A System for Protecting Human Research Participants:

NIH Initiatives

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Essential Components of the System

- Required education for key personnel
- Required data and safety monitoring for all clinical trials
- Required monitoring plan for phase I/II trials
- Improved reporting of adverse events for multisite clinical trials
- Financial conflict of interest

NIH Required Education in the Protection of Human Research Participants

Who Must Comply?

All key personnel responsible for:

- Study design
- Conduct of research
- Analysis of data
- Presentation of findings

Which Funding Mechanisms Are Affected?

- All research grants and cooperative agreements, including subawards
- Contracts and subcontracts
- NRSA research fellowship
- Foreign awards and foreign subcontracts

But NOT

- Institutional research training grants

What Constitutes Educational Documentation?

Prior to any award, the NIH requires a letter that contains:

- Names of key personnel
- Title of the education program completed by each key personnel
- One sentence description of each program
- Signed by both the PI and the institutional official

When Should Documentation be Submitted to the NIH?

Just-in-Time

- New Grants and Cooperative Agreements
- New Contracts

Prior to award

- Non-competing continuations with progress report
- Only once for each grant, cooperative agreement or contract

Data and Safety Monitoring

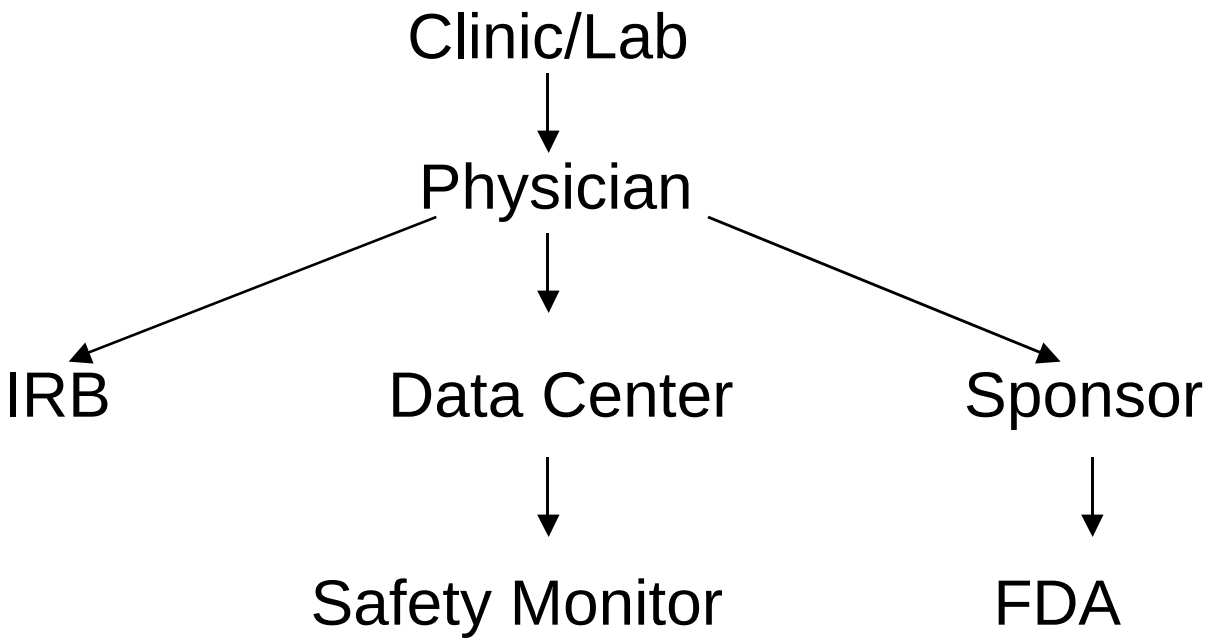
Data and Safety Monitoring

- Pertains to all phases of research
- Different phases may require different approaches
- Monitoring commensurate with level of risk
- Monitoring commensurate with size and complexity
- Must submit plan to NIH for review

Adverse Event Reporting in Phase I, II HIV/AIDS Trials

- General Considerations
- Reporting Pathways
- Data Quality
- Data Analysis
- Acting on Reports

Reporting Pathways



Data Quality

- Internal quality assurance
- Local review
- Data center edits
- Site monitoring

Acting Reports

- Treat AE as indicated
- Discontinue study medication, per protocol
- Apply dose escalation scheme, per protocol
- Safety report

Adverse Event Reporting: Large-Scale Multicenter Clinical Trials

Policy

http://grants.nih.gov/grants/guide/notice-files/not99-107.html

All multisite clinical trials with DSMBs are expected to forward summary reports of adverse events to each IRB involved in the study."

Goal

- Provide an accurate picture of safety
- Deal with problems interpreting individual events
- Coordinate IRBs and DSMBs

Process for Multi Site Trials

- PI sends AER's to local IRBs
- PI sends AER's to Data Coordinator Center
- Data Coordinating Center creates a summary of AERs
- Data Coordinating Center sends summary to DSMB
- DSMB discusses summary report
- PI sends summary to DSMB discussion to NIH
  - NIH forwards summary to all other investigators, and they in turn send it to their local IRB's
  - IRB's should communicate concerns back to DSMB

Improving Protections for Human Subjects:

Reporting FDA Communications to the NIH

Required Reporting From the FDA to the NIH:

- Pertains to FDA warning notices and letters
- Pertains to clinical studies with an IND or IDE
- Pertains to studies with any level of NIH funding
- Investigator must report to funding NIH IC within 72 hours of receipt
- Failure to comply may result in corrective and/or enforcement action

FDA Regulation (21 CFR 312.55)

- FDA communicates with the sponsor of the IND or IDE
- Sponsors are responsible for keeping each participating investigator informed

What must be reported?

- Warning letters
- Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE)
- Notice of Opportunity for Hearing (N00H)
- Notice of Disqualifications
- Consent Agreement
- Clinical Hold Letters

Clinical Hold Letters

- Pertains to breaches of good manufacturing practices and good clinical practices
- Pertains to other major issues that may cause delay or significant change in protocol

Significance:
Why Does NIH Need to Know?

- Information exchange is at the heart of fulfilling program responsibilities.
- As stewards of public funds, we must know when something is amiss and how to fix it.

Financial Conflict of Interest Regulation

Goal:

To promote objectivity in the design, conduct, analysis, and reporting of research

Authority:

42 CFR Part 50, Subpart F

“Responsibility of Applicants for Promoting Objectivity in Research for Which PHS Funding Is Sought”

Implementation:

Authorized organizational official’s signature on application certifies compliance

Examples of Institutional CoI Procedures:

- Public disclosure of all significant financial interests
- Monitor research with independent reviewers
- Modify research plan
- Disqualify all conflicted individuals from some or all PHS funded research
- Require divestiture of significant financial interests
- Sever relationships that create actual or potential conflicts

Investigators' Responsibilities:

- Identify and disclose financial CoI to institution
- Work with institution to manage, reduce, or eliminate financial CoI
- Ensure objectivity in:
    - Study design
    - Conduct of research, including
        - Communication of risks to subjects
        - Selection of subjects
        - Informed consent
        - Analysis of data
        - Reporting of findings

Examples of CoI Strategies for IRBs

- Ensure IRBs are aware of institutional process to identify and manage, reduce, or eliminate financial CoI
- Instruct new IRB members about how to identify and respond to CoI
- Informed consent form to include statement of investigators' compliance with institutional CoI policies and process
- Ask investigators to complete short questionnaire on financial CoI