A CRITIQUE OF CLINICAL TRIALS CONDUCT IN IRAN BASED ON ICH PRINCIPLES

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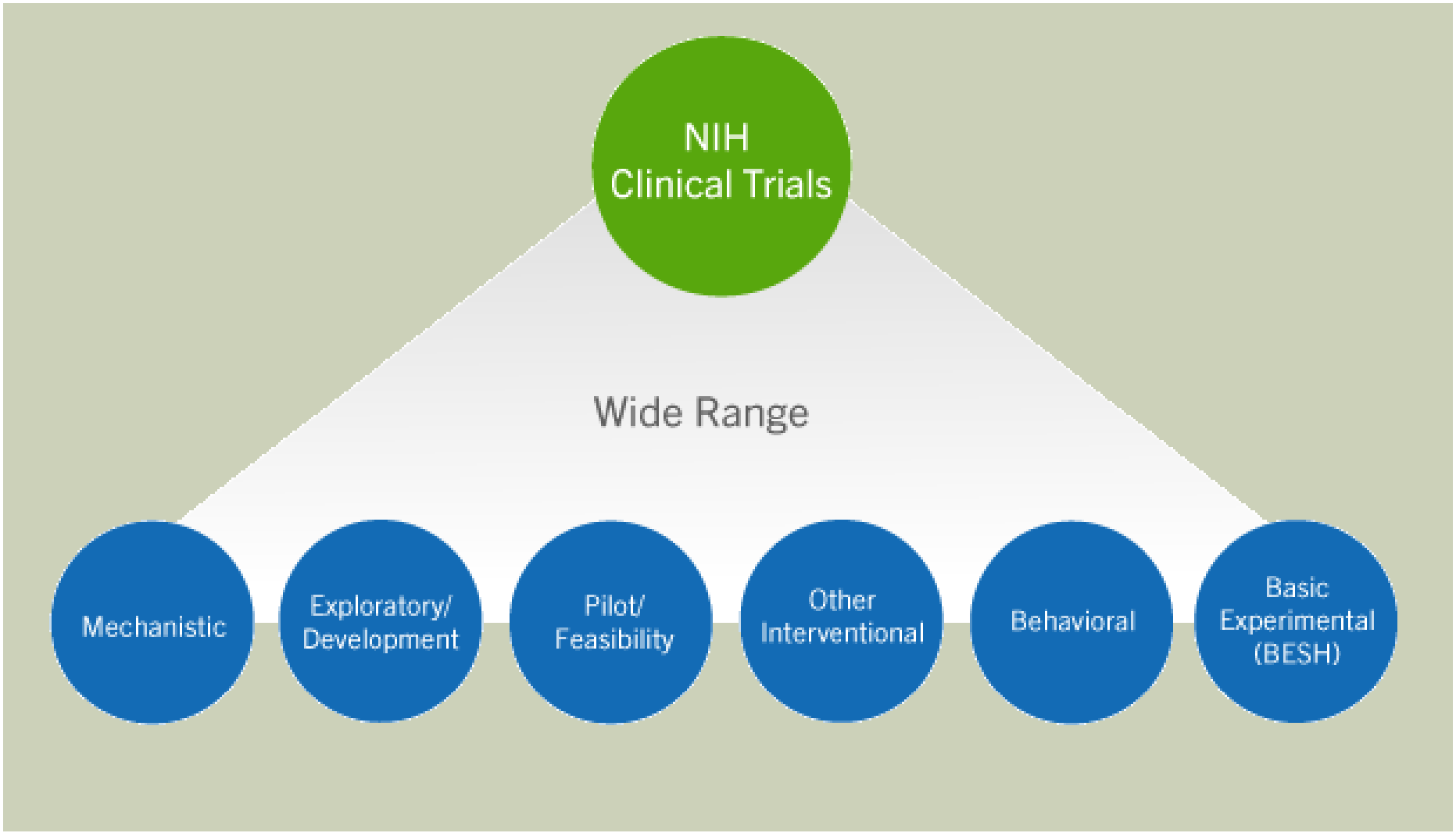
NIH DEFINITION OF CLINICAL TRIAL:

