

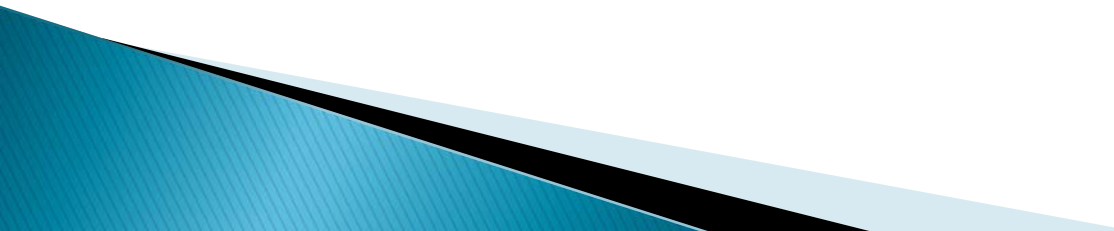
Monitoring Clinical Trials

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Monitoring Clinical Trials

Objectives

- Define monitoring and explain why monitoring is important in clinical trials
 - Provide an overview of the components of an overall monitoring plan
 - Describe what needs to be included in a site monitoring plan
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- ▶ “...IRBs function largely on trust; trust that the investigators will carry out the study according to protocol, trust that the data will be collected carefully, trust that the interests of the subjects will be primary and supercede (*sic*) those of the research, and trust that the investigators' conflicts of interest will not interfere with or bias the study.”

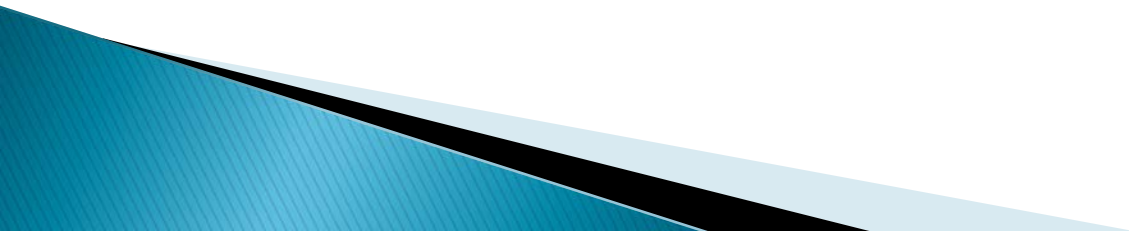
<http://ori.hhs.gov/education/products/ucla/chapter5/default.htm>

Unfortunately:

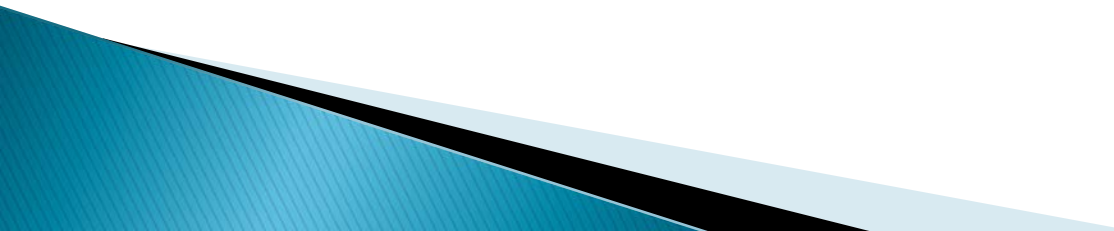
TRUST IS NOT ENOUGH!



Processes must be in place to ensure that an investigation is conducted according to the protocol, data are collected and recorded properly and human subjects are protected.



These processes are
referred to as a
**Data Safety Monitoring
Plan.**



Monitoring Plans

What is Monitoring?

- Monitoring means overseeing an investigation.
- Monitoring is an **ongoing process** of overseeing the progress of a clinical trial, **from start to finish**.
- Monitoring is a quality control tool for determining whether study activities are being carried out as planned, so that deficiencies can be identified and corrected.

Monitoring Plans

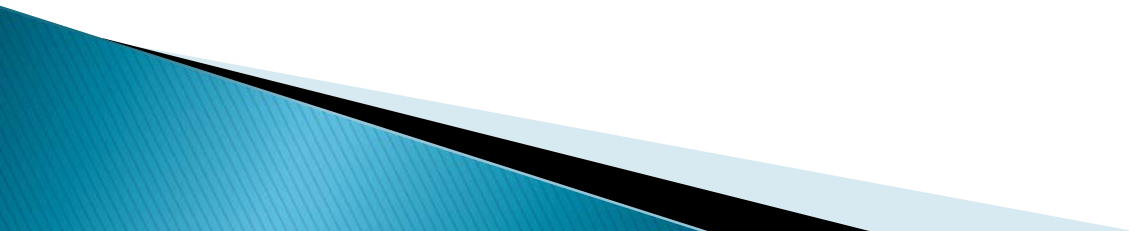
Effective monitoring of clinical trials is critical to

- Human subject protection.
- Conduct of high-quality studies.
- Data Integrity.



