Managing the Practice of Research: DSM, GCP, RSA

Laurie Shaker-Irwin, Ph.D., M.S.

Clinical and Translational Science Institute

Safety

Quality

Integrity

Trust

CTSI Programs 310-794-CTSI

- Facilitation
- Post-Approval Research Oversight
- Clinical and Translational Research Center and Laboratory
- Funding Opportunities
- Technology Resources and Cores
- Education and Training Programs
- Biomedical Informatics
- Study Design, Data Management and Biostatistics
- And MUCH MORE!!!

Where to Start ?
Tools for a Successful Study

- Understand the protocol completely
- Recognize institutional polices 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

- Documentation of research activities should be complete and contemporaneous.
- Every interaction with the research subject, in person, telephone, e-mail, etc. should have a research note written in the research record detailing what transpired during the interaction.
- All procedures, study agent accountability, adverse events, verbal discussions, laboratory results review, subject complaints, etc. are also part of this documentation.
- Clinical research requires diligent and vigilant documentation. SOURCE DOCUMENTATION

Source Document

- Must capture all data required by the protocol
- Assures protocol compliance because all protocol events must be attributed to a source document specific to the visit/event
- Substantiates study responsibility and accountability; affixes ownership to data

Research Record Contents

- IC /signed and dated
- HIPAA Authorization/signed and dated
- Study Inclusion/Exclusion Criteria
- Study Flow chart or checklist identifying all study events/procedures required by protocol
- Protocol-Specific Source Documents
- Final disposition of the subject and subject status at study termination

Research Record Organization

Create Sections for:

- Adverse event reporting/tracking
- Study drug accountability
- Concomitant medication tracking
- Subject waiver forms, protocol deviations, notes to file, data queries, resolutions
- Clinical lab results/other tests/procedures

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.

- 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.

Study Monitoring vs. Data and Safety Monitoring

- Data and safety monitoring is conducted concurrently with study monitoring.
- The two types of monitoring should be conducted on every study involving risk to the research subject.
- Qualified and experienced individuals should perform the two distinct types of monitoring.
- Overall, such monitoring assures the safety of the subjects and the overall integrity of the research study.

The Study Monitor

- The monitor/CRA reviews the data in the source document with the data on the case report form (CRF) that is either in paper or electronic format.
- These CRFs are used for data entry, management, and analysis, the results of which are submitted to the data and safety monitoring board (DSMB) and to regulatory agencies, including the FDA.
- The higher the quality and the degree of completeness of the data increases the integrity of the study and allows for faster compilation and more efficient reviews at regulatory agencies.
- This eventually leads to more rapid approval of efficacious agents to treat patients.

What are the Standards?

- The main quality standard referenced for clinical research is the International Conference on Harmonization Good Clinical Practices (GCPs).
- These GCPs outline the responsibilities of all those individuals involved in the research process – the investigator, the IRB, and the sponsor.
- Sponsors may also have Standard Operating Procedures (SOPs) that must be followed as part of research operations and the sponsor may require that investigators adhere to many of these as well.
- The standards set the goals 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

Background and Definition of Data and Safety Monitoring (DSM)

- Required by regulatory and sponsor agencies
- 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)
- The CTSI Regulatory program is available to help with development of DSMPs.

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 for efficacy, safety, quality assurance, or futility
- Description of the quality assurance efforts

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
  - safety, efficacy, quality, futility
- Reporting Mechanisms

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

UCLA Guidance and Procedure: Post Approval Reporting Requirements for Investigators

- Adverse Event Any untoward or unfavorable medical occurrence in a human subject (physical or psychological harm) temporally associated with the subject's participation in the research (whether or not related to participation in the research).
- 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 – DSMB reports, external SAE reports, etc.

Event Follow-up and Reporting Requirements

- Recognize events
- Record all details of events
- Evaluate in context of study as to relationship and context
- Report events and their details as per policy to: data and safety monitors, IRB, campus departments, FDA, and sponsors

Some Problems Observed with Event Reporting

- Inaccurate/inadequate or missing source documents (medical records)
- Delegation of event identification and review to unqualified personnel
- Insufficient follow up of events to determine resolution
- Events that are not reported to the IRB/other agencies in a timely fashion

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.

Role of the Research Subject Advocate (RSA)

- Serve as the voice of the research subject in the review process
- Assist subjects with issues that may arise
- Review content of informed consent documents and assist in monitoring of discussions
- Assist researchers in addressing ethically sensitive features within a research project
- Assist with Data and Safety Monitoring Plans
- Assist researchers in complying with federal and state regulations, UCLA policies and GCPs

Ensuring Public Trust in the Research Enterprise

- Comprehensive informed consent process
- Disclosing conflicts of interest
- Registration and results reporting of clinical studies (clinicaltrials.gov) and compliance with Public Access Policy
- Supportive and caring personnel working with research patients
- Responsiveness to research subjects' needs and concerns about procedures, billing processes, and follow up care.

Remember…..

Knowing is not enough, we must apply.
Willing is not enough, we must do.

-- J.W. Goethe

Contact Information

Laurie Shaker-Irwin, Ph.D., M.S.
310-794-7504
lshakeririwn@mednet.ucla.edu

UCLA CTRC Clinical Research Networking Seminars:

"Accomplishing Clinical Research Billing Compliance"

Thursday, October 14th MacDonald Research Laboratories, 1st Floor Conference Room

Clinical Trials Paused as India Adopts New Rules

- Indian Supreme Court- Moratorium on new trials
- Previous lax oversight
- Changing rules for preventing injuries and death
- Requiring licensing for ethics committees
- Tightening weak regulatory network
- Impacts patients and their safety
- Impacts NIH trial enrollment
- Health Ministry to have oversight instead of Drug Controller General

- Current Status: Supreme Court to hear case on October 24th of 162 trials approved by the Ministry during the moratorium

Tampered Data Cast Shadow on Drug Trial

- Hypertension drug blockbuster Valsartan
- Data tampering
- $1 billion
- Kyoto Heart Study showed blocking of angiotensin and prevention of cardiovascular events
- Alleged image manipulations, concerns with statistics and conclusions
- Discrepancies with medical records, data set, overstated adverse events in non-Valsartan group, missed events in Valsartan group
- Incorrect conclusion
- Novartis employees wrote published papers
- Outcome: Inadequate public support for clinical research; Possible outcome-focused version (similar to NIH)