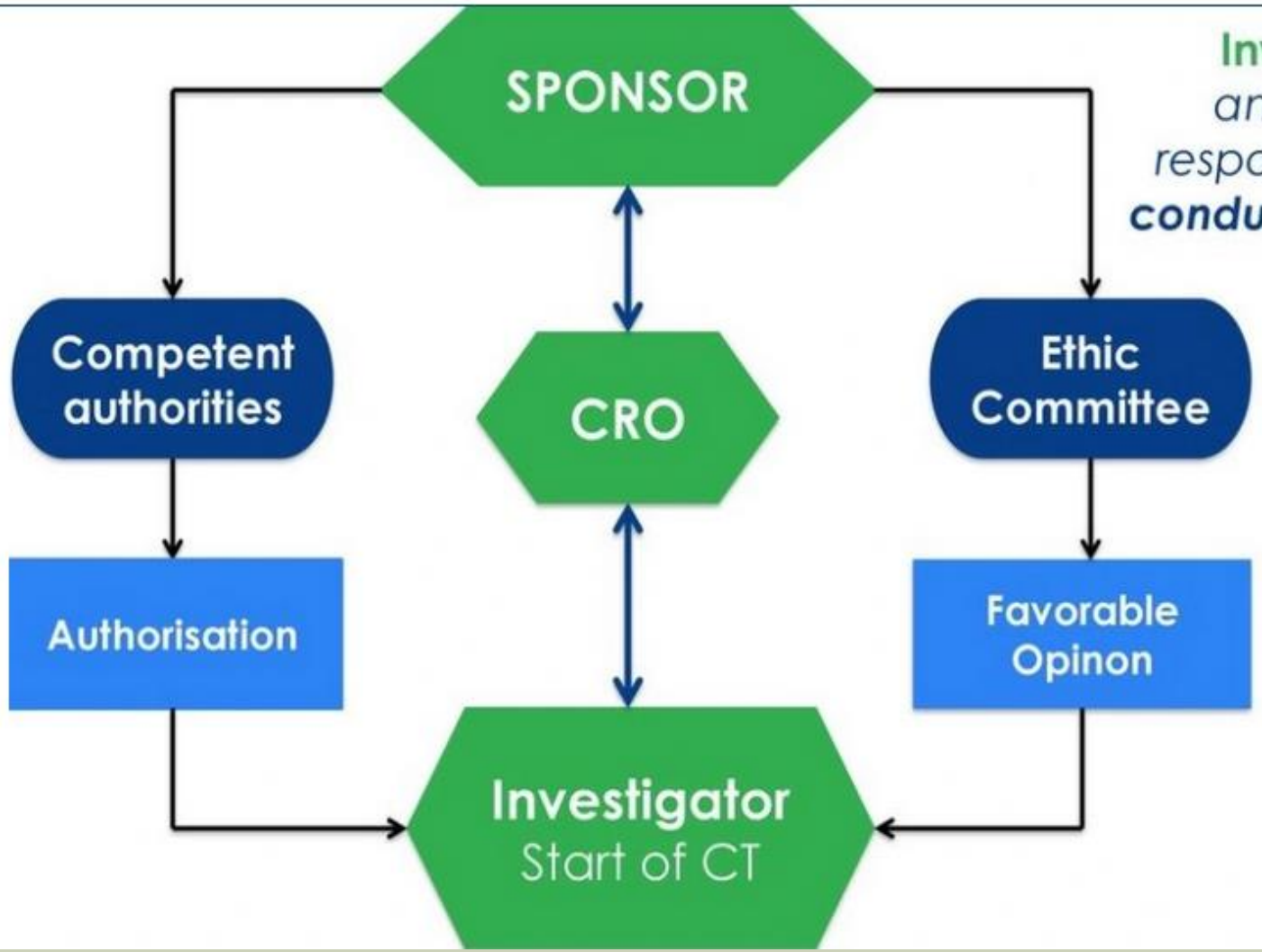
- A research study in which one or more human subjects are **prospectively** assigned to one or more **interventions** (which may include placebo or other control) to evaluate the effects of those interventions on **health-related biomedical or behavioral outcomes**.


