A Comprehensive Look:
Monitoring and Auditing of Human Participant Research

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Welcome – Introductions

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About DSMBs, DSMPs, Audits and Monitoring

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Outline

- Monitoring and Auditing
- Data Safety Monitoring Plan
- Data Safety Monitoring Board
- Wrap Up

Monitoring and Auditing

Monitoring
- Ongoing and continuous oversight of research progress and adherence to the protocol and regulatory requirements
- Done at predefined intervals

Auditing
- Evaluation of compliance with the protocol and regulatory requirements by an independent body
- Can be internal (e.g., IRB, ORCR) or external (e.g., FDA, NIH)
- Done at any time during the study or for-cause
• The portions of a protocol that describe steps the research team will take to identify, address, and report any physical, social or psychological events that may result from participation in a study.

• IRBs are required to ensure that, when appropriate, research plans make adequate provision for monitoring data collected to ensure participant safety.

• DSMPs are submitted as part of the eResearch application and are reviewed as part of the initial review, or are submitted as part of an amendment, and must be approved prior to implementation.
Data Safety and Monitoring Plan (DSMP)

- DSMPs are generally required when the risk of harm to subjects is **more than minimal**
- Some federal agencies require a DSMP if supporting or funding research

Questions a DSMP should address:

- What are the timing, tools, and/or methods for monitoring and evaluating study data during the course of the project?
- What are the procedures for treatment or resolution of issues?
- What circumstances will result in halting or terminating research?
- What are the procedures for reporting to oversight bodies (e.g., IRB, independent monitor, data safety monitoring board, NIH, FDA, etc.)?
Data Safety Monitoring Board (DSMB)

• A formally chartered, independent committee whose stated goal is to protect the welfare and safety of the participants participating in a specified research study and to promote scientific integrity.

Data Safety Monitoring Boards (DSMBs) may be chartered when:

• The study is intended to provide definitive information about the effectiveness and/or safety of a medical intervention
• The study will evaluate mortality, morbidity, or other significant endpoints such that the inferiority of one treatment arm has safety as well as effectiveness implications
• Prior work suggests that the intervention under investigation may induce a potentially unacceptable toxicity
• The study raises ethical issues and it would be important for the study to stop early if the primary scientific question had been definitively answered, even if secondary questions or complete safety information were not yet fully addressed.
### Data Safety Monitoring Board (DSMB) Responsibilities

- Approves proposed safety measures for a protocol
- Provides written documentation of protocol review and agreement with study design
- Reviews study progress as provided in its charter
- Reviews cumulative data at established intervals to assess safety and efficacy
- Consults with PIs concerning safety or integrity issues arising during the course of the study
- Provides written reports to the PI, IRB and other oversight authorities summarizing its oversight activities and any recommendations

### A DSMB charter should include at least the following elements:

- Description of the membership, including qualifications and experience
- Roles and responsibilities of the DSMB
- Authority of the DSMB
- Timing and purpose of DSMB meetings
- Procedures for maintaining confidentiality
- Format, content and frequency of DSMB reports
- Guidelines outlining the procedure for the PI’s interaction with the board and whether the PI may be invited to attend any open sessions
- Statistical procedures, including monitoring guidelines, used to monitor the identified primary, secondary, and safety outcome variables
- Plans for changing the frequency of interim analyses as well as procedures for recommending protocol changes.
Data Safety Monitoring Board (DSMB)

- DSMB membership generally should include:
  - Multidisciplinary representation of at least three individuals, including:
    - physicians and scientists from relevant specialties
    - biostatistician
  - Members that have no involvement in the design and/or conduct of the trial
  - Members that have no significant conflicts of interest with the study (financial, intellectual, professional, or regulatory in nature)
  - An appropriate number of members (beyond three, as necessary) to address the size and complexity of the study

- Typically the IRB does not communicate with the DSMB, the PI and study team are responsible for facilitating requests and providing the IRB with monitoring reports from the DSMB
DSMPs, DSMBs, monitoring, and auditing are done to:

• Ensure the safety of participants
• Ensure the validity and integrity of data

About DSMBs, DSMPs, Audits and Monitoring

Thank you!

