation 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.

ANDA check list:

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

Additional comments Regarding the ANDA?

Each component and section of the check

and control, with a copy of application form and any reference to drug masters 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)

- ① ANDA is an application for a US generic drug approval for an existing licenced medication or approved drug.
- ② 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.
- ③ 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.

Necessary items of ANDA:

- Composition of drug.
 - name
 - Amt. of each ingredient
- active
inactive

I identify place of drug manufactured
Processed
Packaged, labeled.

name of suppliers:

- ① Identify any person other than applicant who perform a part of operation.
- ② Certifications from applicant and method used in process facilities controls use in mfg, processing, packaging, labeling.
- ③ Assume that dosage form and comply to specifications and tests to official compendium.

Outline } method used

} facility

control used for

mfg

processing

packaging

- ④ If drug require a long ANDA require adequate data to assume bioavailability.

Goals of ANDA →

- ↓ price of drug.
- ↓ time of development.
- ↑ bioavailability of drug.

WAXMAN HATCH ACT →

Using the bioequivalence as the basis for approving generic copies of product was established by drug price and patent term restoration act of 1984. unknown as Waxman Hatch act.

This act expedites the availability of less costly generic drugs by permitting FDA to

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:

① Participants have an equal chance to be assigned to one of two or more groups.

① One gets the most widely accepted treatment (standard treatment)

① The control group is made up of the people who get the most widely accepted treatment for the disease.

Randomization in clinical trials 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 assignment.

Introduction →

A good clinical trial minimizes variability of the evaluation and provides an unbiased evaluation of the intervention by avoiding confounding from other factors. It also provides a basis for the statistical methods used in analyzing data.

* Criteria for Randomization:

1. Unpredictability →

① Each participant has the same chance of receiving any of the interventions.

② Allocation 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 trials = placebo

The random member generator is generally used. It is simple and easy to implement and treatment.

2. Block Randomization:

The basic idea of block randomization is to divide potential patients into m -blocks of size $2n$ and 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.

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 subjects on baseline covariates.

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 given total sample size. This may not be the most economically efficient 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.

Why is Randomization important?

So all groups are as alike as possible. Provides the best way to prove the effectiveness.

Methods of post marketing Surveillance phase IV studies

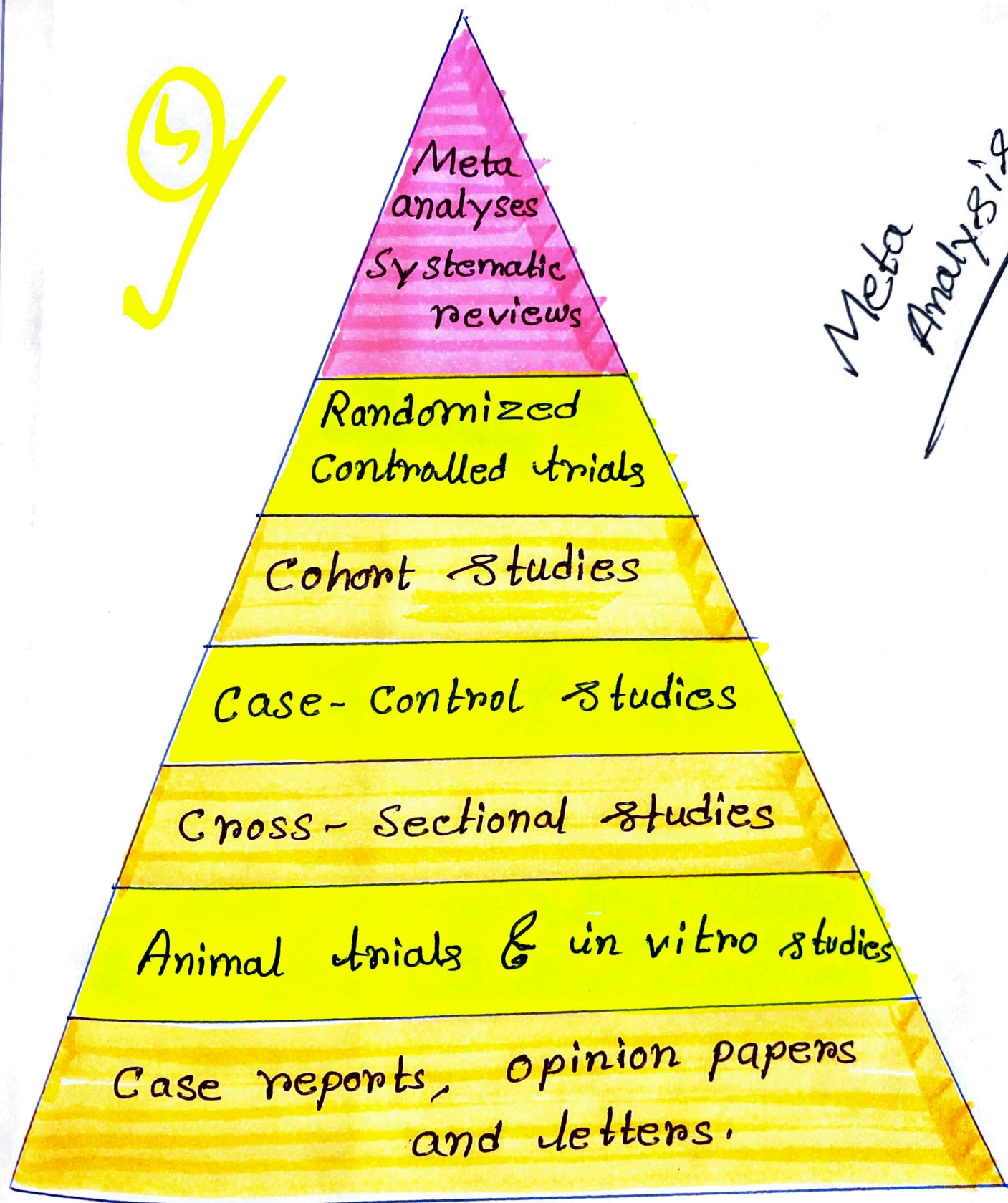
Also known as post marketing surveillance trials involve the safety surveillance (pharmacovigilance) and ongoing technical support of drug after it receives permission to be sold. Phase IV studies may be required by regulatory authorities or may be undertaken by sponsoring company for competitive (finding a new market) or other reasons.