NIH
Clinical Trials
Wide Range
Mechanistic
Exploratory/
Development
Pilot/
Feasibility
Other
Interventional
Behavioral
Basic
Experimental
(BESH)

4 PHASES OF BIOMEDICAL CLINICAL TRIALS:

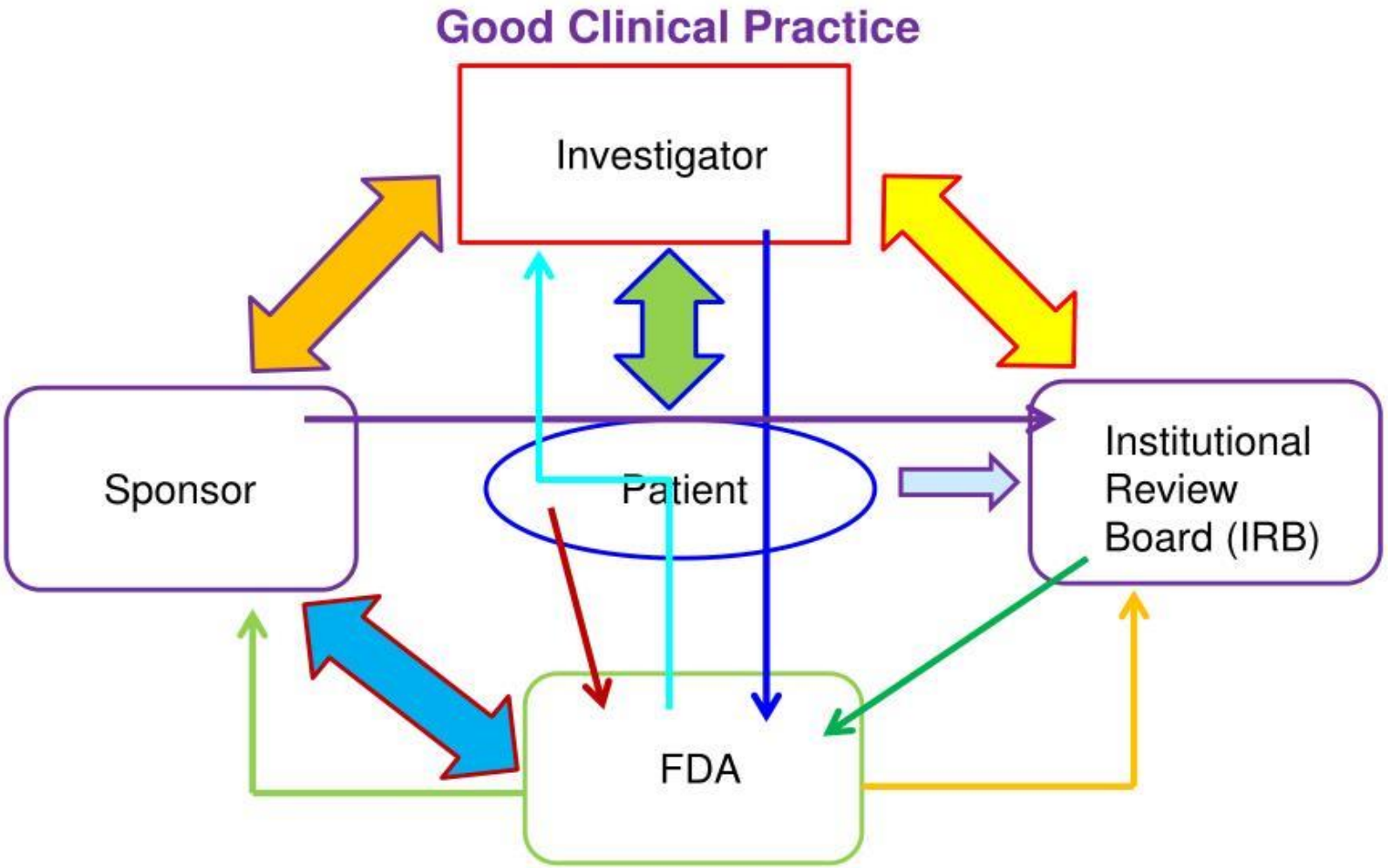
- Phase I studies usually test new drugs for the first time in a small group of people to evaluate a safe dosage range and identify side effects.
- Phase II studies test treatments that have been found to be safe in phase I but now need a larger group of human subjects to monitor for any adverse effects.
- Phase III studies are conducted on larger populations and in different regions and countries, and are often the step right before a new treatment is approved.
- Phase IV studies take place after country approval and there is a need for further testing in a wide population over a longer timeframe.

