CLINICAL TRAILS

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To Discuss~ *At Glance*

- Definition and Types
- General Concerns
- Benefits and Risk of Participation
- CFR
- Institutional Review
- Principles of Informed Consent

DEFINITION

- A CLINICAL TRAIL is a prospective organized, systematic procedure in human volunteers to answer some questions about the intervention of some kind.
- Clinical Trails are the fastest and safest way to find treatments of diseases and ways to improve health.
- The objective of clinical investigation is to access whether a drug is of value in treatment or prophylaxis of a disease or condition, its risks or undesirable effects and relative relationship of assessments.
- The guidelines have been developed from experience with prior drugs and many require modification with completely new entities.

TYPES OF CLINICAL TRAILS

- **1. Treatment Trail Test** – for treatment, new combinations of drugs or new approaches to surgery / radiation therapy.
- **2.PreventionTrails**–for medicines, Vitamins, Vaccines, Minerals...etc
- **3. Diagnostic Trail**s -finds better tests or procedures for diagnosing a disease
- **4. Screening Trails Tests** – best way to detect certain diseases or health conditions
- **5. Quality of life trails / supportive care trails.**

GENERAL CONCERNS

- The principles concerning Institutional Review and Informed Consent are stated in March 13, 1975 FEDERAL REGISTER, Technical Amendments concerning " PROTECTION OF HUMAN SUBJECTS ".

- Clinical Trail team includes
  - 1. Doctors, Nurses, Social Workers and other Health Care Professionals
  - 2. They check the health of participant at beginning of trail, give specific instructions and monitor the participant carefully during the trails and stays in touch after completion of trail.

- Ideas of the clinical trails come from RESEARCHERS.. during the trails, more information is gained about a new treatment, its risk and how well it may or may not work.

- Sponsors for Clinical Trails are Physicians, medical institutions, certain foundations, voluntary groups and pharmaceutical companies in addition to National Institute of Health (NIH), Department of Defense (DOD) and Department of Veteran Affairs (VA).

- PLACEBO is an inactive pill, liquid or powder that has no treatment value. They are used in order to compare then access the treatments effectiveness.

- CONTROL GROUP is the standard by which experimental observations are evaluated. In general it is given a standard treatment.

BENEFITS AND RISK OF PARTICIPATION

BENEFITS…

- Play an active role in their own health care
- Gain access to new research treatments
- Help others by contributing to medical research.

RISKS….

- They may be unpleasant, serious and life threatening side effects.
- Treatment may not be effective for participant
- Protocol may require more of their time and attention.

CODE OF FEDERAL RIGHT (CFR)

- A codification of the general and permanent rules published in Federal Register by executive departments and agencies of the Federal Govt.

- The code is divided into 50 titles

- The titles that would most frequently apply are

  45 CFR – Department of Health and Human Devices

  21 CFR – Food and Drug administration.

INSTITUTIONAL REVIEW

- An Institutional Review Board (IRB) is composed of NLT 5 persons with varying background to assure complete and adequate review of activities commonly conducted by the institution.

- Board must be able to ascertain the acceptability of applications and proposals in terms of institutional commitments, regulations, applicable law, standards for conduct and practice and community attitudes.

- No member of Board is involved in either initial or continuing review of an activity expect to provide information requested by board.

- No Board shall consist of persons who are officers, employees or agents of or otherwise associated with institution.

PRINCIPLES OF INFORMED CONSENT

- Informed Consent is the process of learning the key factors about a clinical trail before deciding whether or not to participate

- It is also a continuing process throughout the study to provide information for participants.

- The document of the informed consent to be signed by the participant includes..

  - Details about the study

  - Key content

  - Risks and potential benefits of study

- Fair explanation of procedures to be followed
- Disclosure of alternative procedures that might be advantageous
- Offers to answer any inquires concerning the procedures
- Instruction that the person is free to withdraw his consent and to discontinue participation in the project or activity at any time without prejudice to subject.

DESIGN AND ANALYSIS CONSIDERATIONS

- Statistical expertise is helpful in the planning, design, execution and analysis of clinical investigations to ensure validity of estimates

- The inferences about the drug responses as well as other aspects in well defined target populations are drawn from objective of study.

