

Data Monitoring: Assuring Safety & Study Integrity in Clinical Research

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Where to Start ?

Tools for a Successful Study

- ◆ Understand the protocol completely
- ◆ Recognize institutional policies and practices that apply to the protocol
- ◆ Organize and maintain regulatory documents
- ◆ Create protocol-specific research record
–(shadow chart, research file)
- ◆ Create protocol-specific source documents
- ◆ Practice good data management

Study Documentation

- ▶ The documentation of research activities should be as complete as possible. “Source documentation”
- ▶ Unable to “re-create” a research record.
- ▶ Every interaction with the research subject must have a research note in the record detailing what transpired during the interaction. This should be written as soon as possible so that the details can be preserved.
- ▶ All procedures, study agent accountability, adverse events, verbal discussions, laboratory results review, subject complaints etc. are part of this documentation.
- ▶ Clinical research requires diligent and vigilant documentation.

Data Monitoring

- ▶ Study monitoring – performed to assess the quality and completeness of the study documentation – it is usually performed by a clinical research associate (CRA), also known as a study monitor, who is affiliated or hired by the study sponsor. In certain situations, it may also be conducted by study staff
- ▶ Data and safety monitoring – performed to assess the safety of the ongoing study – usually performed by medical monitors, also known as data and safety monitors/board members, who are usually contracted with the sponsor to conduct the reviews. In certain situations, it may also be conducted by study investigators.

The Study Monitor

- ▶ The monitor/CRA reviews the data in the source documents, the place where the data is originally recorded in the research record. The monitor will compare the data to the case report form (CRF) (paper or electronic).
- ▶ These CRFs are used for data entry, management, and analysis. The results may be submitted to the data and safety monitoring board (DSMB) and regulatory agencies, including the FDA.
- ▶ The quality and completeness of the data allow for faster compilation and more efficient reviews at regulatory agencies.
..... Leading to to more rapid approval of efficacious agents to treat patients.

What are the Standards?

- ▶ The main quality standard is the International Conference on Harmonization Good Clinical Practices (GCPs).
- ▶ GCPs outline the responsibilities of all involved in the research process – the investigator, the IRB, and the sponsor.
- ▶ Sponsors may also have Standard Operating Procedures (SOPs) for research operations and may require that investigators adhere to them as well.
- ▶ The standards set the priorities for assuring that the highest quality data is submitted as part of regulatory reviews.

What are the Components of Quality Assurance?

- ▶ Accrual Rates and Recruitment Sources
- ▶ Eligibility Criteria
- ▶ Informed Consents
- ▶ Accuracy of Data
- ▶ Completeness of Data
- ▶ Confidentiality of Data

Problems or Deficiencies

- ▶ When the data is not complete or there are large numbers of preventable protocol violations, this leads to delays, requiring follow up correspondence back to the study team in the form of data queries.
- ▶ Such data queries may involve significant amounts of time to review the research record to find or clarify the missing data points and to correct the CRF as part of the query.

Research Data Integrity

(general definitions)

- Error – Deviation from the truth or accuracy; unintentional; either due to ignorance or sloppiness
- Misconduct – Knowingly doing something wrong
- Fraud – Willful deception; may include: falsification of data, creating, altering recording, or omitting data in such a way that they do not represent what actually occurred.

Study Monitoring vs. Data and Safety Monitoring

- ▶ Data and safety monitoring is conducted concurrently with study monitoring.
- ▶ Both are performed on every study involving risk to the research subject
- ▶ Performed by qualified and experienced individuals
- ▶ Assures the safety of the subjects and the overall integrity of the research study

Definition of Data and Safety Monitoring (DSM)

- ▶ Systematic review of the data and adverse events at regular intervals to assess the ongoing safety of the participants and the conduct and integrity of the overall study
- ▶ Data and Safety Monitoring methods are usually detailed in a specific Data and Safety Monitoring Plan (DSMP)

Fundamental Principles of Data and Safety Monitoring

- ▶ Safeguard the interest of study participants
- ▶ Preserve the integrity and credibility of the study
- ▶ Ensure that definitive and reliable results be available in a timely manner to the medical community and to the public

Ellenberg S, Fleming T, DeMets D. Data Monitoring Committees in Clinical Trials
John Wiley & Sons, Ltd. 2002

Regulations

- ▶ NIH Guidelines
- ▶ Federal Regulations 45 CFR 46.111(a)(6)
- ▶ FDA Guidelines
- ▶ IRB Review