References
• IRBMED Standard Operating Procedures: https://az.research.umich.edu/medschool/sops/irbmed-standard-operating-procedures
• ICH-GCP E6(R2), 5.18 and 5.19: https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
• FDA Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees: https://www.fda.gov/media/75398/download
• FDA Guidance for Industry: Oversight of Clinical Investigations—A Risk-Based Approach to Monitoring: https://www.fda.gov/media/116754/download
FDA Inspections as a Form of Audit

Melanie Chladny
Office of Regulatory Affairs

Regulatory Affairs

Terminology

<table>
<thead>
<tr>
<th>Term</th>
<th>Meaning</th>
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| FDA Inspection  | • Initiated by FDA  
                   • Conducted by FDA Investigator  
                   • Site visit and data audit to determine compliance with applicable laws and regulations |
| Audit           | • Conducted internally for internal quality control  
                   • Distinct from routine monitoring  
                   • Independent and objective evaluation of trial conduct and compliance with the protocol, SOPs, GCP, and applicable regulatory requirements |
| Monitoring Visit| • Conducted internally or by sponsor or CRO monitor to oversee the progress of a clinical trial  
                   • Ongoing, continuous process  
                   • Intended to be collaborative, helpful, and keep the study/team on track  
                   • Monitor will discuss issues with study team and follow up to ensure corrections are made |
Bioresearch Monitoring (BIMO)

A comprehensive program of on-site inspections and data audits designed to monitor all aspects of the conduct and reporting of FDA regulated research.

Who Can be Inspected?

• Clinical Investigators (CI)
• Sponsors
• Monitors
• Contract Research Organizations (CRO)
• Institutional Review Boards (IRB)
• Nonclinical (animal) laboratories
• Bioequivalence analytical laboratories
Why Inspect?

- To protect the rights, safety, and welfare of subjects
- To verify the accuracy, reliability & integrity of clinical trial data submitted to the FDA
- To assess compliance with FDA's regulations (including institutional policy) governing the conduct of clinical trials

Types of Inspection

- **Pre-Approval Inspections:**
  - After an application is submitted to FDA to market a new product
  - Focus on data verification
  - FDA will recommend for or against FDA approval

- **Compliance Follow-Up Inspections:**
  - Follow up to previous inspection with 483 observations or Warning Letter
  - Focus on assessing adequacy of corrective actions, continuing violations, or determining if escalated regulatory action is warranted

- **Inspection of a Complaint Submitted to FDA:**
  - Investigate a specific problem that has been reported to FDA
  - More focused & in-depth than routine inspections
Routine Inspections / Data Audit

Usually at:

- Higher enrolling sites
- Sites with SAEs
- Sites with significant deviations
- Sites where staff have a financial interest in product/sponsor
- Sites with a regulatory history or linkage to other regulatory issues
- Clinical Investigator (CI) has a large portfolio of SI clinical trials (INDs/IDEs)

Directed / For Cause Inspections

- Follow-up to previous inspectional deficiencies
- Specific complaints made directly to the agency (FDA or DHHS)
- Data may appear unrealistic/suspicious
- Reports of possible misconduct received from outside sources (sponsors, IRBs, employees, subjects)
- Site closed out prematurely
- Issues of public perception such as critical pieces in major publications
FDA’s View of Clinical Investigator

A CI should....

• Live, breathe, and follow the protocol
• Be actively and fully engaged in supervising study staff
• Be attentive to subject safety and rights
• Make required reports to IRB, sponsor, etc.
• Ensure accurate, clear documentation that tells the complete story
• “Get It”

With FDA...It’s all about the CI!

How Does an Inspection Work?

• Possible alert from sponsor (application submitted, etc.)
• Call to make appointment
• Opening interview
• Investigator Site File (ISF) review (regulatory binders)
• Source data review (subject binders & medical records)
• Interviews of CI and staff
• Facility tour
• Exit conference
• Review any findings
• Clarify & address issues or concerns
• Response and follow up

Inspections will compare practices and procedures of the clinical investigator & study team with the commitments made in the:

• Protocol
• Regulations
• Institutional & IRB policies
Before the FDA Arrives:
Gather & Review Study Documents

- Statement of Investigator (Form FDA 1572) & financial disclosures
- Delegation & training logs
- IRB approvals
  - protocols and amendments
  - informed consents
  - recruitment material
- Protocol deviations
  - reported deviations
  - documented corrective actions
- Screening and enrollment logs
- Signed informed consents
- Medical records
- Complete source documentation (CRFs, labs, etc.)
- Standard operating procedures
- Monitoring visit follow-up letters
  - evidence that issues were addressed

