Safety Monitoring During Clinical Trial

INTRODUCTION:

- Clinical trials are a cornerstone in medical advances; hence there is progress in the design and conduct of a clinical trial. This led to increasing awareness of ethical issues and safety monitoring.
- Monitoring patient safety during a clinical trial is critical throughout the Drug Development Process.
- Over time, regulations play an important role regarding **risk management** associated with medical products.
- **Pharmaceutical Sponsors** must take the most care of patient safety during a clinical trial, enclosing several processes and hence, several stakeholders are involved.
- Sponsors need to work in collaboration with all the stakeholders to achieve an effective and efficient approach to Monitoring patient safety.

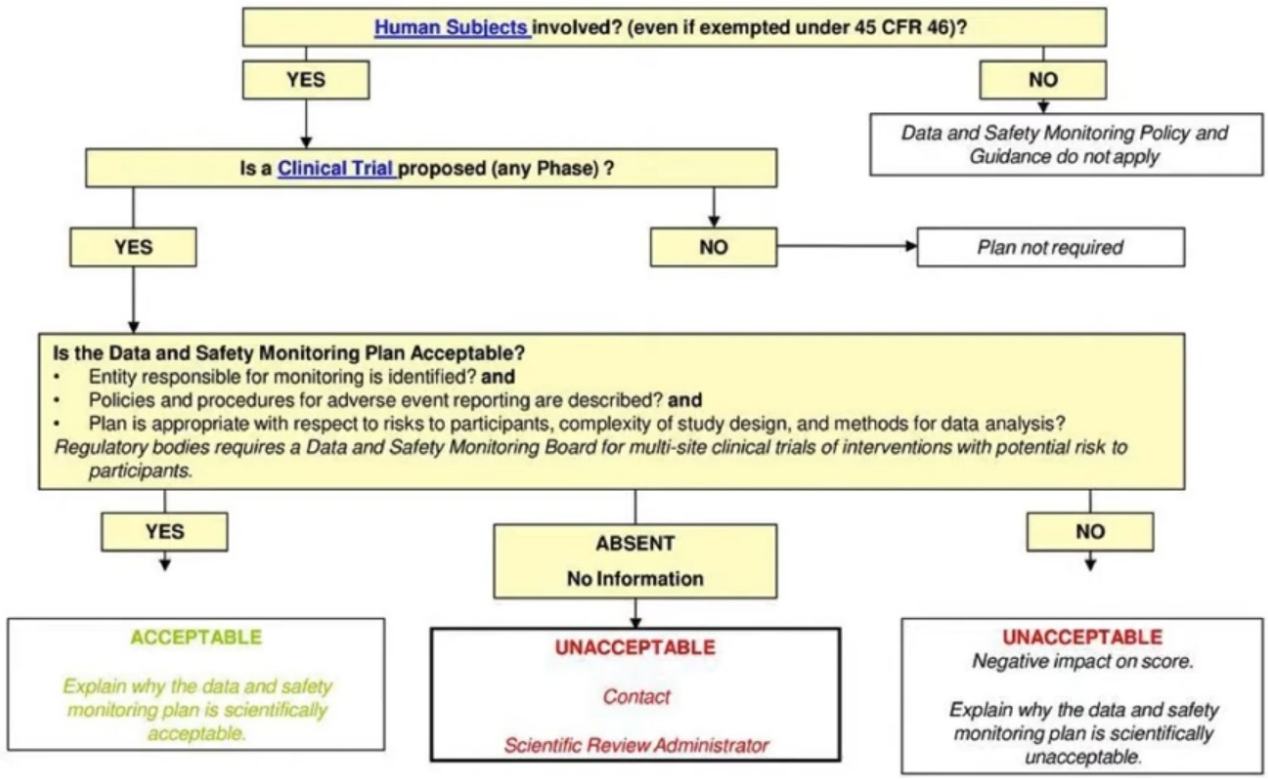