Monitoring Plans

Monitoring is important, but is a monitoring plan required?



Monitoring Plans

A monitoring plan is required by the Emory IRB for studies which are more than minimal risk.

- Emory IRB P&P 50
 - Data and Safety Monitoring Plan (DSMP): ... a detailed DSMP is required for all research that is not exempt under Federal regulations applicable to Human Subjects Research.



Monitoring Plans

FDA drug and device regulations make monitoring of clinical investigations by sponsors mandatory, not optional.

FDA mandates that the sponsor monitor a clinical investigation. Monitoring is not optional:

- 21 CFR 312.50 and 812.40:

- Sponsors are responsible for ensuring proper monitoring of the investigation

- 21 CFR 812.25(e):

- Requires written monitoring procedures



Monitoring Plans

FDA Warning Letter Excerpts

- “Our investigation revealed that protocol X was not monitored. It appears that had the study been monitored as required by FDA regulations, the observations discussed below might have been prevented.”
- “Your practice of conducting monitoring visits once during the course of the study or only during study closeout is a serious violation of your responsibility as the study sponsor.”



Monitoring Plans

- Emory has auditors. What's the difference between Monitoring and Auditing?

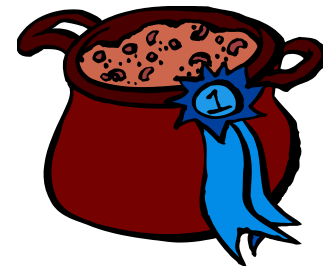


Monitoring Plans

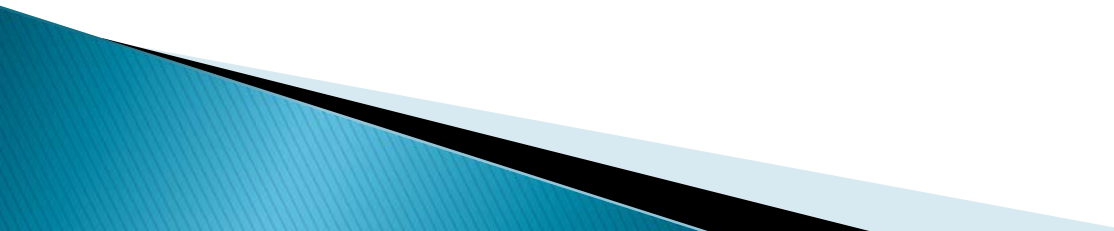
- Monitoring is an **ongoing process** of overseeing the progress of a clinical trial, **from start to finish**.



- Auditing is an **independent, systematic** review of a clinical trial; a compliance **snapshot**.



Monitoring Plans

- Both monitoring and auditing processes assess compliance with federal regulations, the scientific protocol, sponsor requirements, and institutional policies.
 - Audits are performed by Emory auditors to ensure that clinical trials are being conducted according to appropriate regulations and guidance, and to evaluate the quality of research undertaken at Emory.
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Monitoring Plans

- ▶ Monitoring is important and required, but what needs to be included in the monitoring plan?



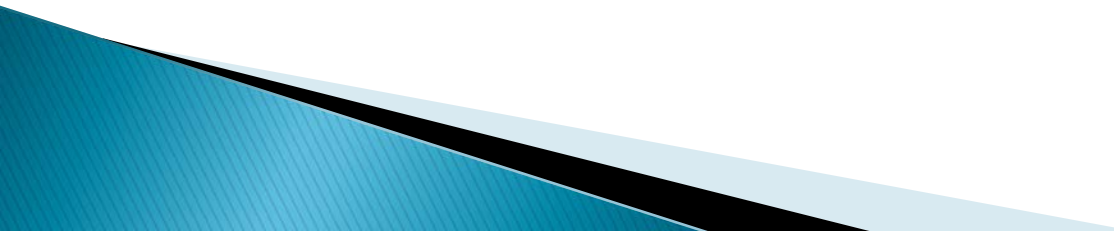
Monitoring Plans

- ▶ The Overall Data Safety Monitoring Plan must be able to
 - detect and address safety issuesAND
 - ensure protocol compliance and data quality.