Before the FDA Arrives:
Gather & Review Study Documents

- Review:
  - protocol
  - pertinent study dates, numbers, and other facts
  - medical record if needed to be sure AE reporting is complete
  - findings of monitor visits
- Initiate and submit any missing reports to IRB (ORIOs)
- Ensure that all required documents are available, organized, complete, and current

**FDA: “If it wasn’t documented, it didn’t happen”**
Before the FDA Arrives: Huddle

• Huddle with RA and relevant others
• Consider problems:
  • Deficiencies cited by monitors
  • Lapses in IRB approval
  • Tardy reports to sponsor or IRB
  • Changes implemented without prior IRB approval
  • Voluntary holds
  • Prior findings of non-compliance
  • Suspensions

“It is what it is”

Before the FDA Arrives: Plan

• Secure inspection space
  • quiet area away from traffic and conversations
• Ensure access to:
  • copier and printer
  • EMR if necessary
• Assign an individual to provide administrative support
  • every document reviewed by the FDA should be copied and logged in an inspection log
  • notetaking during interviews is permitted
Opening Interview

FDA Investigator:
- presents credentials
- requests introductions
- issues FDA Form 482: Notice of Inspection
- offers introductory remarks
  - Which FDA center requested inspection (CDER, CBER, CDRH)
  - Why? (premarket submission by sponsor, result of a complaint)
  - Focus and scope of inspection
  - Logistics and expected duration
- poses questions to CI/study team

During Inspection: Check-Ins and Updates

Regulatory Affairs will:
- create email list for communicating with entire team including IRB, RA, and OGC
- check in daily with study team and FDA Investigator
- work with study team to:
  - explain possible misunderstandings,
  - point to other documentation that FDA is not noticing, and
  - do any necessary pushback
During Inspection: Human Subjects Protection

Is there **documented evidence** to verify that:

- Eligible subjects were enrolled?
- Participants were consented and treated per protocol?
- Participants received the correct intervention and that all handling and storage conditions were met?
- All study interventions and assessments were conducted in accordance with the investigational plan?
- IRB review/approval was obtained?
- Study was conducted according to the protocol?
- AEs (start, stop, severity, causality) and deviations were reported?
- Were deviations beyond the control of the CI or the result of a poorly managed trial?

During Inspection: Data Integrity

Do study records fully tell the research story? Now and 10 years from now?

- Who did what?
- Were study team members qualified?
- Were all approvals in place?
- Were documents available & accurate?
- Were all test articles accounted for properly?
- Were all monitoring reports available and findings addressed?
- Why you deviated from the protocol?
- When and why a CRF value was corrected?
- Why CRFs don’t match source documents?
During Inspection: Adherence to Regulations

- Electronic Records; Electronic Signatures (21 CFR Part 11)
- Protection of Human Subjects (Informed Consent) (21 CFR Part 50)
- Financial Disclosure by Clinical Investigators (21 CFR Part 54)
- Institutional Review Boards (21 CFR Part 56)
- Good Laboratory Practice for Nonclinical Laboratory Studies (21 CFR Part 58)
- Investigational New Drug Application (21 CFR Part 312)
- Applications for FDA Approval to Market a New Drug (21 CFR Part 314)
- Bioavailability and Bioequivalence Requirements (21 CFR Part 320)
- Applications for FDA Approval of a Biologic License (21 CFR Part 601)
- Investigational Device Exemptions (21 CFR Part 812)
- Premarket Approval of Medical Devices (21 CFR Part 814)
- Institutional Policy
- ALCOAC Principles

During Inspection: Interviews & Tours

FDA Investigator will ask to interview study team and key players (IRB, Research Pharmacy, etc.) and tour facilities

- Be prepared, respectful, honest
- Acknowledge obvious problems
- If problem can be corrected, fix it asap
- Accept the silence
- Stick to the facts you know (don’t speculate)
- Follow through on promises
  - answer questions
  - deliver documents
  - arrange tours & interviews
Completion of Inspection

• Schedule exit conference to ensure CI availability and invite IRB, RA, OGC
• Investigator summarizes purpose, scope and findings
• Each finding is read and discussed so that there is a full understanding of what the findings are and what they mean.