- The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use(ICH) is unique in bringing together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of pharmaceuticals and develop ICH guidelines.

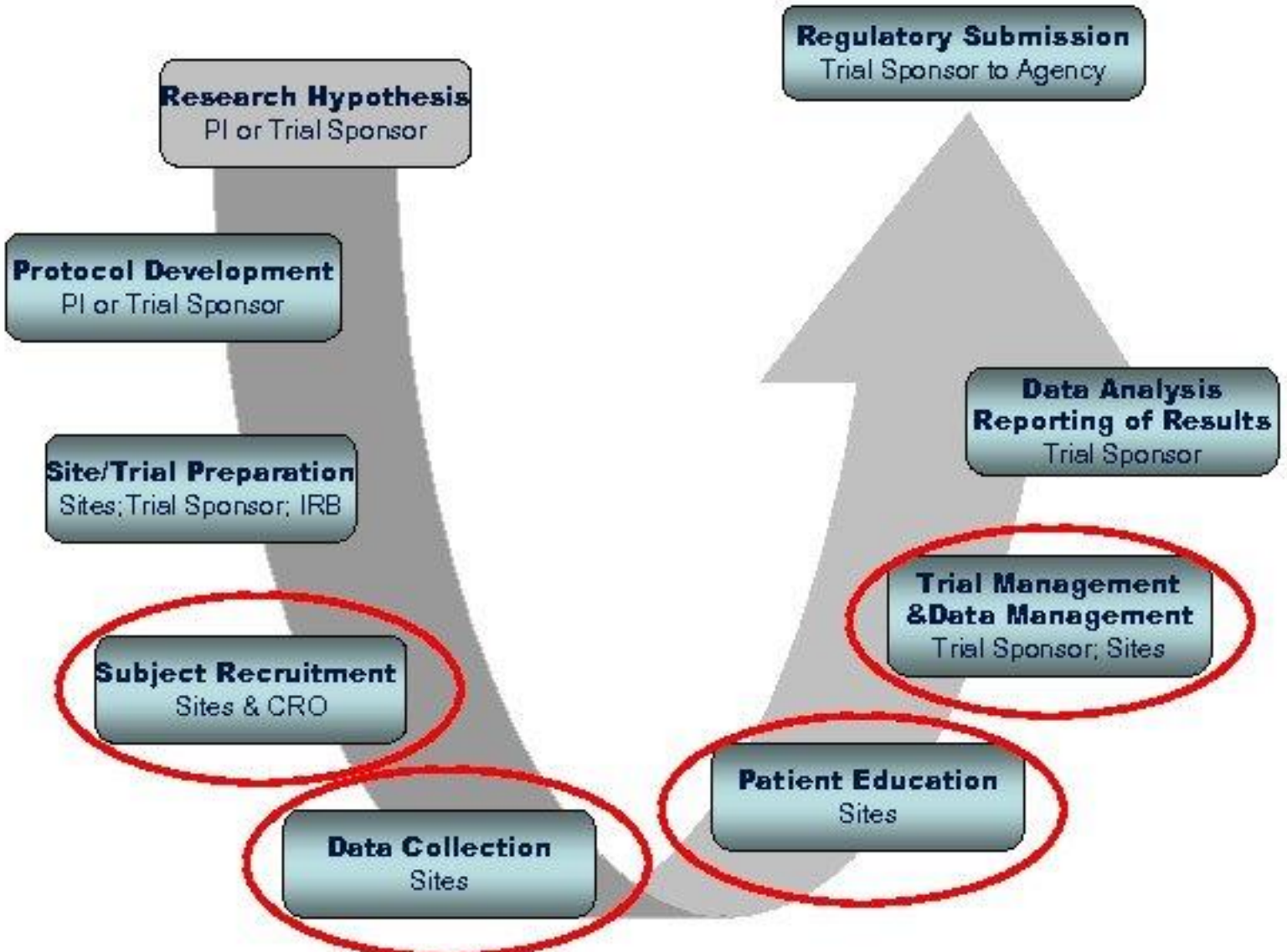


Investigator:
*an individual responsible for the **conduct** of a CT at a CT site.*

Clinical Trial Chain of Command



Today's Clinical Trial



Adapted from

CDISC

ACADEMIC CLINICAL TRIAL

- An **academic clinical trial** is a clinical trial not funded by pharmaceutical or biotechnology company for commercial ends but by public-good agencies (usually universities or medical trusts) to advance medicine

THE PRINCIPLES OF ICH GCP

- Clinical trials should be conducted in accordance with the ethical principles
- A trial should be initiated and continued only if the anticipated benefits justify the risks.
- The rights, safety, and well-being of the trial subjects are the most important considerations
- The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
- Clinical trials should be scientifically sound, and described in a clear, detailed protocol

THE PRINCIPLES OF ICH GCP

- A trial should be conducted in compliance with the protocol that has received prior **institutional review board (IRB)/independent ethics committee (IEC)** approval/favourable opinion.
- Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
- Freely given **informed consent** should be obtained from every subject prior to clinical trial participation

THE PRINCIPLES OF ICH GCP

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

INSTITUTIONAL REVIEW BOARD (IRB)/ INDEPENDENT ETHICS COMMITTEE (IEC)

- 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.
- 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

THE IRB/IEC SHOULD OBTAIN THE FOLLOWING DOCUMENTS:

- Trial protocol(s)/amendment(s)
- Written informed consent form(s) and consent form updates
- Subject recruitment procedures (e.G. Advertisements),
- Investigator's brochure (IB),
- Available safety information
- Information about payments and compensation available to subjects
- The investigator’s current curriculum vitae.

IRB/IEC SHOULD INCLUDE:

- a) At least five members.
- b) At least one member whose primary area of interest is in a nonscientific area.
- c) At least one member who is independent of the institution/trial site.
- Only those IRB/IEC members who are independent of the investigator and the sponsor of the trial should vote/provide opinion on a trial-related matter.