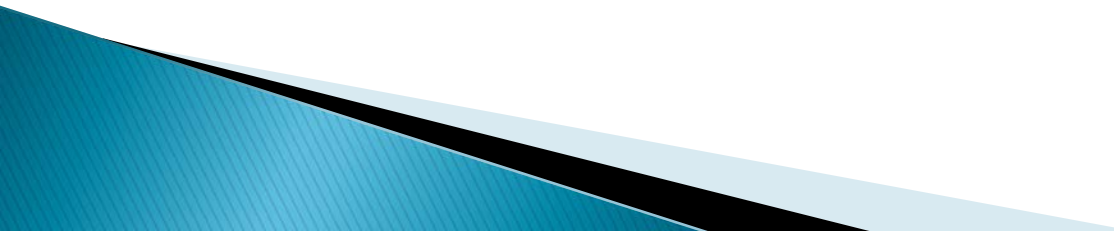
Monitoring Plans

Overall Data Safety Monitoring Plan may require review of safety reports and trial data by a Data Safety Monitoring Board (DSMB) or medical monitor.



Monitoring Plans

If a DSMB or medical monitor is required to review safety data

- the monitoring plan must describe how often the review will occur along with any stopping rules.
 - This review may be part of the overall monitoring plan, but it is not the entire monitoring plan.
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Monitoring Plans

- **Overall Monitoring Plan** should describe the Principal Investigator's specific plans for:
 - Monitoring the progress of the trial
 - Assuring data accuracy and protocol compliance
 - Collecting & evaluating safety information from sites and from other sources (e.g., other studies, other countries where drug is approved, etc.)
 - Providing information & managing communication in multi-site trials

Monitoring Plans

A **Site Monitoring Plan** is part of the overall monitoring plan and describes how information is collected about protocol compliance at each site and the quality of the data being collected.



Monitoring Plans

A site monitoring plan should:

- Delineate how data accuracy and protocol compliance will be ensured and validated.
- Delineate reporting obligations for protocol deviations/violations and noncompliance.

Monitoring Plans

- ▶ Monitoring is important and required, but how does a sponsor or an investigator develop the site monitoring plan?



Monitoring Plans

A recent FDA Draft Guidance document provided recommendations:

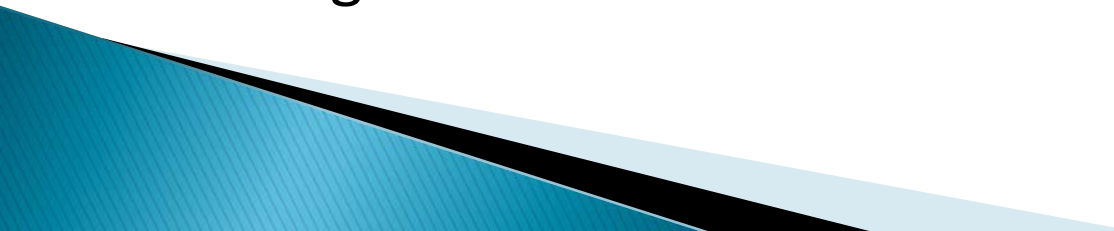
- The monitoring plan should be tailored to the specific human subject protection and data integrity risks of the trial.
 - The level of detail in the plan should be based upon the degree of risk to the subjects.
 - The intensity and frequency of monitoring should be tailored to fit the expected risk level, complexity, and size of the particular study.
- Sponsors can use a variety of approaches to fulfill monitoring responsibilities.

Monitoring Plans

- FDA also makes clear that the monitoring plan must be written and the activities must be documented.



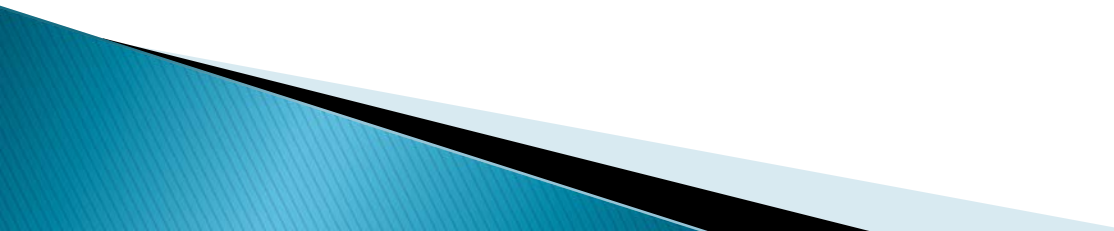
Monitoring Plans

- Consider these factors when developing a site monitoring plan:
 - Stage of study, complexity of study design & types of study endpoints
 - Experience of the investigator and study staff
 - Clinical complexity of study population
 - Study intervention
 - Relative safety of investigational product
 - Quantity of data
 - Single site or multi-site
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Monitoring Plans

Describe the monitoring methods, responsibilities, and requirements for the trial.