Fig. 1: Decision Tree for Data and Safety Monitoring for Clinical Trials

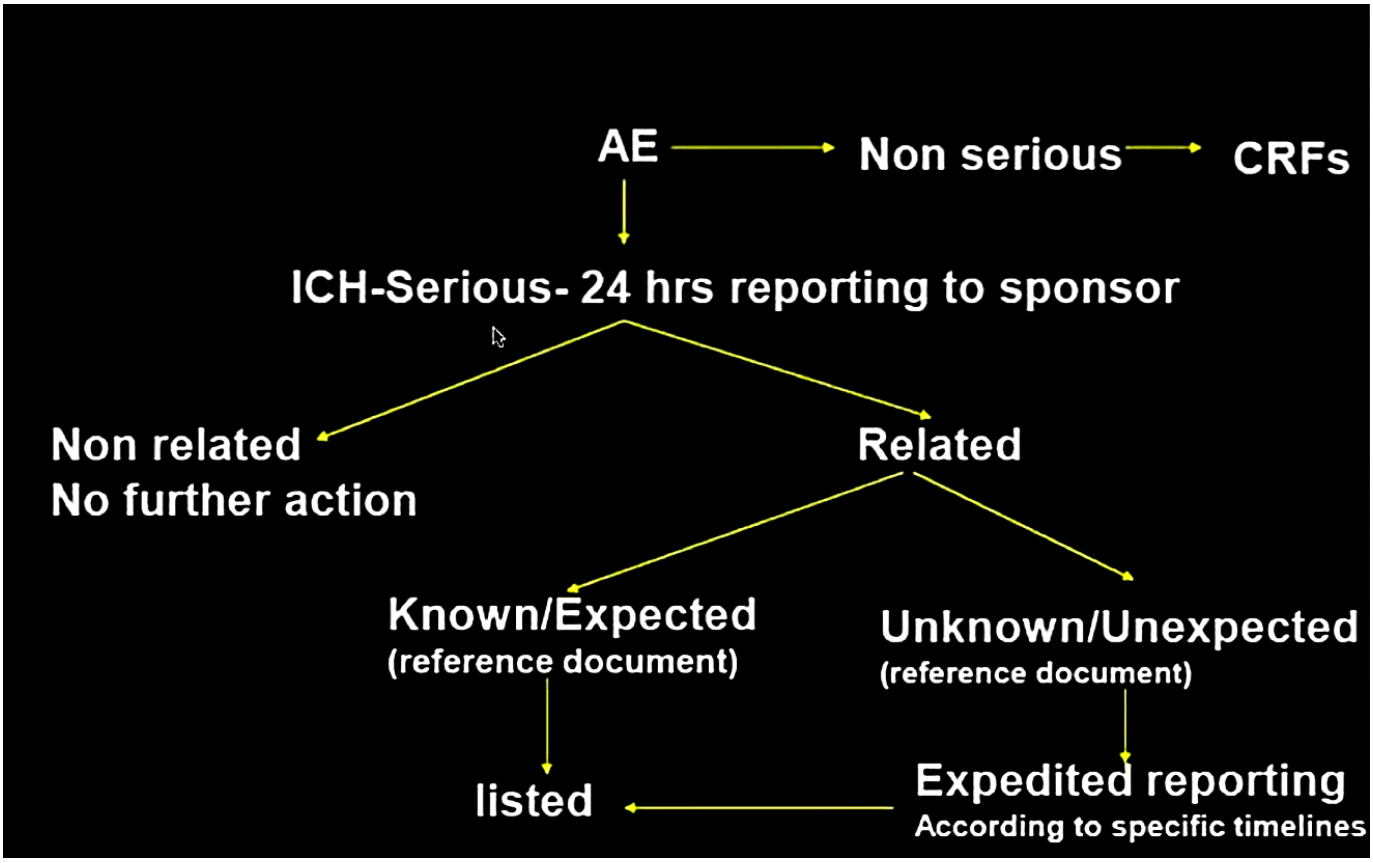

Fig. 2: How an adverse event will be monitored by stakeholders.

Definitions

1. DATA SAFETY MONITORING PLAN (DSMP)

- Describes how the study investigators plan to oversee research subject safety and how adverse events will be characterized and reported.
- The intensity and frequency of monitoring should be tailored to fit the study's expected risk level, complexity, and size.

2. DATA AND SAFETY MONITORING BOARD (DSMB/DMC)

- A group of individuals - with pertinent expertise that review on a regular basis accumulating data from ongoing clinical trials.
- Advises sponsor regarding the safety of current and future participants and the validity and scientific merit of the trial.