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 - II clinical trials.

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.

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Meta Analysis

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 sections of society and possible develop and approach to meet these costs.

Methods:

1. Descriptive Studies.
2. Cross-Sectional Studies.
3. Case-control studies.

If the case and controls both come from the same population the results of the study are more easily validated.

- ① There is no randomization and blinding.
- ① patients can be directly monitored to ensure they take the drug appropriately and to observe drug effects.
- ① 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 on trial design that are specified and the greater the control that is built into the study

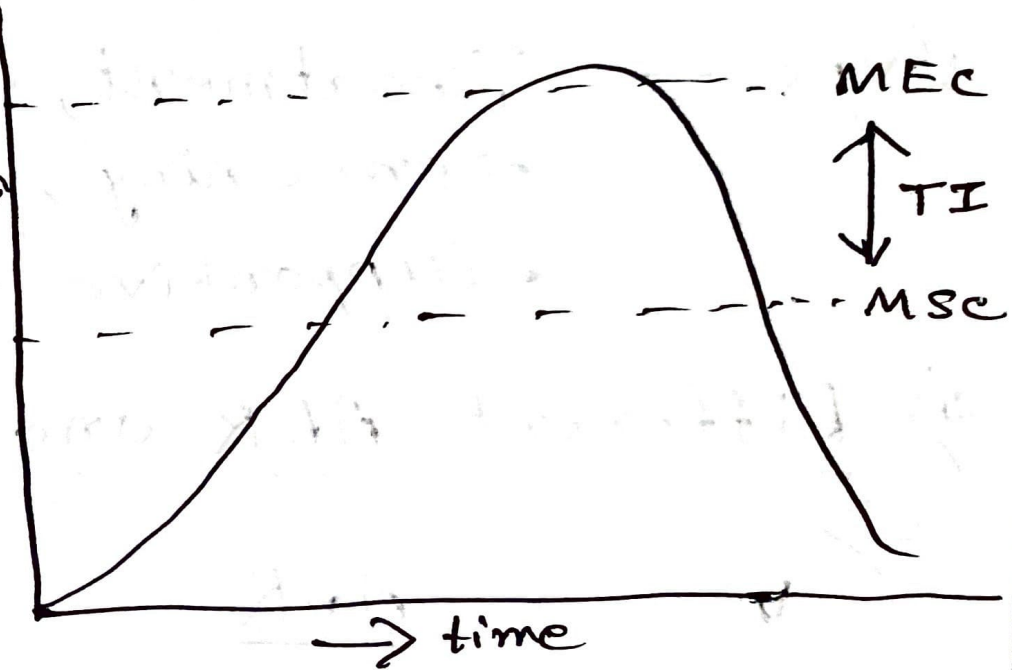
used to identify drugs beneficial as well as ADR.

How often the effects occur (frequency).

Define therapeutic index.