- Good planning results in questions being asked which permit direct inferences i.e. the study is designed and useful in planning phase to consider listing of questions to be answered in order of priority.

1.Principles are followed in conduct of clinical trails

- A statement as to rationale for a particular length of the study may be useful
- Any pooling of data across investigations should be accompanied by specific summaries of each investigator and a statement as to rationale for pooling results.

2. The report of findings should include a description and documentation of statistical methods used.

- 3.Principles are stated in May 8, 1970 Federal Register Statement concerning adequate and well controlled clinical investigations (21 CFR) and are as follows..
  - 1. To clearly state the objective of study
  - 2. To define the selection criteria and show comparability of studies
  - 3.To document the method of randomization and analysis.
- 4. To plan the suitable size of clinical experiment and also depends on appropriate decision like…..
  - ✓ Degree of responses to detect
  - ✓ Desired assurance against a false positive findings
  - ✓ Acceptable risk of failure to demonstrate the response.

- 5.To include when and where appropriate, comparison groups.
- 6. To perform studies blind whenever feasible.
- 7. To vigorously define response variables, including description of methods of observation and quantification.
- 8. To maintain strict adherence to the protocol.
- 9.To specify the limits imposed upon the study by failiures to comply with written protocol.

PROTOCOL OF CLINICAL TRAILS

- A PROTOCOL is a study plan on which all clinical trails are based and it should be carefully in order to safeguard the health of participant and answers the specific questions.

- The protocol includes the following….
  - 1. Brief description of drug and disease treated
  - 2. Types, Selection and number of subjects to participate
  - 3. Schedule of tests
  - 4. Procedures (Stages of Trails)
  - 5. Dosages
  - 6. Length of study
  - 7. Patient compliance and drug dynamic studies.

Brief description of drug and disease treated

It has to obtained in order to carry out the trails that are to be accurate and precise.

Subjects To Participate

- It should include the selection, types, number and methods of the selection

Selection of the subjects

It is based on…

- 1. Qualification of the investigator
- 2. Investigational facilities available
- 3. Proposed plan of investigation
- 4. Amount of information available on compound
- 5. Patient population available and
- 6. Availability of adequate deer review.

Number of Subjects

- It is based on previous experience with these studies and it should not be considered as absolute
- Randomization of patients among various treatment groups is generally satisfactory when one is treating the same disease.

Method of Selection

- It is by inclusion / exclusion criteria.
- The factors that allow someone to participate in clinical trails are called as Inclusion Criteria and those disallow someone from participating are called as Exclusion Criteria.
- The various factors to be considered are…
    - 1. Age
    - 2. Gender
    - 3. Type and stage of disease
    - 4. Previous treatment history
    - 5. Other medical conditions.

Schedule of Tests

- It includes the time of administration, when, how and where to administer the drugs

Procedures

- It includes the various phases of study like Phase I, II, III, and IV.

Dosages

- It is desirable to ascertain a range of effectiveness so that the lowest effective dose and when feasible, the highest safe and effective dose are determined.

Length of the Study

- It is generally carried over years that is from **3 – 5 years**

Patient Compliance and Drug Dynamic Studies

- It is a serious problem in clinical state the compliance and is to be monitored and its degrees for continuation of study is considered.

- Both the nature and frequency of laboratory and other tests for safe clinical evaluation vary with the compound and at times its observation can be an earlier and more dependable index of an effect with which it correlates.

PHASES OF CLINICAL TRAILS

- The Clinical Trails are generally conducted under various phases namely..

» **Phase I Trails** ~ **Health Volunteers**

» **Phase II Trails** ~ **Target Patient Volunteers**

» **Phase III Trails** ~ **Large Number of patients**

» **Phase IV Trails** ~ **After Marketing**

PHASE I CLINICAL DRUG TRAILS

- It include..
  - » Introduction
  - » Subject and setting
  - » Qualification of Investigations
  - » Procedures
  - » Additional considerations

INTRODUCTION TO PHASE I TRAILS

- These trails are used for first time to evaluate its safety, determine a safe dosage range and identify side effects.
- Phase I trails are designed as the first test of a drug in a human population.
- They are designed to determine toxicity, absorption, metabolism and safe dosage range.
- The objective in conducting the study is primarily pharmacological in nature.

