Regulatory Compliance & Conducting Clinical Trial Audits

Dina Avery, DHSc, MA, MAEd
Guru Naik, MPH
Kamilah Frison, MSM

Regulatory Compliance/CLINICAL TRIAL AUDITS = PATIENT SAFETY

REGULATORY COMPLIANCE

- Principal Investigator
  Sub-Investigator(s)
- Research Manager
  Regulatory Manager
  Financial/Budget Team
  Research Coordinators
  Data Managers
- Hospital Clinical Team
  Clerical Team

RESEARCH TEAM

Important Questions

1. **Who is the Leader of the Clinical Trial?**

   Principal Investigator

2. **Who helps to ensure everyone is being compliant?**

   The PI along with the entire Research Team = Team Work

3. **Who provides regulatory training and conducts clinical trial audits?**
   Regulatory Manager and/or Quality Assurance Team

PROTOCOL DEVIATIONS = Non-COMPLIANCE

- Deviations can occur because an investigator, research staff or other party involved in the conduct of research intentionally or unintentionally decides to deviate from the approved protocol

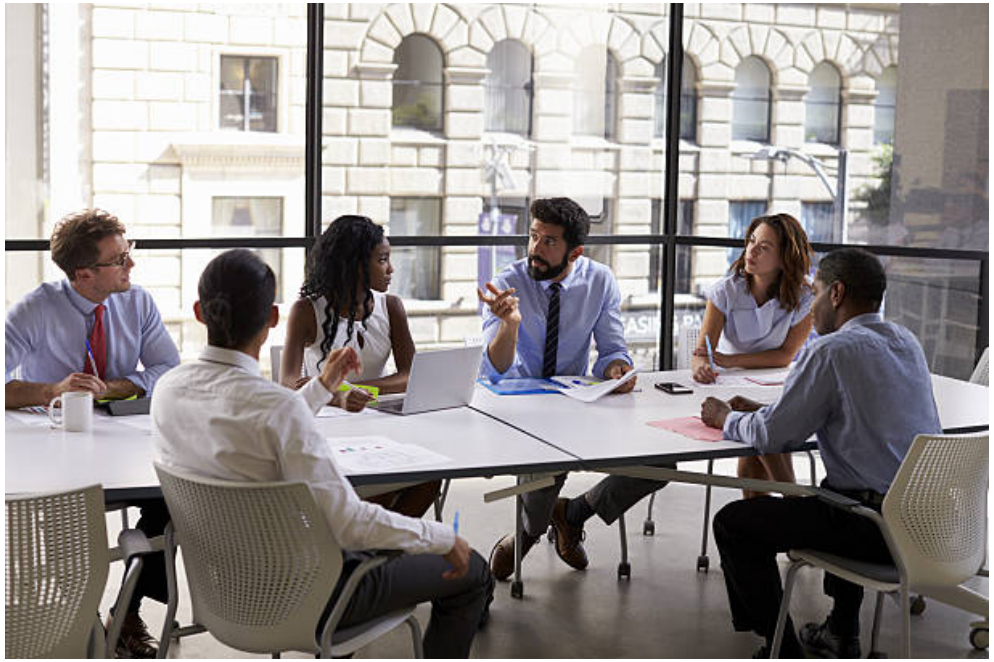
- Deviations can be discovered before or after the protocol is initiated

https://www.hhs.gov/ohrp/sachrp-committee/recommendations/2012-march-30-letter-attachment-c/index.html

Examples of Protocol Deviations

- Inadequate or delinquent informed consent
- Mishandled specimen samples
- Unreported serious adverse events
- Enrollment of a subject outside of the age range requirements

Weekly Team Meetings



Team Meeting Topics

Study Patients

- Status
- Toxicity
- Adverse Events/Serious Adverse Events

Weekly clinic schedule

- Discuss upcoming days off by staff members
- Who will cover patients?
- Are clinic rooms available based upon # date of visit

Data Management

- Status of Case Report Forms
- Data Entry

Other Administrative Tasks

How do we prevent non-compliance among the Research Team?

