Sponsor-Investigator Responsibilities

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January 17, 2019

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Objectives

- Identify sponsor-investigator responsibilities related to clinical research regulations and guidelines
- Summarize common problems found during FDA inspections
- Apply methods to ensure compliance with regulations and guidelines for sponsor-investigators

Definitions

- Sponsor – a person who **takes responsibility** for and **initiates a clinical investigation**. The sponsor may be an individual or pharmaceutical company, government agency, academic institution, private organization, or other. **The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator.**

- Investigator – an individual **who actually conducts a clinical investigation** (i.e., under whose immediate direction the intervention or investigational product (IP) is administered or dispensed to a subject).

Who is a Sponsor- Investigator?

FDA

- An individual who both initiates and conducts an investigation, and under whose immediate direction the investigational product (IP) is administered or dispensed.
  - The term does not include any person other than an individual.
  - **The requirements applicable to a sponsor-investigator include both those applicable to an investigator and a sponsor.**

[21 CFR 312.3 and 21 CFR 812.3]

GCP

- An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). **The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.**

Key Responsibilities

- Follow Good Clinical Practice (GCP)
  - GCP in research is not the same as good clinical practice in caring for patients
    - For example, there are regulations and guidelines with very specific requirements for following the protocol, recordkeeping, and drug accountability

Key Responsibilities

- Submission and maintenance of Regulatory Authority submissions
  - IND/IDE submissions
    - New protocols under the same IND/IDE
    - Annual progress reports
    - Significant protocol revisions
    - Change in PI
    - Adding additional sites
    - Safety reporting
      - Notify FDA of any unexpected fatal or life-threatening suspected adverse reactions within 7 calendar days
      - Notify FDA (and participating investigators) via an IND safety report of potential serious risks within 15 calendar days

Resources offered through NC TraCS and ReGARDD.org

Key Responsibilities

- Monitoring of the clinical investigation
  - Protection of the rights and well-being of subjects
  - Accurate data reporting
  - Adequate oversight

Key Responsibilities

- Ensuring adequate and accurate case histories

- Ensuring documentation of receipt, shipment and disposition of investigational product

Key Responsibilities

- Oversight of third parties specifically retained to conduct study assessments, including, but not limited to:
  - Clinical Research Organization (CRO)
  - Site Management Organization (SMO)
  - Outside laboratories
  - External Pharmacy

Protocol Development

- During protocol development, the sponsor should identify those processes and data that are critical to ensure human subject protection and the reliability of trial results.
  - Simplify the protocol and outcomes
  - Review for consistency and errors

- Protocol Review Process
  - Scientific Review Committee (Non-Oncology)
  - Protocol Review Committee (Oncology)

Standard Operating Procedures (SOPs)

- The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and applicable regulations. Applicable personnel should be trained on the SOPs.
  - Informed Consent Process
  - AE Management and Reporting
  - IP Handling and Accountability
  - Multisite Management
  - Data Management

ClinicalTrials.gov

The **sponsor is responsible** for registering clinical trials when they begin, providing timely updates, submitting summary results, and making this information publicly available fulfills a number of purposes and benefits a variety of people.

- Patients and families can search for recruiting studies or learn about new treatments that are being considered.
- Researchers can stay up to date on developments in their field, find collaborators, and identify unmet needs.

ClinicalTrials.gov

	Register WHEN?	Phase 1	Phases 2-4	Device	Other Interventional*	Observational	Post Results?
ICMJE	Before enrollment of 1st subject	Yes	Yes	Yes	Yes	No	No
NIH	Within 21 days of 1st subject's enrollment	Yes	Yes	Yes	Yes	No	Yes
FDA	Within 21 days of 1st subject's enrollment	No	Yes	Yes	No	No	Yes
CMS	Prior to claims submission (for Qualifying Clinical Trials)	Yes (if qualifying)	Yes	Yes	No	No	No

* Health-related or Behavioral Interventional Trials

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Data Management

- Database
  - Secure access
  - Data sign-off capabilities
  - Audit trail for revisions

- Data Review
  - Data Safety Monitoring Board (DSMB)
  - AE review and management
  - Source-data verification

Monitoring: Definition

- The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), GCP, and the applicable regulatory requirement(s).
  - Ongoing process
  - Periodic spot-checks
  - May be risk-based

Monitoring: Why?

- The purposes of trial monitoring are to verify that:
  - 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, with GCP, and with applicable regulatory requirements.

Monitoring: How?

- The Monitoring Plan
  - Develop a systematic, prioritized, risk-based approach and document the chosen strategy in your monitoring plan.
    - On-site vs. remote monitoring
    - When to start
    - Frequency of monitoring visits
    - Documentation of visits and findings

Monitoring: How?

- Prioritize high risk areas
  - Informed consent
  - Eligibility and protocol compliance
  - IP accountability
  - Integrity and accuracy of data

Monitoring: Who?

- Selection of Monitors
  - Monitors should be appointed by the sponsor
  - Appropriately trained with the clinical knowledge needed to monitor the trial adequately; document the qualifications and training
  - Thoroughly familiar with the IP, protocol, SOPs, GCP, and applicable regulations

Monitoring: What?

