

Study Monitoring & Regulatory Compliance for Global Health Research

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Outline

- What is monitoring?
- Why is monitoring necessary?
- Who should be responsible?
- How to ensure compliance:
 - writing a monitoring plan
 - setting up monitoring initiatives, and
 - conducting monitoring activities
- Monitoring Methods

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Definitions

- **Monitoring:** An act or a process of overseeing the progress of a clinical research project, and of ensuring that it is conducted, recorded, and reported in accordance with the IRB/REC-approved protocol, applicable international and/or local ethical and regulatory requirements, as well as institutional policies and procedures
- **Monitoring plan:** A plan, as part of the research protocol, that describes who reviews the data, what data are reviewed, and how often the review occurs

Definitions (cont.)

- **Data and Safety Monitoring Board (DSMB):**
An independent monitoring committee that may be established by the sponsor or the principal investigator (PI) to assess at intervals the progress of a clinical research protocol, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor or PI whether to continue, modify, or stop a study

Case Study #1

Tanzanian Investigators at National University propose to examine the efficacy of distraction with watching cartoon, parental presence and combined with watching cartoon and parental presence on reduction of anxiety during inhalational induction of anesthesia using sevoflurane. Children, ages 1-7 years, will be randomized to one of the three study arms.

Data Safety Monitoring Board or Plan?

Case Study #2

European Investigators plan to investigate the efficacy of a new antiobesity drug, sveltix, versus placebo for reducing the risk of myocardial infarction, stroke, or cardiovascular death in patients with abdominal obesity at increased risk for such cardiovascular events. Several study sites have been recruited to conduct this study, including Botswana, Tanzania, and Nigeria. Men and women, ages 55 and older, will be randomized to one of two arms.

Data Safety Monitoring Board or Plan?

Definitions (cont.)

- **IRB or Research Ethics Committee (REC):** An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a study by, among other things, reviewing, approving, and providing continuing review of research protocol and modifications and the methods and materials to be used in obtaining and documenting informed consent of research subjects

Definitions (cont.)

- **Investigator:** A person responsible for the conduct of the clinical research at a study site. If a study is conducted by a team of individuals at a particular site, the investigator is the responsible leader of the team and may be called the principal investigator (PI)
- **Sponsor:** An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical research project

Definitions (cont.)

- **Sponsor-Investigator:** An individual who both initiates and conducts, alone or with others, a clinical research project, and under whose immediate direction the investigational product is administered or dispensed to, or used by a subject. Sponsor-investigator assumes responsibilities of both sponsor and investigator

Monitoring for Ethical and Regulatory Compliance

- Respect for persons
 - Proper informed consent process approved by the IRB/REC and followed by investigators
- Beneficence
 - Proper data and safety monitoring by sponsor and investigators to ensure risks are reasonable in relation to benefits
- Justice
 - Equitable selection of subjects by investigator, sponsor and IRB/REC

Monitoring for Ethical and Regulatory Compliance (cont.)

- US FDA-regulated studies (21 CFR 312, 812, 50, 56)
 - Responsibilities of Sponsors and Investigators
 - Protection of human subjects
 - Institutional Review Board
- US HHS-funded studies (45 CFR 46)
 - Protection of human subjects
 - NIH-funded studies include monitoring requirements
- Studies required to follow ICH GCP Guidelines (E6)
 - Specific requirements on monitoring (§5.18)
- Country-specific regulation/guidelines
 - OHRP 2014 Edition of the International Compilation of Human Research Standards

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Responsibilities of IRB/REC

- Consider the qualifications of the investigator
- Conduct initial review
- Conduct continuing review
- Notify investigators about IRB/REC decisions
- Review and approve changes in research activities
- Review the method, timing and schedule of payment to subjects

Responsibilities of IRB/REC (Cont.)

- Ensure prompt reporting to appropriate institutional officials, regulatory agencies and funding sources of:
 - unanticipated problems including serious adverse events involving risks to subjects or others
 - serious or continuing noncompliance with applicable regulatory requirements
 - suspension or termination of approval

Responsibilities of Investigators

- Protect rights, safety and welfare of subjects
- Conduct study according to signed investigator statement, protocol, and applicable regulations/guidelines, as well as institutional requirements (i.e., reporting adverse events, protocol violations)
- Obtain informed consent
- Control of investigational products
- Secure IRB/REC review and approval

Responsibilities of Sponsors

- Select qualified investigators
- Ensure proper monitoring
- Ensure compliance with protocol
- Proper record keeping
- Maintain effective IND/IDE, if applicable
- Prompt reporting of SAEs to regulatory agency (i.e., FDA) and all participating PIs
- Disposition of unused investigational products

Top Ten Common Deficiencies

1. Unaware of regulatory requirements/institutional policies
2. Failure to follow IRB/REC-approved protocol
3. Failure to report protocol violations
4. Failure to report adverse events
5. Improper documentation of informed consent
6. Failure to document subject eligibility
7. Incomplete/inaccurate source documentation
8. Poor/insufficient record keeping
9. Lack of local REC approval
10. Lack of study monitoring

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Responsible for Monitoring

- Institution/IRB/REC
 - IRB/REC review and approve monitoring plan
 - Request modifications to the approved monitoring plan, as needed
 - Ensure proper implementation of monitoring plan
 - Review monitoring & DSMB reports

Responsible for Monitoring (cont.)

