BUILDING QUALITY INTO DEVICE CLINICAL TRIALS: SPONSOR'S AND INVESTIGATOR'S ROLES AND RESPONSIBILITIES

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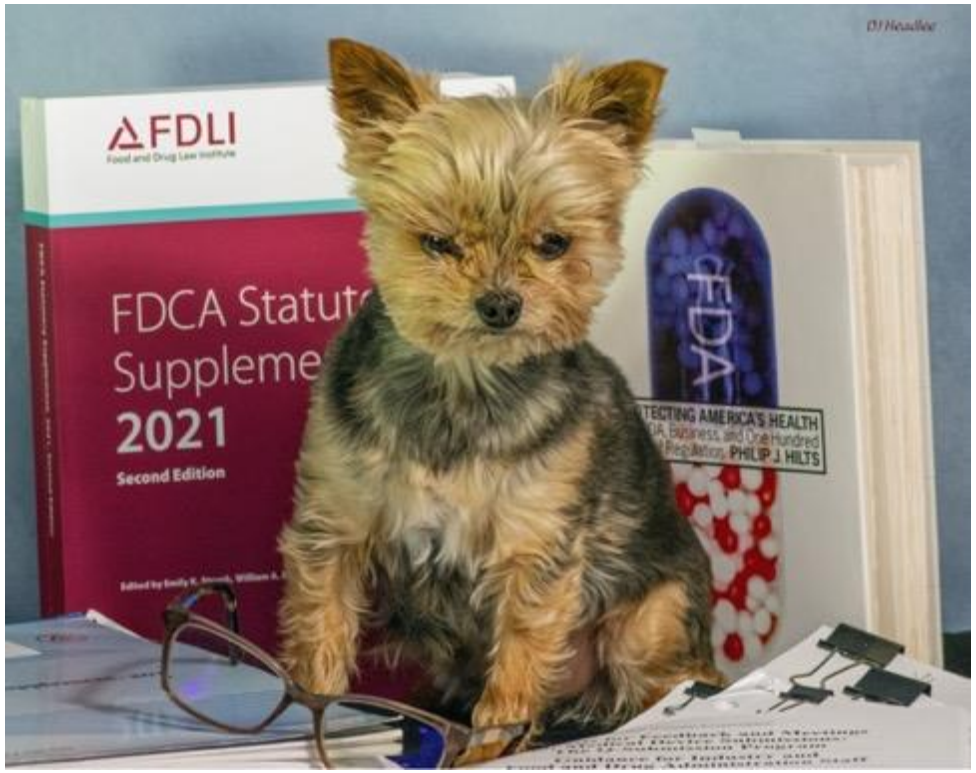
JOINT UMSON MRS AND BMORE SOCRA CHAPTER MEETING:

OBJECTIVES



- Describe roles and responsibilities of sponsors
- Describe roles and responsibilities of investigators
- Describe FDA/CDRH/BIMO inspectional findings
- Discuss strategies for how to be prepared, what to do during, and after FDA/CDRH BIMO inspections

SPONSOR ROLE AND RESPONSIBILITIES

GENERAL RESPONSIBILITIES: SPONSOR

- Select qualified investigators
- Provide investigators with information
- Monitoring
- IRB review and approval are obtained
- Submit an IDE application to FDA
- Inform reviewing IRB and FDA of significant new information

21 CFR 812.40

SPONSOR RESPONSIBILITIES

- Obtain signed Investigator Agreements
- Ship investigational devices
- Obtain financial disclosure information
- Select qualified monitors

MONITORING

- Act of overseeing an investigation
- Qualified by training and experience
- Assure the protection of human subjects and data integrity

RISK BASED MONITORING

Guidance for Industry: Oversight of Clinical Investigations-A Risk-Based Approach to Monitoring
https://www.fda.gov/downloads/Drugs/.../Guidances/UCM269919.pdf

IDENTIFY CRITICAL DATA AND PROCESSES TO BE MONITORED

- Factors to Consider when Developing a Monitoring Plan
  - Complexity of the study design
  - Types of study endpoints
  - Clinical complexity of the study population
  - Experience of the CI and of the sponsor with the CI
  - Electronic data capture
  - Relative safety of the investigational product
  - Stage of the study
  - Quantity of data

CAN THE RESPONSIBILITY OF MONITORING BE DELEGATED?