Important Common Elements of DSMPs

- ▶ Description of the collection, review and reporting mechanisms for adverse events and safety information to the study monitors, IRB, FDA, sponsor (NIH, industry), and other applicable offices
- ▶ Description of any setpoints or guidance for modifying or stopping the study
- ▶ Description of the quality assurance efforts

Important Study Considerations for Development of a DSMP

- ▶ Risk to Participants
- ▶ Type and Complexity of Study
- ▶ Other Factors

Types of Risk

- ▶ Physical
- ▶ Psychological
- ▶ Social
- ▶ Economic

Likelihood of Risk

- ▶ Common
- ▶ Possible
- ▶ Rare
- ▶ Theoretical

Type and Complexity of Study

- ▶ Intensity of the intervention
(e.g. type of agent, dose escalation, early phase studies)
- ▶ Vulnerability of the population
(e.g. age, cognitive function, disease condition, healthy volunteers, pregnant women)

Other Factors Related to DSMP Preparation

- ▶ Blinded
- ▶ Placebo-controlled
- ▶ Multi-center
- ▶ New science
- ▶ Investigator IND/IDE
- ▶ Investigator experience
- ▶ DSM oversight by external entities

Nuts and Bolts of the DSMP

- ▶ Deciding on the Monitoring Body
- ▶ Selection of Monitor(s)
- ▶ Content of Monitoring
- ▶ Frequency of Monitoring
- ▶ Decision-Making
Criteria/Guidelines
- ▶ Reporting Mechanisms

Biostatistical Considerations

- ▶ **WHAT:** Primary vs. secondary endpoint decisions
- ▶ **WHEN:** Short-term vs. long-term treatment effects determines when to analyze the data
- ▶ **HOW:** Subgroup analysis, when certain groups have different responses than others (e.g. by gender or a specific risk factor)
- ▶ **WHAT ELSE?** Available external information from other research

WebIRB Section on DSMP

- ▶ Risks and Benefits
 - Data and Safety Monitoring Plan
- ▶ All interventional studies involving more than minimal risk must include a DSMP
- ▶ Refer to UCLA OHRPP Policies and Guidance

Sample DSMP

- ▶ “An independent data and safety monitoring board (DSMB) will be established to monitor the course of the clinical study. The responsibilities of the board will be to review, control, and assess the adverse events and other safety data and to give advice when considered necessary regarding the management of the trial and the trial protocol, always trying to ensure the safety and well-being of the study patients and the trial integrity”

Sample DSMP (continued)

- ▶ “The members of the DSMB will be experts who are independent of the sponsor and the contract research organization (CRO). The procedures and responsibilities for the collection, analysis, and review of the data by the DSMB as well as communication and documentation of their opinions and recommendations will be defined in the DSMB charter which will be agreed upon and written before the trial starts.”

DSMB Responsibilities

- ▶ Evaluates research protocol and monitoring plan
- ▶ Regularly reviews all clinical research data
- ▶ Makes recommendations to sponsor, IRB, and investigators regarding the continuation, modification or conclusion of the trial based upon issues related to safety, superiority, futility, or lack of quality
- ▶ Maintains confidentiality of the data

Communicating with Research Participants about DSMB Decisions

- ▶ Maintain confidentiality until it is absolutely necessary to disclose
- ▶ Notify all participants as quickly as possible and document notification
- ▶ Follow-up with hardcopy notice of changes to study, if applicable
- ▶ Ensure that all methods used in communicating study information have been reviewed by the IRB.

Adverse Events and Data and Safety Monitoring

- ▶ The most important component of data and safety monitoring is the adverse event reporting and its completeness and accuracy.
- ▶ The DSMB makes important decisions about the study and thus needs the most up-to-date accurate and detailed data to do so.
- ▶ There are many historical examples of studies that continued even though safety issues were a problem.
- ▶ Inaccurate and/or inadequate reporting of adverse events leads to an incomplete or misinterpreted final AE compilation and statistical analysis.

Events in Data and Safety

Monitoring:

Adverse Events, Incidents, Unanticipated Problems

- ▶ Protection and safety of study subjects
- ▶ Greater understanding of overall safety profile of the study
- ▶ Recognition of dose-related toxicities
- ▶ Appropriate modification of study protocols
- ▶ Improvements in study design and/or procedures
- ▶ Adherence to regulatory requirements

Definition of an Adverse Event (AE) – OHRPP

- ▶ “Any untoward or unfavorable medical occurrence in a human subject (physical or psychological harm) temporarily associated with the subject’s participation in the research (whether or not related to participation in the research”.

In other words:

- ▶ If a subject displays or describes any change in their health status, either a new occurrence or an increase in the intensity of a pre-existing condition prior to study enrollment, it must be recorded by the research team and described in as much detail as possible. This may include abnormal laboratory or procedure results.