SUBJECTS AND SETTING

- The studies should ordinarily be performed in adults who are hospitalized or in other settings permitting close observation.
- They are limited to relatively few subjects (20 to 80) .
- In most cases, normal volunteers are involved in initial studies, when their use is contraindicated because of potentially toxic or pharmacologic nature of drug.
- In general, patients receiving concomitant drug therapy should be excluded, except perhaps where the concomitant therapy is considered mandatory or routine.
- In some other cases, the patients with diseases to be treated are utilized.

Exceptions may include but are not limited to…

- 1. A drug which has been extensively studied abroad
- 2. Combinations of well known drugs
- 3. Drugs which have been studied previously for other indications
- 4. Drugs whose pharmacologic activity considered safe to utilize out patients
- 5. New Formulations of known drugs
- 6. Topical preparations

QUALIFICATIONS OF INVESTIGATORS

- The investigators skilled in initial evaluation of a variety of compounds for safety and pharmacological effect and they should be experts in the particular disease categories to be treated in evaluation of drug effects on the disease process.

PROCEDURES

- Pretreatment physical examinations.
- Laboratory tests performed to screen out individuals.
- Repeated drug testing, G~6~PD deficiency screening.
- Before investigation subjects are administered with previous drugs for at least 2 to 4 weeks.
- The washout period will be required for return to physiological state.

SINGLE DOSE STUDIES

- In this study no subjects should be placed upon the next higher dose until sufficient exposure has occurred with immediately preceding dose
- Number of subjects is optional
- It is desirable to begin with a small group i.e 5 on placebo for 5 to 7 days and then to larger groups.

ADDITIONAL CONSIDERATIONS

- Recent experience with ECGs is supposedly normal studies by seeing the occurrence of T wave ST segment abnormalities, bundle branch block, arrhythmias etc…
- The ECGs are obtained under standardized conditions in normal conditions and there after with drug changes are noted
- Specialized laboratory tests are indicated from the safety and the pharmacologic stand point, inorder to measure certain pharmacologic effects.
- Occurrence of abnormalities with possible appearance of physical findings is generally indicated.
- Blood level studies should be performed with single and also with multiple dose of drug.

- If the drug is expected to have significant toxicity, as is often the case in cancer and AIDS therapy, volunteer patients with the disease are used in phase I rather than normal volunteers.

- Phase I trials are done to determine whether humans and animals show significantly different responses to the drug and to establish safe clinical dosage range.

- These trials are “non-blind” or "open," i.e, both the investigators and the subjects know what is being given.

- Many predictable toxicities are detected in this phase.

- This phase includes trials designed to assess the safety (Pharmacovigilance), Tolerability, Pharmacokinetics, and Pharmacodynamics of a drug.

SAD : SINGLE ASCENDING DOSE

- Small groups of subjects are given a single dose of the drug while they are observed and tested for a period of time.
- If they do not exhibit any adverse side effects, and the pharmacokinetic data is roughly in line with predicted safe values, the dose is escalated, and a new group of subjects is then given a higher dose.
- This is continued until pre-calculated pharmacokinetic safety levels are reached, or intolerable side effects start showing up.
- At this point the drug is said to have reached the Maximum tolerated dose (MTD).

MAD: MULTIPLE ASCENDING DOSE STUDIES

- In these studies, a group of patients receives multiple low doses of the drug.
- Samples of blood and other fluids are collected at various time points and analyzed to understand how the drug is processed within the body.
- The dose is subsequently escalated for further groups, up to a predetermined level.

FOOD EFFECT

- A short trial designed to investigate any differences in absorption of the drug by the body, caused by eating before the drug is given.

- These studies are usually run as a crossover study, with volunteers being given two identical doses of the drug on different occasions; one while fasted, and one after being fed.

PHASE II AND PHASE III CLINICAL TRIALS

- Introduction
- Subjects
- Qualification of Investigators
- Procedures and additional considerations

INTRODUCTION

- It is a controlled clinical trial, used to design the test efficacy and obtain additional data on the safety of drug.