Study Risk Definitions

MINIMAL-RISK: Non-therapeutic trials such as survey research, questionnaires, blood samples, or observations.

One standard definition is: A study where the magnitude of harm or discomfort is not greater than that encountered in daily life or the performance of routine physical or psychological examinations or tests.

MODERATE RISK: Phase II or phase III multi-intuitional industry-sponsored trials with independent data monitoring.

HIGH-RISK: Clinical trials with investigational agents, phase I clinical protocols, investigator-initiated INDs, manufacturing of products on campus, some phase II clinical trials, and investigator-initiated phase III clinical trials.

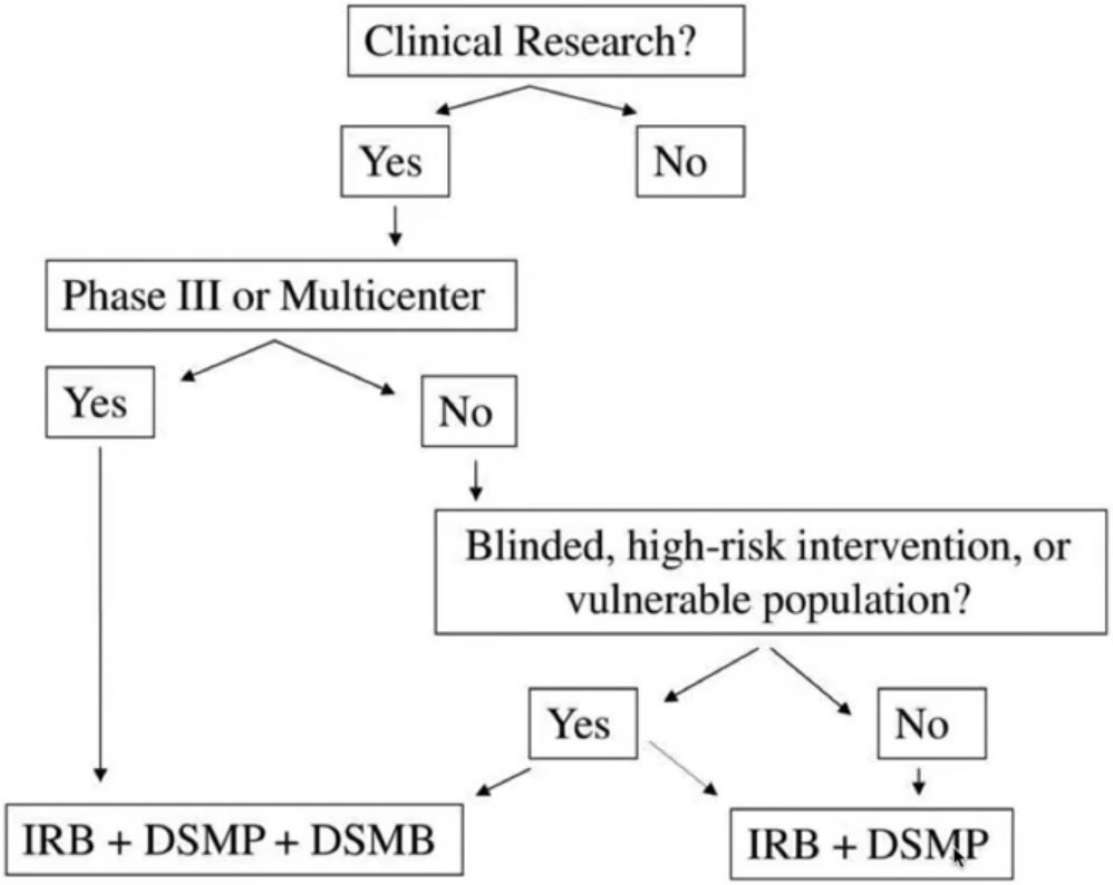

Fig. 2: Which Studies are required for Clinical Research Monitoring?

Safety Monitoring in Different Phases of Clinical Trials

PHASE-I:

The experimental drug is given to a small group of people (20-80) to evaluate its safety, determine a safe dosing range, and identify side effects.