- No
- Yes

★The sponsor is ultimately responsible

SPONSOR RECORDS

- Correspondence with another sponsor, monitor, CI, IRB and FDA
- Shipment and disposition of the investigational device
- Signed Investigator Agreements and Financial Disclosure
- Non-significant risk device records
- Adverse device effects and complaints
- Other

21 CFR 812.140(b)

SPONSOR REPORTING

Type Report	To FDA	To all Reviewing IRBs	To Other Investigational Sites
Unanticipated Adverse Device Effects	X	X	X
Withdrawal of IRB approval	X	X	X
Withdrawal of FDA approval	X	X	X
Investigator List	X		
Annual Progress Report	X	X	X
Recall and Device Disposition	X	X	X
Final Report	X	X	X
Use of Device Without Informed Consent	X		
Significant Risk Determination	X	X	X
Protocol Amendments	X	X	X
Protocol Deviations	X	X	
Other Reports requested by FDA or IRBs	X	X	

INVESTIGATOR ROLE AND RESPONSIBILITIES

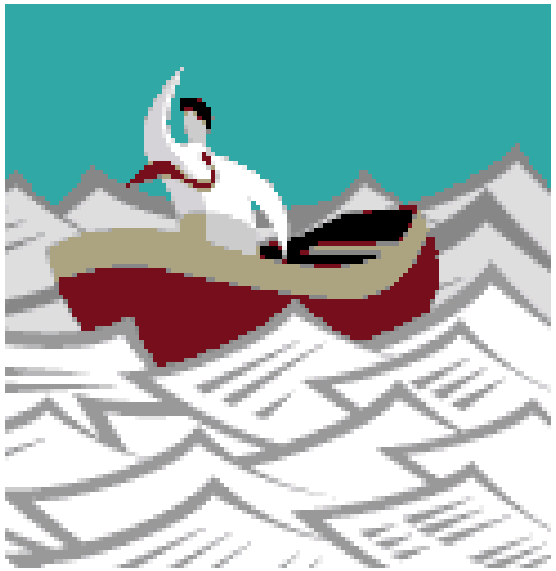
INVESTIGATOR RESPONSIBILITIES

- Obtain IRB approval prior to enrolling any subjects
- Obtain and document informed consent
- Follow the protocol

INVESTIGATOR RESPONSIBILITIES (CONT.)

- Implant/use device only in/on subjects enrolled on study
- Ensure adverse effects (AEs) are appropriately documented and reported
- Maintain adequate records

INVESTIGATOR RECORDS



- All Correspondence with other investigators, the IRB, the monitor, and the FDA

DEVICE RECORDS

- Records of receipt, use, and disposition of device including:
  - **Type and quantity** of the devices, **dates of receipt**, and **batch number or code mark**
  - Name of all **persons who received**, **used, or disposed** of each device
  - Why and how many devices have **been returned, repaired, or other wise disposed of**

PROTOCOLS

- All IRB approved approvals
  - Including amendments
- Documentation of protocol deviations and IRB and sponsor approvals

INVESTIGATOR RESPONSIBILITIES -STUDY DEVIATIONS

- Document dates and reasons for any deviations from the study protocol
- Obtain prior approval from the sponsor, IRB, and FDA for changes or deviations from the investigational plan
- Emergency deviations must be reported to the sponsor and IRB within 5 days

CASE HISTORIES

- CRFs and supporting data
  - Informed consent documents
  - Exposure to the device
  - Adverse device effects
  - Any relevant observations

