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Medical Monitoring of Clinical Research Studies

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Introduction

The Medical monitor's (MM's) primary responsibilities in a clinical trial are to oversee the safety and protection of the research subjects and to provide independent oversight to help ensure the scientific reliability, clinical integrity, and quality of the clinical trial. Although the Food and Drug Administration (FDA) has not spelled out the necessity and role of the medical monitor, MM participation is important for compliance with Good Clinical Practice (GCP) guidelines and MMs almost always play a significant role in multicenter clinical trials.[1] The best practices for MMs described in this article can also help study sponsors comply with International Council for Harmonization (ICH) guidelines, Technical Requirements for Pharmaceuticals for Human Use, the United States Code of Federal Regulations (CFR), and FDA regulations and guidances.[2]

The MM collaborates with the project manager, safety, data management, biostatistics and quality departments, principal and sub-investigators, the site coordinator, the Data & Safety Monitoring Board (DSMB), and any other group that directly or indirectly protects the safety of study participants.

Communications

Prompt and transparent communication is an essential element underlying safety in all human clinical studies.[3] The MM should be the point person for medical, scientific and safety questions posed by clinical investigators, their site personnel, and staff at the study sponsor and contract research organization (CRO) involved in the trial. The MM's contact information should be readily available to investigators and their staff. The MM should be available essentially 24/7 with a back-up MM when the primary MM is not available.

MMs often address significant questions on the following topics:

- Documentation
- Protocol and investigator brochure
- Inclusion criteria
- Exclusion criteria
- Safety
- Patient concerns
- Adverse events (AEs)
- Serious adverse events (SAEs)
- Suspected Unexpected Serious Adverse Reactions (SUSAR)
- Pregnancy
- Medication errors
- Concomitant medications
- Laboratory values
- Protocol deviations and waivers

- Informed consent
- Unblinding
- Early termination or withdraw of a subject
- Protocol-stopping rules
- Other topics related to clinical research
- DSMB and pharmacovigilance team questions with respect to adverse events

MMs document all relevant communications in the appropriate database. When there are multiple significant errors at an investigational site, the MM may be called into an investigation to determine the cause and whether corrective actions or new training is required.[4] In rare cases, the MM, together with the project manager and quality assurance, assesses whether a site must be removed from a study due to safety issues, poor data quality, or violation of GCPs.

Maintain a Question and Answer (Q & A) log. Create anticipated Q & A's prior to the study and then maintain a log to help provide quick, accurate and consistent answers to repeat questions. The clinical sites should be able to search the log for themselves.

Protocol and Investigator's Brochure (IB)

The MM may write all or just parts of the protocol and investigator's brochure. At minimum, the MM should review and approve these documents.[5] Since the MM is expert on the protocol and the specific therapeutic indication being studied, the best practice is to involve the MM in training sponsor and/or CRO staff as well as the investigators and their personnel on the protocol and IB.

The MM should ensure that protocol endpoints make medical and scientific sense and are safely achievable. The clinical trial's expected benefits must outweigh its risks.[6] Inclusion and exclusion (I/E) criteria must align with this goal. I/E criteria must prevent the enrollment of subjects who are unlikely to obtain a positive therapeutic clinical endpoint or would be put at unacceptable risk in the study. For instance, a patient with a childhood history of bronchial asthma may not be appropriate to enroll in a clinical trial testing a medication that has properties of beta blockers, which can exacerbate symptoms of asthma.

The MM reviews permitted and prohibited concomitant medications (including over-the-counter drugs, herbs and dietary supplements) for possible interactions with the molecule being studied. The MM also ensures that the protocol does not specify types or numbers of procedures that would pose unnecessary risks for study subjects. The MM may recommend ways mitigate such risks.

The MM ensures that the IB clearly describes non-clinical studies and any adverse events of special interest (AESIs). An example of an AESI would be an abnormal electrocardiogram when all cardiac adverse events are of special interest to the regulatory authorities. All current knowledge about the drug, device or biologic must be clearly spelled out in the IB, not hidden in esoteric study reports.[7] It is unfortunate that many investigators do not read the IB in detail. Therefore, the MM should try to convey the important aspects of the pharmacokinetics, pharmacodynamics, metabolism, drug interactions and expected adverse events associated with the study therapy to the investigator and the appropriate staff at the clinical site.