PHASE-II:

An experimental (study) drug is given to a large group of people (100-300) to see its effectiveness and to further evaluate safety.

PHASE-III:

The experimental drug is given to a large group of people (1000-3000) to confirm its effectiveness, monitor side effects, and collect information for safety.

PHASE-IV:

1. post-marketing studies give additional information including drug risks, benefits, and optimal use.

2. For drugs being studied under investigational new drug application (INDA), the FDA published a regulation, establishing a new safety reporting paradigm.

3. According to this clinical investigator and sponsor must be more responsible in reporting and analysis of serious, unexpected events that might be caused by drugs.

Data and Safety Monitoring Board [DSMB]

- DSMB is a group of individuals with pertinent experience that reviews on a regular basis the accumulating data from an ongoing clinical trial.
- It is usually appointed by the sponsor.
- It is mainly used for Randomized control.

Purpose of a DSMB:

- Protect the safety of the trial participants.
- Identify high rates of ineligibility determined after randomization.
- Identify protocol violations under suggested changes to the protocol.
- Identify unexpectedly high dropout rates that threaten the trial's ability to produce credible results.
- Ensure the credibility of the study.
- Ensure the validity of study results.
- Advise the sponsor regarding the continuing safety of trial subjects.

DSMBS have generally been established for:

- Large randomized multisite studies that evaluate treatments intended to prolong life (or) reduce the risk of a major adverse health outcome.
- Any controlled trial of any size that will compare the rate of mortality (or) major morbidity.

DSMB committee composition:

- The sponsor/trial steering committee generally appoints members of a DSMB.
- Most DSMBs are composed of:
  - Clinicians, with expertise in relevant clinical specialties.
  - At least one biostatistician knowledgeable about statistical methods for clinical trials and sequential analysis of trial data
  - For trials with unusually high risks or with broad public health implications, the DSMB may include a medical ethicist knowledgeable about the design, conduct, and interpretation of clinical trials.
- Some trials may require the participation of:

- Toxicologist epidemiologists and clinical pharmacologists in particular cases when such expertise appears important for the informed interpretation of interim results.
- One or more individuals (often non-scientist) who may help bring to the DSMB, the perspectives of the population under study. Generally, such a DSM remember could be someone with a disease under study or a close relative of such an individual.
- DSMB for international trials will usually include representatives from at least a subset of participating countries (or) regions.

- The criteria for selecting all appointees should be:
  - Their respective expertise and experience.
  - Their ability to commit to attending DSMB meetings.
  - Their ability to maintain the confidentiality of the interim results they have reviewed.
  - Conflict of interest.

Responsibilities of DSMB:

- Interim monitoring
  1. Monitoring of effectiveness.
  2. Monitoring for safety.
  3. Monitoring study conduct.
  4. Consideration of external data.
  5. Studies of less serious outcomes.
- Early studies
- Other responsibilities
  1. Making recommendations,
  2. Maintaining meeting records.

INTERIM MONITORING:

1. Monitoring for effectiveness:

- A DSMB will recommend early termination on the basis of positive results, only when the data are truly compelling, and the risk of the false positive conclusion is acceptably low.
- The second type of consideration is whether the hypothesized benefit is likely to be achieved.
- If the interim data suggests that the new product is of no benefit i.e., there is no trend, indicating the superiority of the new product, a DSMB may consider whether continuing the study is futile and we recommend early termination on this basis.

2. Monitoring for safety:

If the subjects who are given the investigational intervention (drug) are found to be at higher risk of the outcome of interest (for example Mortality, disease progression, loss of organ function) sooner than those in the control, the DSMB may recommend early termination on safety grounds.

However, there are some false conclusions that there is an adverse effect.

Hence it is appropriate to demand, less rigorous proof of harm to justify early termination.

3. Monitoring study conducted:

DSMB will review data related to the conduct of the study. These data may include:

- Rates of recruitment, ineligibility, noncompliance, protocol violations, and dropouts.
- Completeness and timeliness of data
- Degree of concordance between site evaluation of events and centralized review.

"The DSMB may issue recommendations to the sponsor regarding trial conduct when concerns arise that some aspects of the trial conduct may threaten the safety of participants (or) the integrity of the study".