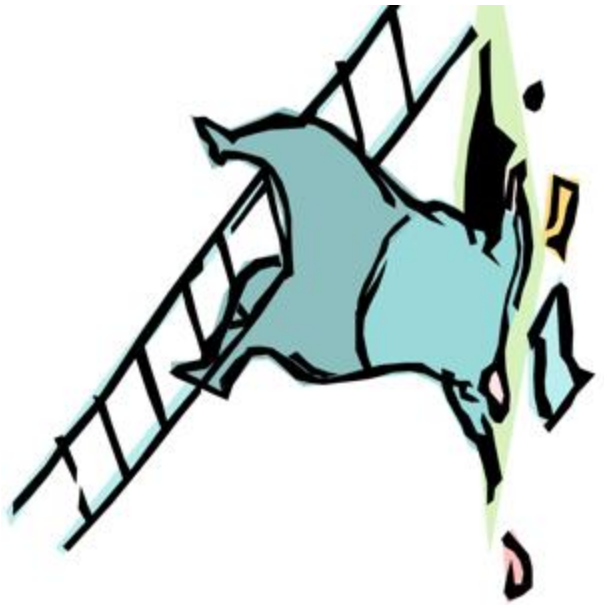
DOCUMENTATION

If is not documented,

it did not happen

ADVERSE EFFECT (AE)

- Any adverse medical occurrence that may or may not be related to the investigational device



UNANTICIPATED ADVERSE DEVICE EFFECT (UADE)

- Any serious adverse effect that is possibly caused by or related to the investigational device:
  - Not previously identified in nature, severity, or degree, or
  - Any other unanticipated serious problem associated with a device

21 CFR 812.3(s)

INVESTIGATOR REPORTS

- Unanticipated Adverse Device Effects
- Withdraw of IRB approval
- Progress reports
- Deviations from the investigational plan
- Informed consent
- Final report
- Other

BIMO INSPECTIONS

ROLE OF BIORESEARCH MONITORING DIVISION (DBM)

- Seeks to protect human research subjects from undue hazard or risk
- To ensure the quality and integrity of data submitted in support of device applications

TOP SPONSOR DEFICIENCIES

CFR Regulation	Description
812.46(a)	Sponsor's failure to secure investigator's compliance/device return/disposal or comply with agreement
812.140(b)	Sponsor correspondence records, device shipment, disposition, or investigator agreement incomplete, inaccurate or lacking
812.40	General duties of sponsors
50.27(a)	Consent form not provided, approved, signed or dated
812.43(c)	No investigator agreement; no financial disclosure

TOP INVESTIGATOR DEFICIENCIES

CFR	Description
812.110	Failure to follow investigational plan, investigator agreement, or protocol
	Record and report protocol deviations
812.140(a)	Failure to document case hx/device exposure
812.150(a)	Failure to report UADEs
50.27(a)	Failure to obtain adequate informed consent
	Failure to obtain IRB Approval
812.140	Product Accountability

SI- MOST FREQUENT SPONSOR VIOLATIONS

- IDE violations
  - submit IDE application
  - submit IDE supplement(s)
- Reporting violation
- Secure Investigator compliance
- Monitoring violations

SI-MOST FREQUENT INVESTIGATOR VIOLATIONS

- Follow Investigational Plan & FDA Regulations
- Maintain records
- Obtain IC in accordance with Part 50
- Reporting

Failure to ensure that the current, IRB-approved version of the informed consent was executed by each of the subjects in that the 38 unapproved consent forms signed by study subjects were missing basic elements required by regulation to be in an informed consent document.

Response: *"you cited us on a technicality."*

EXAMPLE OF AN INADEQUATE RESPONSE:

Failure to secure the investigator's compliance with the signed investigator agreement, the investigational plan, applicable FDA regulations, and any other conditions of approval imposed by the reviewing Institutional Review Board (IRB) or FDA. [21 CFR 812.46(a)]

You failed to secure investigator compliance with the investigation plan and applicable FDA regulations.