Main line of contact for sites
Verifying that investigators have adequate resources to conduct the trial properly
Verifying IP accountability
Verifying protocol compliance
Verifying proper informed consent procedures
Verifying proper training
Verifying source is accurate and complete
Source-Data verification
Determining if AEs are appropriately reported
Determining if Investigators are maintaining essential documents
Communicating findings and discrepancies to the investigator and taking appropriate action for resolution

Essential Documents

Investigator's Brochure/Investigational Plan	Shipping records for IP and materials
Protocols and Amendments	Unblinding Procedures
Contract and Budget	Master Randomization List
Regulatory Authority Approvals	Trial Monitoring Reports
Sample IP Labels	Trial Initiation Reports
Instructions for handling IP	Record of retained specimens

Essential Documents – Multisite Study

Protocol Signature Pages	Relevant Communications/Correspondence
Information provided to subjects (i.e., informed consent forms, patient handouts)	Completed Case Report Forms
IRB Approvals and annual reports	AE/SAE reporting
Curriculum Vitae and Medical Licenses	Screening/Enrollment Log
IP Accountability	Delegation/Signature Log
Lab accreditations and reference ranges	Financial Disclosure Forms

Auditing: Definition

- A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
  - Independent review
  - Less frequent
  - Formal approach

Common mistakes – Risk factors for non-compliance

- Poor supervision and training of study staff
- Insufficient investigator involvement in study conduct
- Inappropriate delegation of study tasks to unqualified persons
- Failure to adequately protect study subjects
- Overworked investigator and study staff (e.g., too many subjects, complex study with large data collection, too many concurrent studies)

Frequent Findings during FDA Inspections

- Failure to ensure the investigation was conducted according to the investigational plan [21 CFR 312.60].
- Failure to ensure proper monitoring of clinical investigations [21 CFR 312.50 and 312.56(a)].
- Failure to submit an IND for the conduct of a clinical investigation with an investigational new drug [21 CFR 312.20(a), (b) and 312.40(a), (b)].
- Failure to maintain adequate records of the disposition of the IP, including dates, quantity, and use by subjects [21 CFR 312.62(a)].
- Failure to maintain accurate, complete, and current records related to the investigation [21 CFR 312.62(b)].

Frequent Findings during CTQA Reviews

- Missing essential documents
- Lack of training documentation
- Lack of correspondence
- Lack of database management and review

DON'T

- Over-delegate to non-physicians (e.g., diagnosis that qualifies/determines eligibility for entry into the study)
- Erase, white-out or obliterate original data entry
- Accept suggested changes to study data without checking the source documents or without justification for such changes
- Backdate the consent forms and signatures
- Forget to obtain IRB approval of consent form or protocol revisions
- Implement changes to a protocol without Sponsor and IRB approval
- Destroy study records

How to ensure high quality data and subject safety?

- Select qualified staff and ensure adequate training and supervision
  - Ensure staff are not performing tasks they are not qualified to do (e.g., assessing eligibility, performing physical exams, assessing adverse events)
  - Ensure oversight of sub-investigators and study staff

Improve Process – Be Proactive

- Address human factors in systems
  - Hire experienced, qualified staff
  - Avoid conflicts of interest/financial incentives
  - Decrease number of times data are handled
  - Assess ability to comply with protocol visits, laboratory testing, electronic systems for data capture, archiving and transmission to sponsor, maintaining records, etc.

Improve Process – Be Proactive

- Create systems that limit opportunities for errors
  - Simplify protocol and outcomes
  - Be realistic about the amount of data to be collected
  - Standardize systems and formats where possible
  - Use validated instruments/definitions
  - Write down all procedures (SOPs). Use checklists.
  - Don’t re-invent the wheel
  - Keep amendments to a minimum and check the CRFs and consent form against each change

Improve Process

- Develop an integrated framework
  - Data and Safety Monitoring Plan, Data Management Plan, Quality Assurance Plan, Data Analysis Plan
  - Insist on training and then test it
  - Have a disaster management plan (for floods, etc.)
  - Have a new hire management plan (for staff turnover, etc.)
  - Do beta-testing/dry-runs
  - Have weekly team meetings/calls
  - Audit yourself – be open and honest

Implement Systems to Detect and Correct Errors in Real Time

- Do real-time cleaning of the data
- Pay attention to monitoring queries and respond promptly
- Audit trail of changes should make clear what was changed, who changed it, and why it was changed
- Evaluate the need for system wide corrections and training

Resources

- ICH GCP E6(R2) dated 9Novemer 2016: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf
- Office of Clinical Trials - Links to internal and external resources (FDA, OHRP, NIH, Associations, Policies, etc.): http://research.unc.edu/clinical-trials/resources/
- Office of Clinical Trials - Links to Forms/Templates (DOA log, SAE log, Start-up Checklist, Training log, etc.): http://research.unc.edu/clinical-trials/resources/forms/
- NC TraCS – Protocol development, data management, etc.: https://tracs.unc.edu/
- ReGARDD – IND/IDE applications and maintenance: ReGARDD.org

QUESTIONS

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