4. Considerations of external data:

- In some cases, particularly when unexpected safety issues arise in plated studies, the sponsor may bring external data to the attention of the DSMB.
- Then, the DSMB may be asked to consider the impact of external information on
- the study, being monitored.
- Such data may lead to recommendations like termination of the study (or) one (or) more study arms (or) changes to the consent form (or) investigator brochure, (or) letters from the sponsor to study participants describing the new results.

5. Studies of less serious outcomes:

- These studies are generally short-term, evaluating treatments' effects over periods of a few days to a few months. DSMBs have not been commonly established for such short-term studies.
- Early termination for effectiveness is rarely appropriate in some studies. except for ethical reasons. In such a case, an outcome group to monitor data regularly is probably warranted.

Early studies:

- DSMBs are not usually warranted in early studies, such as phase-1 (or) early phase-II studies (or) pilot/feasible studies, but formal monitoring groups may be used for certain types of early clinical studies.
- While these formal monitoring groups will often consist of individuals internal to the sponsor, and/ or investigators, a DSMB overseeing safety may be considered when the risk to participants appears unusually high.
    - Example: with novel approaches to treating a disease condition.

Other responsibilities:

1. Making recommendations:

- A fundamental responsibility of a DSMB is to make recommendations to the sponsor concerning the continuation of the study.

- The DSMB recommendations after an interim review may be:

  1. Studied to continue as a design

  2. Study termination

  3. Study continuation with major (or) minor modifications.

  4. Temporary suspension of enrollment and/or study intervention until some uncertainty is resolved.

  5. Both written recommendation and oral communication with opportunities for questions and discussions are advised.

2. Maintaining meeting records:

- The DSMB should keep the minutes of all meetings.
- The DSMB should divide meetings of confidential data (usually unblind compared to data) After each meeting, the DSMB should issue a written report to the sponsor based on the meeting minutes.
- This report should include sufficient information to explain the rationale for any recommended changes.
- If no changes are recommended, the report may be as simple as the DSMB recommends that the study continue as designed.

Meetings

- DSMB meetings will be held at least annually (or) as required by the timings of the protocol.
- The DSMB will review the status of the trial including toxicity, efficacy outcomes, and next formal monitoring data as specified in the protocol.
- The review of each trial includes three parts:

  1. The first is an open session in which the principal investigator may be present to clarify the status of the study.

  2. Second is it closed session limited to DSMB members and study statisticians and, the statistician presents the outcome results.

  3. Third is a closed session in which the DSMB members discuss outcome results and develop recommendations.

Role Of Stakeholders in Safety Monitoring During Clinical Trials:

1. SPONSORS:

- are responsible for developing;
    - ***Clinical Trial Protocol*** which explains all the aspects of the clinical investigation including safety aspects (which includes safety data, safety reporting timeline, procedures, etc.)
    - ***Informed Consent Form*** which details all the information currently available about the investigational drug and the procedures, risks, and benefits for research subjects of the trial.
- They are also responsible for ***Database creation and management*** of clinical trial data.
- ***Case Report Forms (CRFs)*** which are data collection tools designed by the **sponsors.**
- They need to communicate key safety information to all stakeholders properly and timely. So that **stakeholders** can act accordingly.

2. INVESTIGATORS:

- Leads the research.
- They are well-qualified, trained, and experienced individuals, who provide medical care to research subjects enrolled in the trial.
- They are ultimately accountable and responsible for conducting the clinical trial.
- They also hold the responsibility for the safety of the research subject. They identify the potential subjects and educate them about trial participation to ensure that they can take informed decisions regarding participation in the trial.
- During the conduct of the trial, investigators ensure that the trial is conducted according to the
    - Study protocol,
    - Prescribed guidelines and,

  - required regulations.
- They carefully observed all the aspects of the trial such as proper care to patients, proper data collection, documentation, and so on.
- They also ensure communication required for safety information is done promptly. (e.g., Reporting of adverse effects)
- Also responsible for notifying the Ethics Committee and the sponsor of any issue that can be a threat to the safety and well-being of the trial subjects.