Exit Conference: Observations

• Any Objectionable Conditions are listed on form FDA-483 “Inspectional Observations”. The 483 will be:
  • issued directly to the CI
  • include study-specific examples for each observation cited
• The 483 does not reflect final FDA findings
• Save rebuttal for the written response, unless significant factual errors must be corrected
• Ask for clarification
• Indicate intent to respond within 15 business days
Exit Conference: Discussion Items

- Discussion items (suggestions) will be presented orally. These won’t be on the 483, but will be in the Establishment Inspection Report (EIR).
  - EIR is a summary covering all aspects of the inspection.
- Take good notes
- Ask for clarification where needed
- Save rebuttal for the written response
- Correct significant factual errors in discussion items during the exit conference since there is still the opportunity to keep the “discussion items” out of the Investigator’s EIR report to headquarters

After the FDA has Gone

- If 483 issued, prepare to respond
- Response is due to FDA 15 business days after exit interview
- Huddle with study team, RA, and OGC to strategize response – be prepared for challenging questions/requests
- Study team should:
  - dissect the observations
  - understand what really happened (root cause analysis)
  - identify helpful information the FDA investigator may have overlooked
  - develop/implement CAPAs
- RA will prepare template for response letter
- RA and OGC will assist with draft and consult IRB as necessary
Corrective And Preventive Actions (CAPA)

Corrective Action:
Addresses specific instance(s) of the error

Preventive Action:
Ensures the error is not repeated

“Clinical Investigator is responsible to take corrective action to address the cited objectionable conditions and any related non-cited objectionable conditions that might exist”


Exhibit 1: Corrective and Preventive Action Plan

<table>
<thead>
<tr>
<th>Description</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical trials management system: Initiation of automated email for deviation-report</td>
<td>Completed</td>
</tr>
<tr>
<td>Informed consent footer revisions (for ongoing and future studies)</td>
<td>Drafted</td>
</tr>
<tr>
<td>Standing agenda item regarding deviation reporting</td>
<td>Implementation</td>
</tr>
<tr>
<td>SPG 469 for Informed Consent Revision Policy revision to require commonly referenced name</td>
<td>Drafted</td>
</tr>
<tr>
<td>SPG 461 for Deviation/Other Reportable Information or Occurrences (O.R.I.O.) Reporting Guideline revision</td>
<td>Approved</td>
</tr>
<tr>
<td>Study team training on 483 findings and CAPA plan</td>
<td>Expected Completion: May 12, 20XX</td>
</tr>
<tr>
<td>Study team initial training on tools and SPGs</td>
<td></td>
</tr>
<tr>
<td>Quality Assurance check of CAPA implementation</td>
<td>Expected Completion: June 20XX</td>
</tr>
</tbody>
</table>
Meanwhile, Back at the FDA...

Local office:
- FDA investigator prepares the Establishment Inspection Report (EIR) within 15 working days (more detailed than the 483)
- Our response needs to be delivered to the local FDA office before the EIR is sent to headquarters

Headquarters:
- reviews the EIR together with our response (if it made deadline)
- may consult with local FDA investigator
  - CI/UM rapport with investigator can be helpful at this point
- makes a determination...

Possible FDA Determinations

- Once headquarters is satisfied that any violations have been corrected (appear to be adequate), the inspection is "closed"
- When the FDA has concluded its review, no further action is warranted
- FDA will issue an acceptance letter and a copy of the EIR to the inspected establishment (usually by email), addressed to the CI
- This can take anywhere from a few months to more than a year, depending on the time it takes to review all evidence and make a final determination
FDA Inspection Classification Codes

<table>
<thead>
<tr>
<th>Classification</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Action Indicated (NAI)</td>
<td>No objectionable conditions or practices were found during the inspection</td>
</tr>
<tr>
<td>Voluntary Action Indicated (VAI)</td>
<td>Objectionable conditions were found, but were adequately addressed by the explanations and corrective and preventative actions volunteered and described in the clinical investigator’s response to the 483</td>
</tr>
<tr>
<td>Official Action Indicated (OAI)</td>
<td>Objectionable conditions were found and regulatory and/or administrative sanctions by FDA are indicated (typically communicated in a Warning Letter)</td>
</tr>
</tbody>
</table>