- The objective of the study is to determine the safety of drug.

SUBJECTS

- Patients selected for early Phase II studies should be free of hematologic, hepatic, renal, cardiac or other serious diseases.

- Patients in later Phase II and III studies may be included if they have concomitant diseases and concomitant therapy since they would be expected to be representative of certain segments of population who receives the new drugs for market approval.

- The number of subjects are around 200 to 300 (phase II) and 1000 to 3000 for phase III.

QUALIFICATIONS OF INVESTIGATORS

Phase II studies

- Performed by experts in the particular disease categories to be treated and evaluation of drug effects on diseases

Phase III studies

- Performed by experts and experience clinicians depending upon the nature of studies.

PROCEDURES AND ADDITIONAL CONSIDERATIONS

- In phase II, the frequency of the visits and of the laboratory tests will vary depending upon the nature of and safety of drug.
- Patient should ordinarily be seen by the investigator atleast weekly for 2 to 4 weeks.
- Specialized safety and pharmacological laboratory tests should be performed as required by the nature of the drug.
- The visits should then be biweekly for another 6 to 8 weeks and patients seen at monthly intervals for 2 to 3 months and bimonthly there after.

- Significant change in formulation or manufacture of the drug during the course of late phase II or phase III clinical trials will require bioavailability studies so that meaningful comparison can be made among clinical trials.

- For drugs that are administered for shorter periods in clinical trials eye examination should be performed at the end of drug administration.

- Tests are performed in a representative number of patients followed for 6 months or preferably longer durations.

- Phase II studies are sometimes divided into …
  - Phase II A and
  - Phase II B.

- **Phase II A:**

  Designed to assess dosing requirements (how much drug should be given).

- **Phase II B:**

  Designed to study efficacy (how well the drug works at the prescribed dose(s).

- Phase III studies can be difficult to design and execute and are usually expensive because of the large numbers of patients involved and the masses of data that must be collected and analyzed.

- The investigators are usually specialists in the disease being treated.

- Certain toxic effects especially those caused by immunologic processes may first become apparent in phase III.

- A single-blind design is often used, with an inert placebo medication and an older active drug (positive control) in addition to the investigational agent.

- Phase II trials are usually done in special clinical centers (ex: university hospitals).

- A broader range of toxicities may be detected in this phase.

PHASE IV CLINICAL TRIAL STUDIES

- They include Post Marketing Studies delineate additional information including drug risks, benefits and optimal use for FDA approved drug.

- In an open label study subjects are assigned to one treatment only and 2 doses of drug are often compared.

EXPANDED ACCESS PROTOCOL

- Use of investigational new drugs takes place in controlled clinical trials to assess safety and efficiency of new drugs

Data from clinical trials can serve as the basis for the drug marketing application

- FDA regulations of new drugs are used to provide expanded access and
- Primarily intend is to provide for access to new drug for people with a life threatening serious disease for which there is no treatment
- Treatment protocol is to generate additional information about the drug especially its safety

- Phase IV studies may be required by regulatory authorities or may be undertaken by the sponsoring company for ..