- Sponsor
 - Establish written procedures for monitoring
 - Include detailed monitoring plan in protocol
 - Establish DSMB, when necessary
- Investigator
 - Be familiar with monitoring plan
 - Include detailed monitoring plan
 - conduct monitoring activities

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Writing a Monitoring Plan

■ Recommended elements for a monitoring plan

1. Safety monitoring

- Safety information
 - Specific parameters for review
 - Frequency of the safety reviews
- Stopping rules
 - Subject stopping rules
 - Study stopping rules
- Adverse event reporting

Writing a Monitoring Plan (cont.)

■ Recommended elements for a monitoring plan

2. Data monitoring

- Specific information/documentation to be reviewed
 - Informed consent documentation
 - Subject eligibility
- Frequency of the data review, based on
 - The complexity of the study
 - The number investigators conducting the study
 - The nature of the disease or other condition under study

Writing a Monitoring Plan (cont.)

- Recommended elements for a monitoring plan
 3. Investigational product accountability
 - Who responsible for dispensing drug/device
 4. Privacy and confidentiality
 - Procedures to protect subjects' privacy interests
 - Procedures to protect confidentiality of research data
 5. Person(s) responsible for review

Setting up Monitoring Initiatives

- Selecting qualified monitor
 - Education
 - Training
 - Experience
- Developing proper monitoring tools
 - Checklists
 - Logs
- Routine communication with all involved individuals

Conducting Monitoring Activities

1. Pre-study-initiation visit – ensure the PI
 - Understands and is familiar with the protocol
 - Understands and accepts obligations to obtain informed consent in accordance with applicable regulatory requirements
 - Understands and accepts obligation to obtain IRB/REC approval prior to initiating any research-related activities
 - Has access to an adequate number of suitable potential subjects
 - Has adequate facilities and sufficient time to conduct the study

Conducting Monitoring Activities

2. Periodic visit

- Protocol is being followed (violations are reported)
- Changes to the protocol have been approved by the IRB/REC
- Accurate, complete, and current records are being maintained
- Accurate, complete, and timely reporting is being made to the sponsor and IRB/REC
- The investigator has delegated study-related responsibilities properly

Conducting Monitoring Activities

3. Review of subject records

- Study record is complete, accurate, and eligible
- There are no omissions in the reports of specific data elements
- Missed visits or examinations are noted in the subject records
- Reasons for subject withdrawal are noted
- Informed consent has been documented in accordance with regulatory requirements

Conducting Monitoring Activities

4. Monitoring reports

- Purpose of the monitoring
- Findings
- Conclusions
- Actions taken to correct deficiencies/violations
- Distribute to the appropriate parties in a timely fashion

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Monitoring Methods

- Onsite Monitoring
 - In-person evaluation carried out at the sites where the study is being implemented
- Centralized Monitoring
 - Remote evaluation carried out at a location other than the sites at which the study is being implemented
 - Encouraged by FDA, where appropriate

Centralized Monitoring

- Depends on...
 - The PI' s use of electronic systems
 - Access to participant records
 - Timeliness of data entry
 - Communication tools available to the investigators
 - Infrastructure/site-specific support, e.g., power supply; internet connectivity, etc.

When to Favor Centralized Monitoring

- Routine review of submitted data
- Conduct statistical analyses to identify data trends not obvious on-site
- Analyze site characteristics, performance metrics
- Verify critical source data remotely as per the monitoring plan
- Complete administrative and regulatory-related tasks, e.g., verify IRB review

Platforms to Support Centralized Monitoring

- Interactive video and audio chat. e.g., Skype, Facetime, google chat
- To facilitate secure file sharing:

File Sharing Applications	Maximum File Size	Registration Required	Premium Account	Password Protected	Website
Pando	1GB	Yes	Yes	Yes	http://pando.com/
Wikisend	100Mb	No	No	Yes	http://wikisend.com/
SendThisFile	Unlimited	Yes	Yes	Yes	http://www.sendthisfile.com/
Dropbox	Unlimited	Yes	Yes	Yes	https://www.dropbox.com/
Box	Unlimited	Yes	Yes	Yes	http://www.box.com/

- To interview investigators/study staff on site or provide site-specific education/training, WebEx.com, GotoMeeting.com

Questions?