Possible FDA Determinations

<table>
<thead>
<tr>
<th>OAI Letter</th>
<th>Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untitled Letter</td>
<td>• cites violations that do not meet the threshold of regulatory significance for a Warning Letter</td>
</tr>
<tr>
<td></td>
<td>• serve as an initial notification to CI that FDA is aware of their violations of federal law</td>
</tr>
<tr>
<td>Warning Letter</td>
<td>• issued to achieve voluntary compliance and establish prior notice</td>
</tr>
<tr>
<td></td>
<td>• issued for violations of regulatory significance that may lead to enforcement action if not promptly and adequately corrected</td>
</tr>
<tr>
<td>FDA Escalation for Continued Noncompliance</td>
<td></td>
</tr>
<tr>
<td>Notice of Opportunity for Hearing (NOOH)</td>
<td>• invitation to a hearing on a regulatory action</td>
</tr>
<tr>
<td>Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE)</td>
<td>• repeated or deliberate violation of FDA’s regulations</td>
</tr>
<tr>
<td>Debarment &amp; Disqualification</td>
<td>• prohibits CI from engaging in FDA regulated clinical trials</td>
</tr>
</tbody>
</table>
What We’ve Learned

<table>
<thead>
<tr>
<th>Observations</th>
<th>Examples</th>
<th>Best Practices / Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol adherence</td>
<td>• Unreported / unapproved changes&lt;br&gt;• Protocol deviations / violations&lt;br&gt;• Ineligible subjects</td>
<td>• Follow the investigational plan (protocol)&lt;br&gt;• Train &amp; supervise staff&lt;br&gt;• Report all deviations in a timely way&lt;br&gt;• Perform all protocol-prescribed exams (clinical judgment can’t supersede protocol eligibility)</td>
</tr>
<tr>
<td>Informed consent</td>
<td>• Missing&lt;br&gt;• Wrong version&lt;br&gt;• Signature / date irregularities&lt;br&gt;• Misleading / overly technical language</td>
<td>• Document everything&lt;br&gt;• Track versions &amp; use the right one&lt;br&gt;• Follow COI plans, who is allowed to consent</td>
</tr>
<tr>
<td>Documentation deficiencies</td>
<td>• Incomplete / inaccurate CRFs&lt;br&gt;• Missing source documents&lt;br&gt;• Corrections not auditable</td>
<td>• Maintain organized, complete, and current records&lt;br&gt;• Documents should tell the entire story&lt;br&gt;• Corrections must be clear (no white out, sticky notes, pre-fab signatures)</td>
</tr>
</tbody>
</table>
## What We’ve Learned

<table>
<thead>
<tr>
<th>Observations</th>
<th>Examples</th>
<th>Best Practices / Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missing / delayed reports to sponsor and IRB</td>
<td>• AEs and protocol deviations</td>
<td>• Initiate and submit all required reports to IRB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Know your reporting plan</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• general or study specific</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• what categories get reported when</td>
</tr>
<tr>
<td>Missing or delayed IRB approval / reporting</td>
<td>• Amendment implemented before approval</td>
<td>• Stick to the protocol</td>
</tr>
<tr>
<td></td>
<td>• Missing or late reports</td>
<td>• Ensure timely IRB review and approval</td>
</tr>
<tr>
<td></td>
<td>• Lapse in IRB approval</td>
<td>• Submit reports on time</td>
</tr>
<tr>
<td>Poor test article accountability</td>
<td>• Chain of custody</td>
<td>• Protect the study article; adequate security as well as documentation</td>
</tr>
<tr>
<td></td>
<td>• What went to who when and what did they do to it?</td>
<td>• Know the rules and follow them; devices in particular have special requirements</td>
</tr>
<tr>
<td></td>
<td>• Returned drug/device count and disposition</td>
<td>• Keep track of all drug/device</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Document everything</td>
</tr>
<tr>
<td>Special issues for FDA Sponsor-Investigators</td>
<td>• Inadequate monitoring</td>
<td>• Follow the regulations</td>
</tr>
<tr>
<td></td>
<td>• Missing or delayed reports to FDA</td>
<td>• Supervise and ensure proper monitoring</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Obtain IRB approvals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Submit timely IND/IDE application &amp; reports to FDA</td>
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<tr>
<td></td>
<td></td>
<td>• Remember NSRs still entail obligation to monitor</td>
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**Thank you**
Overview

- Definitions
- What is monitoring?
- Monitoring responsibilities
- Monitoring visit preparation
- How is monitoring performed?
- Monitoring visit follow-up
- Initiating monitoring services
- MICHR Monitoring Communication Plan
Who is a Sponsor-Investigator?