- Training
- Communication
- Data Checking
- Clinical Trial Audits

Quality Assurance (QA)

Quality Assurance

“All those planned and systemic actions that are established to ensure that the trial is performed and data are generated, documented (recorded), and reported in compliance with GCP and the applicable regulatory requirement(s)” [ICH1.46]

Quality Control

“the operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities are fulfilled” [ICH 1.47]

Auditing

“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), GCP and the applicable regulatory requirement(s)” [ICH 1.6]

Monitoring

“the act of overseeing the progress of a clinical trial, and ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures(SOPs), GCP, and the applicable regulatory requirement(s)” [ICH 1.38]

Auditing vs Monitoring

Auditing Function

Monitoring Function

Importance of Quality Assurance Program

- Compliance with ICH-GCP
- Contribute to site’s ability to generate first rate data

Audits

- FDA Audits
- Sponsor Audits
- Institutional Audits

Institutional QA program

- Internal (self) audits
- Actively implementing and revising SOPs
- Recording protocol deviations
- Initiate procedures to correct any shortcomings and prevent their recurrence
- Training/education of staff

Key points for conducting clinical trial audits

- When to audit - Timing
- Who should audit - Personnel
- Why to audit - Reasons
- What to audit - Documents
- Where to audit - Location

Common findings or deficiencies

- Informed Consent form
- Site Regulatory administration
- Staff qualifications
- Protocol compliance
- Subject records
- Data management
- Documentation practices
- Subject protection and reporting of adverse events
- Investigational product
- Facilities and equipment

Outcomes

- No deviations or violations
- Minor deviations
- Major deviations or violations
- Implications for PI or staff

Corrective and Preventive Actions (CAPA)

- Identify the problem
- Conduct a Root Cause Analysis (RCA) to identify the cause of the problem
- Develop an action plan to correct the problem and prevent recurrence
- Implement the plan
- Evaluate the effectiveness of the correction

CAPA may include

- Correcting or implementing revisions to the documentation
- Retraining study personnel
- Re-consenting study subjects
- Revising your department SOPs
- Reporting to the IRB/FDA or other agency, as required

Quality Improvement

- Continuous
- Evaluation
- Education
- Best practices

CLINICAL TRIALS FINANCIAL MANAGEMENT

Identify cost to conduct a clinical trial

- Start-up
- Per patient costs
- Protocol Maintenance costs
- Close-out costs

Questions to Answer

1. Is there staff time involved? What are their tasks? If so, how much time?
2. Is the service provided by a department or vendor outside of your operations? If so, obtain costs from the department or vendor for their service.
3. What procedures, labs, device are needed?

BUDGET						
P.I.:	PROTOCOL TITLE					
Sponsor/Protocol No.:						
	CPT	Unit	Screening	Cycle 1		
PATIENT CARE/ACTIVITY	Code	Cost		D1	D15	D28
Pharmacy						
--Infusion drug dispensing	N/A	75		75.00		
Treatment						
---Infusion,1st hr	36396413_96413	200.15		250.19		
Laboratory						
---CBC/Plt + Manual Diff	85027, 85007,85025	17.93	22.41	22.41	22.41	
---CMP	13529517_80053	36.45	45.56	45.56	45.56	
---Serum Preg Test	13520335_84702	24.72	Invoice	Invoice		
---Venipuncture	36336415_36415	10.19	12.7375	12.7375	12.7375	
Biologic Sampling						
---Unstained Tumor Slide, 20	2091724_0	10.00	Invoice			
Procedures						
---EKG	93010/93005	35.79	44.74	44.74	44.74	
---Brain MRI w/contrast	70552/A9579	391.80	Invoice	Invoice		
---Tumor Biopsy	Multiple Codes		Invoice			Invoice
Office Visits						
PE, Lev 4, Ret Pt	99214	158.01	197.51	197.51	197.51	
Labor						
Study Coordinator Hours	N/A	N/A	8.00	4.25	1.25	1.00
Study Coordinator	N/A	70.00	560.00	297.50	87.50	70.00
Data Management Hours	N/A	N/A	6.00	3.25	1.25	1.00
Data Management	N/A	50.00	300.00	162.50	62.50	50.00
Research Lab Tech Hours	N/A	N/A	0.50	1.00	0.50	
Research Lab Tech	N/A	50.00	25.00	50.00		
P.I. Fee Hours	N/A	N/A	3.75	1.75	1.50	
P.I. Fee	N/A	150.00	562.50	262.50	225.00	
	Visit Sub-Total (w/o OH):		1,770.46	1,420.65	697.96	120.00
	Visit Sub-Total (w/ OH):		2,301.60	1,846.85	907.35	156.00