- An IRB/IEC may invite nonmembers with expertise in special areas for assistance.

THE IRB/IEC SHOULD

- Specifying

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

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

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

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

except immediate hazards to the subjects

CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT

- ***General Information***
- ***Background Information***
  - A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.
  - Summary of the known and potential risks and benefits, if any, to human subjects.
- ***Trial objectives and purpose***

TRIAL DESIGN

- A specific statement of the primary endpoints and the secondary endpoints.
  - Sample size calculation
  - 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
- A description of the measures taken to minimize/avoid bias, including:
  - Randomization
  - Blinding

RANDOMIZATION

- Randomization removes the potential of bias in the allocation of participants;
- Direction of the allocation bias may go either way
- Comparable groups with regard to unknown prognostic factors; sometimes might not work; stratified randomization and stratified analysis may help
- Validity of statistical tests of significance is guaranteed
- The chi-square test for 2-by-2 tables and Student's t-test for comparing two means can be justified on the basis of randomization alone without making further assumptions concerning the distribution of baseline variables
- The argument aimed at randomization is that in the typical trial it deprives about one half the participants from receiving the new and presumed better intervention

SAMPLE SIZE

- The two major factors affecting the **power of a study** are the **sample size** and the **effect size**
- *Too small may produce inconclusive results and could also be considered **unethical***
- *Too large will waste scarce resources* and could *expose more participants than necessary*

PSEUDO-RANDOMIZATION

- Alternating record number
- Date of birth
- Geographical distribution
- Open list
- Hospital record number

TRIAL DESIGN

- The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any
- A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.
- The identification of any data to be recorded directly on the CRFs

TRIAL DESIGN

- ***Selection and withdrawal of subjects***
  - Subject inclusion criteria
  - Subject exclusion criteria
  - Subject withdrawal criteria
    - 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.