Investigator Responsibilities in AE Reporting

- ▶ The protocol investigators and ultimately the PI, have the primary responsibility for AE identification, documentation, grading, and assignment of attribution to the investigational agent/intervention.
- ▶ Investigators are required document and submit AE reports in a timely manner.
- ▶ Failure to provide AE information in a timely manner to assure the safety of current and future participants may result in study suspension or termination.

Collecting and Recording Adverse Event (AE) Data

- ▶ Investigational Drug research requires an effective system for collecting accurate and timely data on adverse experience
- ▶ Adverse events must be reported to the sponsor, the IRB, and other agencies as appropriate, whether or not they are thought to be drug-related
- ▶ The adverse event should be followed until it resolves and/or until the etiology of the experience is determined. There may be varying follow up times depending upon the requirements of the protocol, sponsor, and IRB.
- ▶ The most efficient manner in which to maintain initial documentation and subsequent follow-up of AEs is in the research record (research notes) and on an AE log (electronic or hardcopy) which are readily available and may be provided by a sponsor.

Event Follow-up and Reporting Requirements

- ▶ Recognize events
- ▶ Record all details of events
- ▶ Evaluate the event in the context of the study (relationship)
- ▶ Report per protocol and per policy to: data and safety monitors, IRB, campus departments, FDA, and sponsors utilizing the appropriate web or paper-based reporting systems

Recognizing Unexpected vs. Expected Adverse Events

- ▶ “An unexpected adverse drug experience is one in which the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan.”

FDA

Where Is the Expected AE Information?

- ▶ Protocol Information
- ▶ Investigator Brochure
- ▶ Current labeling/Package Insert
- ▶ Company safety reports
- ▶ Peer-reviewed publications

Adverse Experience Characteristics and Grading*

- ▶ Mild – awareness of a sign or symptom, but easily tolerated by the subject; intervention is usually not indicated
- ▶ Moderate – discomfort enough to cause interference with normal age-appropriate activities; minimal, local or non-invasive intervention
- ▶ Severe – medically significant and incapacitating; limited self-care and activities of daily living
- ▶ Life -threatening –consequences that require urgent intervention; probably hospitalization
- ▶ Death

*Cancer studies utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) for descriptive terminology. Because of the robustness of these criteria, they are often used in other therapeutic areas.

Remember that:

- ▶ “Severity” from a clinical point of view does not mean the same as “serious” from a regulatory point of view.

Serious AE*

- ▶ Results in death
 - ▶ Is immediately life-threatening
 - ▶ Results in permanent or substantial disability
 - ▶ Results in new admission to the hospital or prolongs an existing in-patient hospitalization
 - ▶ Is medically significant or requires intervention to prevent one or other of the outcomes listed above
-
- ▶ *The definition of a serious AE may differ from protocol to protocol, so it is very important to review this section of the protocol every time.

Attribution of AEs

- ▶ Related to study (“definite”, “probable”, “possible”)
- ▶ Unrelated to study (“unrelated”, “unlikely”)
- ▶ Unsure of relation to study (“unknown”)

Expedited Reporting (within hours/days)

- ▶ Some studies require that both serious and unexpected adverse events require expedited reporting.
- ▶ The UCLA IRB requires that all adverse events be reported in an expedited manner if they are 1) unexpected; 2) related or possibly related to the research and 3) place subjects or others at greater risk of harm than was previously known or recognized.

UCLA Office of the Human Research Protection Program (OHRPP)

Guidance and Procedure on Post Approval Reporting Requirements for Investigators

- ▶ Incident – An undesirable and unintended, although not necessarily unexpected, event or outcome involving any aspect of the research study.
- ▶ Deviations and violations – changes in procedures/research activities which are different than the approved protocol and requirements of IRB approval (violation is usually more serious and involves safety issues)
- ▶ Unanticipated problem – Any of the above events or outcomes that is unexpected, related or possibly related to the study, and places subjects or others at greater risk than previously known or recognized
- ▶ Updated safety information including DSMB reports

Practical Pointers

- ▶ Follow guidelines and regulations
- ▶ Use your best ethical judgment
- ▶ Adhere to the protocol and the DSMP
- ▶ Update risks/benefits with experience
- ▶ Maintain ongoing dialogue with the IRB
- ▶ Provide for ongoing informed consent discussions with participants
- ▶ Avail yourself of campus training, education, and CTSI resources
- ▶ (794-CTSI)

Remember.....

Knowing is not enough,
we must apply.

Willing is not enough,
we must do

J.W. Goethe