Response: *"…virtually all of the serious documentation problems appear to have been the work of a single research coordinator who was delinquent in fulfilling her assigned study duties."*

EXAMPLE OF AN INADEQUATE RESPONSE

EXAMPLE OF AN INADEQUATE RESPONSE

Failure to adequately supervise the conduct of the study.

Response: *"I am not, nor ever have been involved with any data collection or entry in any study. If my life depended on it, I could not access data. I do not know how. I do not know which patients are enrolled in the current FDA study."*

RESPONSE TO 483

A well reasoned, complete, and timely response (within 15 days) to a FDA From 483 is in your best interest

No regulatory requirement to respond

WHAT TO INCLUDE IN RESPONSE

- Assessment of the **root cause**
- **Corrective actions**
- Evaluation of the **extent of the problem**
- **Preventative actions**
- **Supporting documentation**
- **Timeline** for implementation

STRATEGIES FOR CONDUCT OF A QUALITY STUDY

RISK DETERMINATION

The assessment of whether or not a device study presents a NSR is initially made by the sponsor

Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors Significant Risk and Nonsignificant Risk Medical Device Studies
https://www.fda.gov/media/75459/download

Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program
www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program

STEPS TO QUALITY STUDY

- Collaborate obtain feedback on protocol requirements
- Communicate with study team, IRB, and Regulatory Agencies

Data Lifecycle

WHAT ARE ELEMENTS OF QUALITY DATA?

- **A**ttributable
- **L**egible
- **C**ontemporaneous
- **O**riginal
- **A**ccurate

SELECT QUALIFIED INVESTIGATORS

- Knowledge, training, & experience
  - appropriate for the device
  - specific use in the study
- Commitment to research
  - clinician vs. researcher

21 CFR 812.43(a)

SELECT ADEQUATE STUDY SITES

- Patient Population
- Staff Availability
- Qualified Personnel
- Resources
- Equipment

PROVIDE ADEQUATE TRAINING

- **Before** study, when essential **staff replaced** & **as needed**
  - Specific study expectations
  - Procedures unique to the device or its use in the study
  - Significant changes in device & protocol
  - Compliance concerns
  - Regulatory requirements
    - Importance of the informed consent process
  - Clinician versus Investigator

21 CFR 812.40

ENSURE ADEQUATE MONITORING

- Early & frequent enough for specific study
- Correct issues before study integrity is jeopardized
- Avoid numerous queries and late database cleanup

21 CFR 812 40 and 812.46

SECURE COMPLIANCE

- Predetermined strategy for obtaining investigator compliance
- Immediate actions to correct noncompliance
- Where applicable, device shipments halted until evidence of compliance
- If all else fails, site’ s participation in study terminated

PROTOCOL DEVIATIONS

- Conduct appropriate training and re-training for study site personnel
- Provide CRF completion guidelines
- Ensure that site understands the difference between "practice of medicine" and clinical research
- Provide instructions on handling protocol deviations

DOCUMENT AND REPORT ADVERSE DEVICE EFFECTS

- Document adverse effects
- Report reporting Unanticipated Adverse Device Effects
  - within 10 working days after first learning of the effect

21 CFR 812.140

QUALITY SYSTEMIC APPROACH

- Build quality into every step
- Evaluate the process at every stage in the data lifecycle
- Ensure accurate, complete, and current data at every stage in the data lifecycle

CORRECTIVE & PREVENTATIVE ACTION PLAN (CAPA)

DEVELOP AND IMPLEMENT A CORRECTIVE AND PREVENTATIVE ACTION PLAN (CAPA) TO ENSURE QUALITY DATA

SUMMARY

- Incorporate the elements of quality throughout the data lifecycle
- Implement best practices for the conduct of Quality Trial
- Develop and implement a corrective and preventative action plan

QUESTIONS

YOUR CALL TO ACTION

- Understand Roles and Responsibilities of Sponsors and Investigators
  - Sponsor investigator dual role
  - Comply with local, state and federal regulatory requirements.
- Conduct Quality Trial
  - Protection of Human Subjects
  - Quality and Integrity of Data