3. RESEARCH SUBJECTS:

- Are patients or healthy volunteers, who agree to participate in a clinical trial by signing the ***informed consent form (ICF).***
- ICF includes all information related to clinical trials including safety details.
- ICF helps the trial participant to understand all aspects of the trial and in making a well-informed decision regarding participation in the trial.
- Participants should carefully read and understand the ICF before giving consent for participation.
- They can also withdraw at any moment from the trial.
- Once the Consent form is done, the investigator can collect all the relevant information (such as health information from participants)

4. INSTITUTIONAL REVIEW BOARD/ ETHICS COMMITTEE:

- Oversight protection of the right and welfare of human subjects in clinical research.
- They ensure that human research subject is carried out ethically by ***applicable regulatory requirements*** and ***prescribed guidelines***.
- IRB/EC reviews the clinical trial protocol. They have the authority to approve, disapprove, or instruct for modifications to protocols.
- They contribute their oversight to make sure that no research subject is placed at undue risk and the participant is giving informed consent to their Participation.
- They ensure that investigators get proper training and education to conduct the trial.

5. REGULATORY AUTHORITY:

- period to comments of clinical trials sponsor needs to get approval from the regulatory authority.
- Responses submit an investigational new drug application to the health authority for review.
- Health authority reviews IMDb for ensuring human subjects' safety during trials.
- they are guidelines provided by health authorities to conduct trials and report safety information.

6. DATA AND SAFETY MONITORING BOARD (DSMB):

- Review the clinical data to ensure the continuing safety of research participants.
- They review efficacy data at pre-defined interim points Advice sponsors regarding the continuing validity and scientific merit of the trial.
- Data generated during clinical trial place an important role in adding information for example safety information to the body of knowledge about the medicinal product or disease.
- These data can be useful for the broader medicinal community and ultimately for the patient and public.
- There are various methods to display this information so that others can access this information for example clinicaltrials.gov is a registry of clinical trials it has been developed to provide patients with information about clinical research studies.

COMMUNICATING SAFETY INFORMATION AMONG STAKEHOLDERS

- Complete proper and timely communication among the various stakeholders is important for ensuring the safety of human subjects in clinical trials.
- Sponsors are ultimately responsible for the whole clinical trial.
- They assured that research subjects are monitored appropriately including long-term follow-up if required.
- The clinical trial protocol describes all details of follow up including what kind of information is to be collected frequency and length of follow up etc.

- Standard operating procedures sops created to perform collection processing evaluation reporting and communication of safety information in an efficient manner to ensure a systemic approach to safety surveillance and monitoring.
- Sponsors should also take care of safety information collected from sources other than clinical trials these data should be shared with other stakeholders like Institutional Review Board regulatory authorities subjects etc.
- It can be shared through:
    - introducing amendments to research protocol to implement procedural changes which are required according to the updated safety information.
    - Periodic update of investigators' brochure with new safety information.
    - It will make the investigator and other personnel involved in the trial aware of new information which helps in conducting correct trial procedures and appropriate decision-making.

PURPOSE OF SAFETY MONITORING IN CLINICAL TRIALS

- Safety monitoring is used to identify evaluate minimize and appropriately manage the risk related to medicinal products.
- Regulatory authorities have developed a risk management system to keep a check on the risk associated with medicinal products.
- Risk evaluation and mitigation strategies (REMS) and risk management plans (RMPs) and risk management systems (RMS) are used by FDA and EMA respectively.
- Both RMPs and REMs work as guides for identification characterizing preventing or minimizing the risk linked to the medicines.
- Both use their approaches but have the same objective of the safe use of medicinal products.

CIOMS RECOMMENDATIONS FOR SAFETY MONITORING DURING CLINICAL TRIAL

- Presence of a Safety Management Team (SMT) within the sponsor organization to handle safety surveillance & decision-making on risk management & minimization activities.

- For trials in earlier stages without DSMBS, sponsors may create a team internally that can perform an ongoing review of the safety data. This independent data review team is empowered to perform similar functions as the DSMB on later-stage trials.

- Use of Development Core Safety Information (DCSI) as the summary of the identified safety issues for an investigational drug. Only safety issues or adverse drug reactions contained in this document should be considered "expected" for regulatory reporting purposes.

- Contrary to the routine expedited case reporting to regulatory authorities, sponsors provide periodic updates of the evolving benefit/risk profile & highlight important new safety information to participating investigators & IRBS.

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