**FDA Definitions**

Drugs (21 CFR 312.3)

Devices (21 CFR 812.3)

*Sponsor* means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.

Investigator means an individual who actually conducts a clinical investigation (*i.e.*, under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. "Subinvestigator" includes any other individual member of that team.
Who is a Sponsor-Investigator?

*Sponsor-Investigator* means an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor.

Sponsor-Investigators have two sets of responsibilities!
Monitoring is a Sponsor Responsibility

A sponsor shall select a monitor qualified by training and experience to monitor the progress of the investigation.

Resources:
312.50 Responsibilities of sponsors
312.53(d) Selecting monitors
12.25(e) Monitoring procedures

Monitoring

The act of overseeing the progress of a clinical trial, and of ensuring that it is:
- conducted,
- recorded,
- and reported

in accordance with
- the protocol,
- Standard Operating Procedures (SOPs),
- Good Clinical Practice (GCP),
- and the applicable regulatory requirement(s).
Monitoring Purpose

The purpose of monitoring is to verify that:

- The rights and well-being of human subjects are protected.
- The reported trial data are accurate, complete, and verifiable from source documents.
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

Frequency and Types of Monitoring Visits

- A “visit” can be in-person or remote.
- Site Initiation Visit (SIV) occurs prior to enrollment.
- Interim/Routine Monitoring Visits (IMV/RMV) begin once the first subject has enrolled.
  - Subsequent interim visits are scheduled based on study needs, usually quarterly.
  - Duration of each visit is typically 1-2 days, dependent upon enrollment rate.
- A closeout visit (COV) will be scheduled once all subjects have completed their visits and previous monitoring action items have been addressed.
Monitoring Responsibilities

The monitor will review the following items:

- Informed consent documentation
- Essential documentation (regulatory binder)
- Source documentation and Case Report Forms (CRFs) to assess protocol adherence and perform source data verification (SDV)
- Investigational Product accountability

Note – The Monitoring Plan includes a more detailed description of the scope of monitoring planned for this study.

Prior to the Monitoring Visit

- Confirmation letter
- Prepare necessary items for review
- Typical requests:
  - Work space for the monitor
  - Complete data entry
  - Update essential documentation – paper or electronic
  - Schedule pharmacy visit, laboratory visit, device storage, etc.
  - Code list (subject names, MRN, study ID)
  - Documentation of resolved action items from previous visits
How is monitoring performed?

Informed Consent
- Was the most currently IRB-approved consent document used?
- Are all blank spaces filled?
- Did the subject and PI or designee sign and date prior to study procedures?
  - Was the designee delegated to perform informed consent?
- Is there evidence of informed consent within the subject medical record?
  - Upload the signed consent document to MiChart
- Best practice - Did the study team document that the consent process was done appropriately within their research notes?

Essential Documentation
- Essential Documentation must be maintained and current throughout the course of the trial
- Study team trainings, credentials:
  - Protocol and other study-specific training
  - Medical licenses
  - CVs
  - GCP trainings
  - PEERRS
- Current and archived versions of IRB approvals and approved documents
How is monitoring performed?

Protocol Adherence and Source Data Verification (SDV)

- Eligibility example:
  - Is there source documentation available to support each inclusion and exclusion requirement?
  - Has the PI acknowledged his/her review of eligibility and deemed the subject eligible or ineligible for participation?
  - Does the reported data (Case Report Form) match source data (MiChart)?
  - Deviations from the protocol should be reported to the IRB utilizing the ORIO reporting guidance from IRBMED.

Exclusion (the subject cannot meet any of the following criteria)

- ☐ AST/ALT greater than 2x U/L
- ☐ Severe heart failure (NY Heart Association functional class greater than or equal to 3)
- ☐ Pregnant women
- ☐ Cardiac transplant recipient
- ☐ Participation in an experimental drug or device study within 30 days of the treatment period

_________________________  _______________  _______________
Principal Investigator Signature   Date   Time
Monitoring Report and Follow-Up Letter

- Format varies based on the monitoring group
- Summary of the monitoring review
- Detailed observations, findings, action items
- May receive the full report, only the confirmation letter, or both documents
After the Monitoring Visit

- Submit your report and follow-up letter to the IRB in accordance with the approved study parameters and monitor indications.
  - The monitor may report concerns directly to the IRB, depending on the nature of the monitoring findings.
- File both of these with your essential documentation (regulatory binder).
- Address monitoring action items and queries.
- Discuss identified issues with your MIAP representative.
  - Changes to the protocol may need to be submitted to FDA.
- Communicate regularly with your monitor.