Between the maximum effective concn and the minimum safe concn the range or the ratio called as therapeutic index

$$TI = \frac{MEC}{MSC}$$



⇒ Orange book → The publication approved Drug

Products with therapeutic equivalence evaluations

① identifies drug products approved on the basis of safety and effectiveness by the Food and Drug Administration.

Bias relates to the problems relates to the study design. Good study designs aims to minimise bias with in.

Randomisation process aims to minimise the bias between intervention and control group.



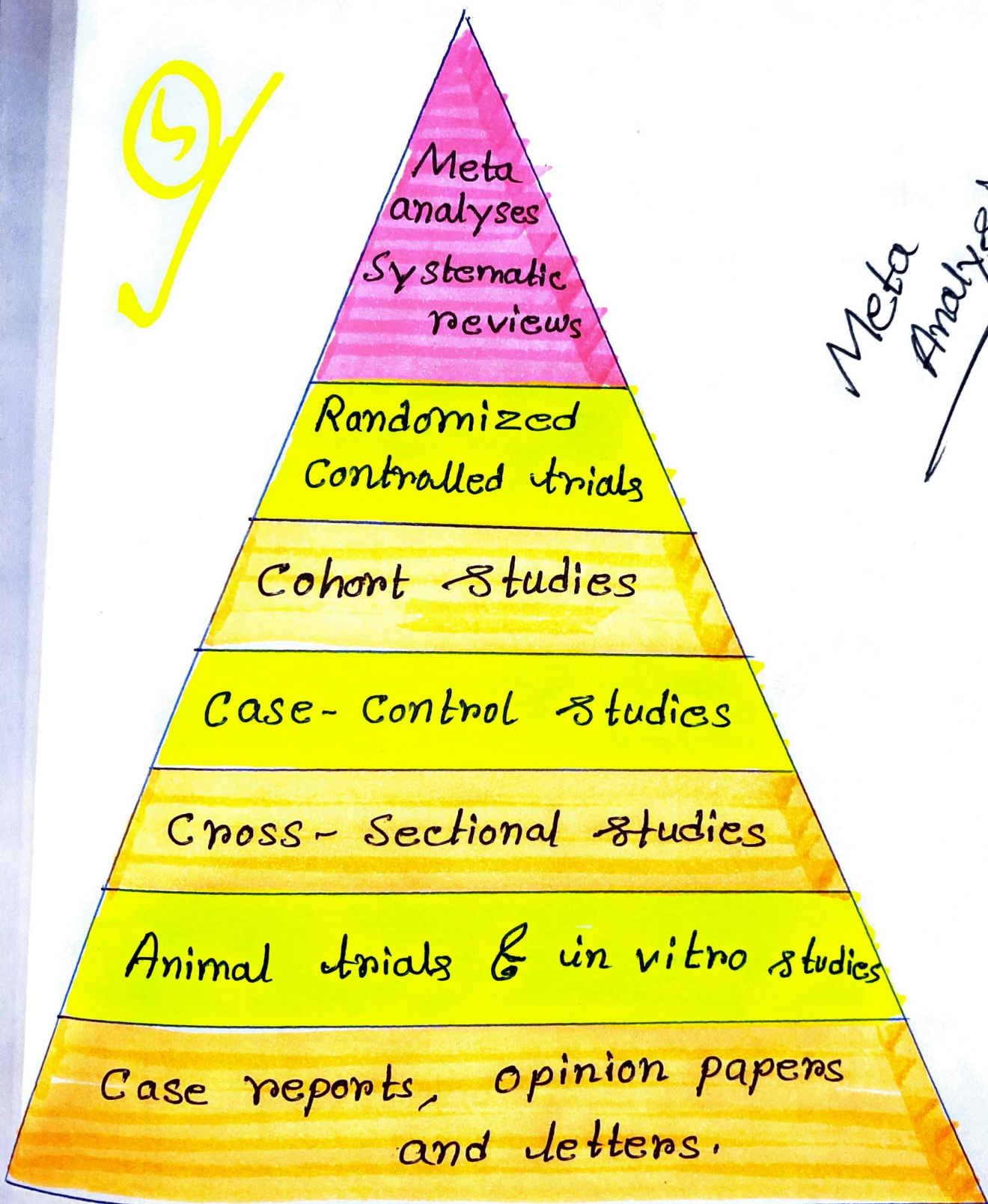
Types of bias:

1. Selection bias (failure to randomise all eligible patient)
2. Performance bias (difference in care provided apart from
drug treatment)
3. Exclusion bias (difference in withdrawal from study)
4. Detection bias (failure to blind assessors)

9) Use of placebo in clinical trials.

⇒ To learn if the new drug or treatment works better than a substance that does not have an active drug in it.

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Meta Analysis