Review and Discussion

The MM reviews each subject's eligibility data, screening physical examination results, medical history, concomitant medications, and laboratory tests before approving their entry into the study. If the investigator is attempting to enroll unqualified subjects, training may be required. The MM thoroughly discusses non-trivial protocol deviations (PDs), which should be rare, with the investigator, and only the most minor ones should be approved. A major PD may affect subject safety, data integrity, or the integrity of the entire study.[8] A dosing error by which a subject received twice the dose of the investigational drug during one dosing interval would be a major deviation. A subject's labs being a few hours out of the visit window would be a trivial deviation.

If time permits, the investigator should consult with the MM before unblinding a subject so the MM can assess and document the decision. The investigator should also discuss with the MM any early unusual termination or withdrawal of a subject from the study.

Data & Safety Monitoring Board (DSMB) or Data Safety Committee (DSC)

If there is a DSMB or DSC, the MM should participate in the blinded section of any meetings to help answer any questions related to adverse events and other potential safety and enrollment issues.[9]

Adverse Events

One of the most significant MM responsibilities is to work with the investigator to determine the most accurate causality of Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs). SUSAR expectedness determinations should be based on the Reference Safety Information section of the IB, or, in studies of marketed drugs, the applicable package insert. Many investigators do not have a good understanding of causality assessment, and poorly defined regulatory terms and examples do not help the situation.[10] Following the CIOMS report recommending a binary approach of "related" or "not related" in determining causality simplifies the complex and confusing terminology.[11] There is no accepted standard for assigning causality to an SAE, but employing the following Bradford Hill Criteria is an excellent way to determine causality:[12,13]

1. **Strength of Association.** A strong association between a treatment and an adverse event indicates causation. For example, each time the drug was given to a subject, it caused vomiting within a predictable time period.
2. **Consistency.** Established adverse event attributions or previous determinations in similar situations indicate causation.
3. **Specificity.** An established mechanism of action connecting the treatment and the adverse event indicates causation.
4. **Temporality.** Exposure to the product must occur before the disease or event, and not after a latency period. However, temporality is not sufficient to establish causation.
5. **Biological Gradient.** A dose response effect is a strong argument for causation.
6. **Plausibility.** The causal relationship is biologically plausible.
7. **Coherence.** The known facts fit the natural history and biology of the disease.
8. **Experiment.** Epidemiologic studies indicate causation.
9. **Analogy.** A similar agent causes the same type of AE.

Safety and Pharmacovigilance Reporting

The MM develops or reviews a brief narrative describing each SAE and SUSAR, which should include the following elements:[14]

- Clinical event (postmortem findings if applicable)
- Course of event, with temporal relationship to experimental product
- Outcome of the event with the nature, severity and intensity
- Relationship of the subject's medical history and concomitant medications to the event
- Significant test results or laboratory findings
- Therapeutic treatment for the event
- Action, if any, taken with regard to experimental product
- Causality assessment by investigator and sponsor
- Review and analysis of similar events with the experimental product

The MM works with the safety/pharmacovigilance team to code adverse events based on the latest edition of the Medical Dictionary for Pharmaceuticals for Human Use (MedDRA).[15] The MM also reviews the coding of concomitant medications using the World Health Organization's (WHO's) latest edition of pharmaceutical names (when it is used in the clinical trial). The MM reviews all SAE and SUSAR reports for accuracy and completeness and is the point person to discuss such events with the sites.

Conclusion

Since there are no regulatory guidelines on MM duties, this article has discussed those that are most significant. With the possible exception of the lead principal investigator, the MM should be the person most expert on the medical and scientific aspects of a multicenter study. The principal investigator at each site and the MM, along with DSMB and the institutional review board (IRB), share primary responsibility for the health and safety of study subjects and ensure the validity of the study. They must establish working relationships to ensure that subjects are protected and study data, including SAE and SUSAR reports, are accurate. This profound responsibility means that the MM for a study must have the requisite expertise, personality, dedication and ability to use the processes outlined in this article.

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