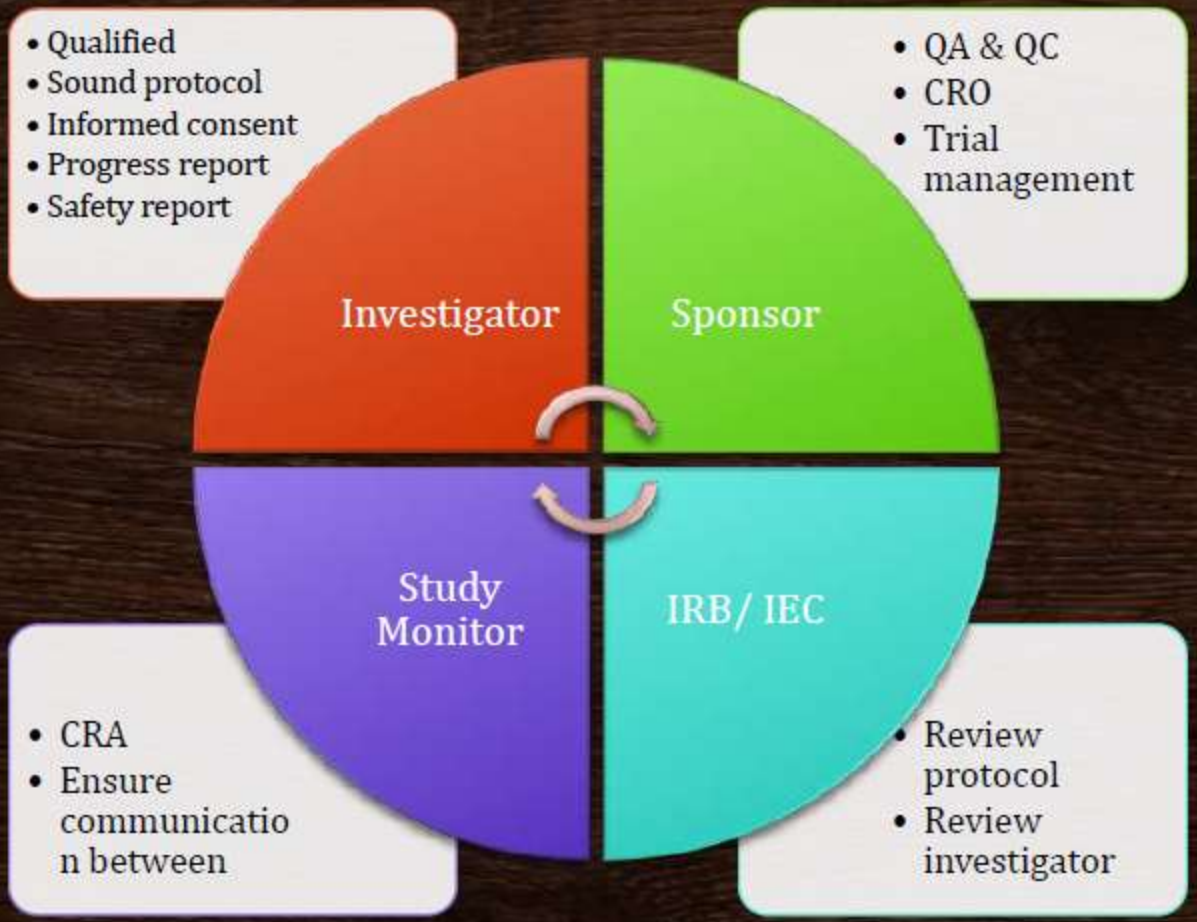
1. Competitive (finding a new market for the drug).

2. To check for drug interactions with other drugs.

3. Certain population groups such as pregnant women, who are unlikely to subject themselves to trials.

- Careful and complete reporting of toxicity by physicians after marketing begins is very important.
- Low incidence drug effects will not generally be detected before phase 4 no matter how carefully the studies are executed.
- Phase 4 has no fixed duration.
- Adverse effects detected by Phase IV trials may result in withdrawal or restriction of a drug.