ANALYSIS

- A description of the statistical methods to be employed, including timing of any planned interim.
  - Intention to Treat(ITT)
    - Modified ITT
  - Per protocol
- Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification
  - Under-power studies which is unethical

INVESTIGATOR

- The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial
- The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements
- The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).
- The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties

INVESTIGATOR

- The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.
- The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.
- The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions

INVESTIGATOR

- A qualified physician who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions
- During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial.
- The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.
- It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed

INVESTIGATOR

- The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies).
- The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects
- The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

INVESTIGATOR

- Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.
- The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol

INVESTIGATOR

- The investigator
  - should follow the trial's randomization procedures
  - should ensure that the code is broken only in accordance with the protocol.
  - If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

ETHICAL ISSUES IN CLINICAL TRIALS

- **Planning and design**
  - Does the question require a clinical trial?
  - Ethics training
  - Randomisation
  - Control group
  - Protection from conflict of interest
  - Informed consent
- **Conduct**
  - Trials in developing countries
  - Recruitment
  - Safety and efficacy monitoring
  - Early termination for other than scientific or safety reasons
  - Privacy and confidentiality
  - Data falsification
- **Reporting**
  - Publication bias, suppression and delays
  - Conflict of interest and publication

INFORMED CONSENT

- 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
- Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favourable opinion in advance of use.
- Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial

- 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

- 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

INFORMED CONSENT SHOULD INCLUDE

- That the trial involves research.
- The purpose of the trial.
- The trial treatment(s) and the probability for random assignment to each treatment.
- The trial procedures to be followed, including all invasive procedures.
- The subject's responsibilities.
- Those aspects of the trial that are experimental.
- The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.

INFORMED CONSENT SHOULD INCLUDE

- The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
- The alternative treatment that may be available to the subject, and their important potential benefits and risks.
- The compensation and/or treatment available to the subject in the event of trial-related injury.(INSURANCE)
- The anticipated prorated payment and expenses if any, to the subject for participating in the trial.
- 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.

- 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, without violating the confidentiality, by signing a written informed consent form, the subject is authorizing such access.
- That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.
- That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness.
- The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.
- The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.
- The expected duration of the subject's participation in the trial.
- The approximate number of subjects involved in the trial.

RECORDS AND REPORTS

- The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects

- Data reported on the CRF (Case Report Form) , that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

RECORDS AND REPORTS

- Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and **should not obscure the original entry**
- Essential documents should be retained until at least 2 years after the last approval of a marketing application
- Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records

SPONSOR

- *Quality assurance and quality control*
- *Contract Research Organization (CRO)*
- *Medical expertise*
- *Trial design*
- *Trial management, data handling, and record keeping*
- *Investigator selection*
- *Compensation to subjects and investigators (insurance)*
- *Financing*
- *Information on investigational product*

SPONSOR

- ***Manufacturing, packaging, labelling, and coding investigational product(s)***
- ***Supplying and handling investigational product***
- ***Safety information***
- ***Adverse drug reaction reporting***
- ***Monitoring***
- ***Audit***
- ***Noncompliance***
- ***Premature termination or suspension of a trial***
- ***Clinical trial/study reports***

CONTRACT RESEARCH ORGANIZATION (CRO)

- 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

MONITORING

- A trial should be monitored about these items:
  - The rights and well-being of human subjects are protected.
  - The reported trial data are accurate, complete, and verifiable from source documents.
  - The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

MULTICENTRE TRIALS

- All investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor and authority(ies)
- The CRFs are designed to capture the required data at all multicentre trial sites.
- The responsibilities of coordinating investigator(s) and the other participating investigators are documented prior to the start of the trial
- All investigators are given instructions on following the protocol, on complying with a uniform set of standards for the assessment of clinical and laboratory findings, and on completing the CRFs