Develop a Financial Plan (Budget)

Outline timeline for protocol required procedures and labs.

Outline timeline for protocol required tasks to be performed by research personnel

Add billing designation: Insurance or to the sponsor

Add invoice items that will be billed to the sponsor per occurrence.

1. Start Up Fee
    - Administrative Start-Up Fee
    - Pharmacy Start-Up Fee
    - IRB Human Subjects Review Fee
    - Research Radiology Start Up Fee
    - Laboratory Initiation Fee
2. Procedures
    - Brain MRI
    - Bone Scan
    - Archived tumor tissue
3. Protocol Maintenance
    - Protocol Amendments
    - Pharmacy Maintenance and Storage
    - SAE Reporting
4. Close out Fees
    - Archive Storage
    - Close Out Fee

Develop a Financial Plan (Budget)

Invoiceable Items:

- Start-up
- Procedures
- Protocol Maintenance
- Close out

Administrative Start Up Activities Examples

- Contact with MSL or CRO by email or phone
- Processing of CDA
- Review of the protocol and investigator brochure
- Site selection questionnaire
- Pre site selection visit by CRO or sponsor
- Preparation of site budget and contracting
- Site initiation visit with sponsor
- Local site initiation meeting
- Study start-up prep
- Prepare and submit regulatory documents
- Financial prep: CTMS, acct set up, bill/invoice set up
- Scientific and feasibility review

Billing Compliance

Billing Compliance begins at the budget development stage.

Document review needed:

- Contract budget
- Internal Budget
- Protocol

Insurance Coverage Analysis

1. Are the billing designations aligned on both the internal and sponsor budget?
   - Billing designation: Billed to insurance or billed to the sponsor or covered by the institution
2. Are all patients billed in the same way for the like visits and procedures?
3. Can the procedure or drug be covered by patient insurance?
4. Is the procedure or drug FDA approved for the indication in which it's being used?

Billing Compliance- During the Trial

Utilize CTMS

- Protocol Visit by protocol
- Budget
- Account Receivables
- Account Payables

Communication between Clinical Staff and Finance Staff

- Verify data regarding completed protocol activity

Tips on Funding Quality Assurance Audits

- Department Overhead Rate
- Cost Sharing
- Audit Fee

Overhead Rate

Department Overhead

$$\text{Overhead Rate} = \frac{\text{Management and Administrative Costs}}{\text{Total Operating Costs}}$$

Management and Administrative Costs:

Operations Manager

Finance Manager

Clinical Manager

Budget and Finance Team

Regulatory Manager

Quality Assurance Auditor

Telecommunications

Supplies and Materials

Travel & Training

Total Operating Costs:

Management and Administrative costs (listed above)

Principal Investigators

Clinical Research Coordinators

Data Coordinators

Cost Sharing

1. Audit Prep
    - QA/QC Manager
    - PI
2. Audit Visit (per day)
    - Data Manager
    - CRC
    - PI

AUDIT FEE

A fee is assessed for an FDA or Sponsor audit. This fee will be charged for staff time to prepare for an FDA audit and time during the audit visit.

A monitoring visit conducted by the sponsor/designee every 4-6 weeks to review source documents and compliance with the protocol is standard.

A sponsor requested audit is not a standard monitoring visit. The additional cost for this special request should be invoiced to the sponsor.


ANY
QUESTIONS
?

THANK YOU

Dr. Dina Avery

dvavery@uab.edu

Kamilah Frison, MSM

kfrison@uab.edu

Dr. Guru Naik

alkanand@uab.edu