Ensure subject wellbeing at all time

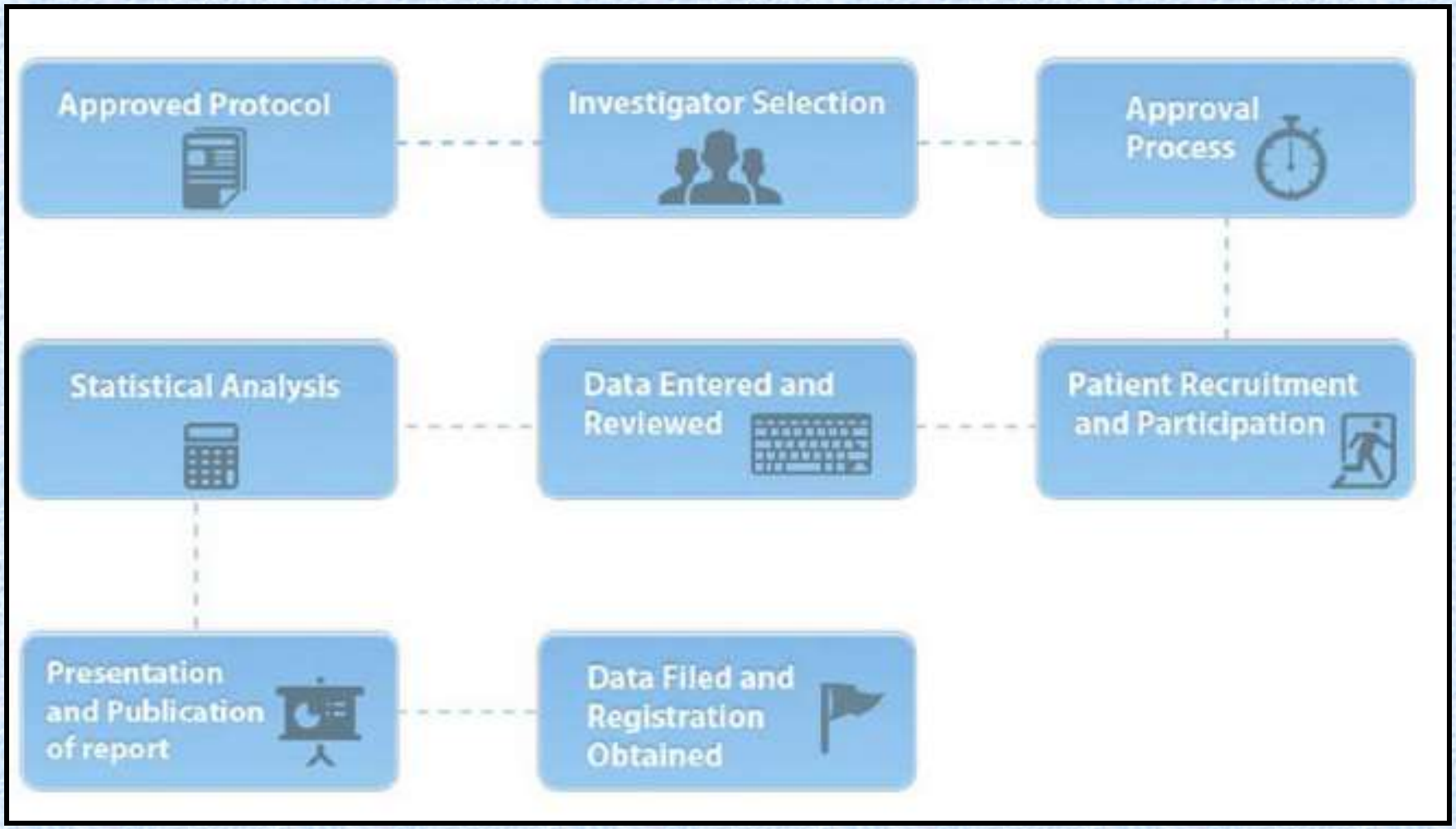


	Phase I	Phase II	Phase III	Phase IV
Population	**Healthy Volunteers**	**Target disease Patients**	**Target disease Patients**	**Mixed**
Design Features:	**-Single, ascending dose tiers -Unblinded -Uncontrolled**	**- Placebo controlled comparisons - Active controlled comparisons - Well-defined entry criteria**	**-Randomized -Controlled -2-3 treatment arms -Broader eligibility criteria**	**-Uncontrolled -Observational**
Sample Size	**20 – 80**	**200 – 300**	**100 – 1000**	**1000 <**
Duration	**1 month**	**Several Months**	**Several Years**	**Ongoing**
Design	**Non blind**	**Single blind**	**Double blind**	**Uncontrolled**

SUMMARY OF THE PRINCIPLES

1. Conduct trials according to GCP
2. Weigh risks vs. benefits
3. Subjects wellbeing exceed the science
4. Have adequate information to justify trial
5. Write a sound protocol
6. Receive IRB/IEC approval
7. Use qualified physicians
8. Use qualified & trained support staff
9. Obtain informed consent
10. Record information appropriately
11. Confidentiality & data protection
12. Handle investigational products appropriately
13. Quality assurance

CLINICAL TRIALS PROCESS



CLINICAL TRIALS PROCESS


Thank
You