➤ Required elements include:

- the frequency of the monitoring
 - who will conduct the monitoring
 - what data will be monitored
 - how the data will be evaluated for problems
 - what actions will be taken upon the occurrence of specific events or end points
 - how/when communication to the IRB will occur
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Monitoring Plans

Site Monitoring Plan Element Examples

- **Frequency of reviews.**

Example : Review after the first three subjects are enrolled.
At a minimum, review is required annually.

- **Identity of site monitor.**

Example: Specify position of person who will monitor or name CRO to which monitoring has been delegated.

- **Scope of site monitoring.**

Example: Informed consent process, eligibility, CRFs, AE reporting

Monitoring Plans

Site Monitoring Plan Element Examples

- **Number of records reviewed.**

Example: 10%; or 2 of the first 5 subjects enrolled

- **Plan for evaluating and documenting findings/observations.**

Example: a monitoring report will be provided within 5 days of review (specify who will be provided with report).

- **Follow-up process.**

Example: Investigator or sponsor-investigator, will document receipt & review of the monitoring report, resolutions and/or corrective actions to findings on the Site Monitoring Log; S-I will notify IRB according to P&P

Monitoring Plans

➤ Types of site monitoring

- On-Site Monitoring-

In-person evaluation carried out by sponsor representatives at the site.

- Centralized Monitoring-

Remote evaluation carried out by sponsor representatives at a location other than the site, e.g., review of investigator documentation submitted electronically to central site.

Monitoring Plans

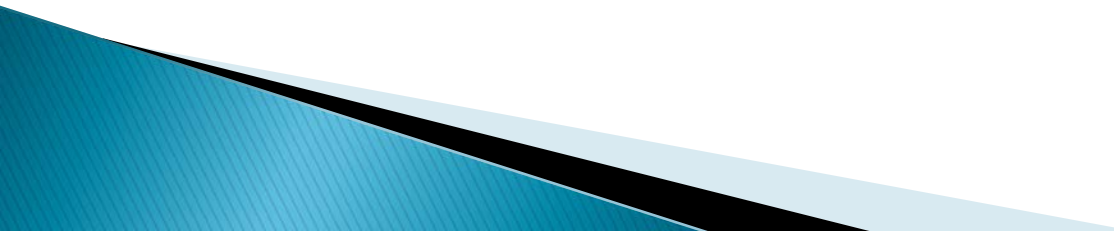
The site monitoring plan may include both centralized and on-site monitoring practices.

Additional self-monitoring is always good practice



Monitoring Plans

Per guidance clarification ORC obtained from FDA Office of Good Clinical Practice, self-monitoring may be an option for sponsor-investigators.

- A site monitoring plan which only includes self-monitoring may be adequate for a study conducted only at Emory sites by an Emory sponsor-investigator(S-I).
 - If the S-I has more than one site (making him/her a sponsor at an external site), self-monitoring by on-site investigator likely will not pass FDA muster.
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Monitoring Plans

Multi-Site Investigations

➤ An Emory investigator may conduct a multi-site study which includes non-Emory sites. These studies require a robust site monitoring plan which may include:

- Centralized monitoring
- On-site monitoring
- Self-monitoring



Monitoring Plans

Multi-Site monitoring plan elements:

- Centralized monitoring:
 - Example: study sites send source documents for comparison with CRFs.
- On-site monitoring:
 - Example: S-I or designated person visits site. Per FDA inspectors, a site visit must occur at least once a year or once during course of study if study duration is less than 12 months. CRO or independent monitor is a good option.
- Self-monitoring:
 - Example: The S-I should provide a monitoring tool to be completed by site at prescribed frequency, with results reported to S-I.
 - Self-monitoring alone of non-Emory sites in a multi-site investigation is unlikely to be considered adequate by FDA.


Monitoring Plans

IRB role

➤ **Initial Assessment of the Overall Monitoring Plan**

- Assesses the overall Monitoring Plan for adequacy in detecting and addressing safety issues AND ensuring protocol compliance and data quality.

➤ **Review Monitoring Plan Results**

- Ensures that site monitoring results are being reviewed by the investigator and events that impact subject safety or data integrity are reported per IRB requirements.
 - Includes review and assessment of overall DSMP and any DSMB reports as part of continuing review process.
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Monitoring Plans

Resources

- ▶ FDA Guidance Oversight of Clinical Investigations-A Risk-Based Approach to Monitoring

<http://www.fda.gov/downloads/Drugs/Guidances/UCM269919.pdf>

- ▶ Emory University Self-Monitoring Tool located on CTAC, IRB, and ORC websites
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Questions

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