Initiating Monitoring Services

- MIAP referral
  - If MIAP determines your study will need an IND or IDE they will refer you to MICHR Monitoring. We work closely with their team to make sure required studies have necessary monitoring support.

- CTSO referral
  - During feasibility your Portfolio Manager can connect you to appropriate MICHR services.

- Contact the MICHR Monitoring team
  - Contact information is available at the end of this presentation.
MICHR Monitoring Communication Plan

Our team communicates regularly with:
- IRBMED
- Office of Regulatory Affairs
- Office of Research Compliance Review (ORCR)
- MIAP

in order to ensure that the guidance provided to study teams does not conflict with UM guidance or policy.

Suspected noncompliance identified during monitoring visits may be escalated to the above groups.

We are here to help!

- Our team has experience working with studies of all different shapes and sizes. Reach out to us for help and support.
- We can refer you the appropriate person or group if we aren’t able to help.
Contact us

Lori Kempf
kempfl@med.umich.edu

Jen Zollars
wolfejk@med.umich.edu

Amanda Phelps
amanowak@med.umich.edu

Thank you!
IRB Requirements for Reporting Monitoring Outcomes

Cameron Shultz, PhD
Compliance Specialist, IRBMED

Overview

• **Why** submit monitoring outcomes and reports to the IRBMED

• **When** to submit monitoring outcomes and reports to the IRBMED

• **How** to submit monitoring outcomes and reports to the IRBMED
But first...

**What not to do:**

![Cartoon](https://www.pinterest.com/pin/165859198764114496/?d=t&mt=login)

“That’s how the clinical team decides which regulations they will follow.”

Cartoon from [https://www.pinterest.com/pin/165859198764114496/?d=t&mt=login](https://www.pinterest.com/pin/165859198764114496/?d=t&mt=login)

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But first...

**And when the need to report is obvious:**

![Cartoon](https://www.castoredc.com/blog/starting-clinical-study/)

“EXPERIMENTAL NUCLEAR IMAGING

WARNING!

COULD YOU TAKE ANOTHER LOOK AT THE PROTOCOL?”

Cartoon from [https://www.castoredc.com/blog/starting-clinical-study/](https://www.castoredc.com/blog/starting-clinical-study/)
Why Monitor? Belmont Report

- **Respect for persons**
- **Beneficence** Maximize possible benefits and minimize possible harms
- **Justice**
  1. Protect participants
  2. Integrity of research results
  3. Satisfy regulatory requirements

Image from [https://s4be.cochrane.org/blog/2015/07/15/balance-benefits-harms/](https://s4be.cochrane.org/blog/2015/07/15/balance-benefits-harms/)
Monitoring Requirements: HRPP-OM part 7.III

- Research plans must make provisions for monitoring to ensure safety
  - physical, social, or psychological harms
- Commensurate with the risk level, complexity, and the size of the study
- Data Safety Monitoring Plan (DSMP)
  - Describes the methods (eg, timing, tools) for evaluating study data
  - Procedures for treatment or resolution (eg, stopping rules)
  - Timing of reports to oversight bodies (eg, DSMB, IRB, FDA)

- Data Safety Monitoring Board (DSMB)
  - A committee of experts who review study data to ensure safety, validity, and integrity

Monitoring Requirements: NIH

- All intervention studies should have provision for data and safety monitoring
- For phase I and II clinical trials:
  - Investigators must submit a DSMP as part of the NIH research application
  - The DSMP must be included as part of the protocol and approved by the local IRB and funding Institute and Center before the trial begins
- DSMB:
  - Generally required for Phase III clinical trials
  - Required for multi-site clinical trials involving interventions that entail potential risk to the participants
- NIH Data and Safety Monitoring Policies:
Monitoring Requirements: FDA

• All clinical trials require safety monitoring

• DSMB: Generally...
  o For large, randomized, multisite studies evaluating treatments to prolong life or reduce major adverse health outcomes
  o Recommended for any controlled trial of any size that will compare rates of mortality or major morbidity
  o Not needed for trials at early stages of product development
  o Not needed for trials addressing lesser outcomes (eg, relief of symptoms) unless the trial population is at elevated risk of more severe outcomes

 o Resources

Monitoring Requirements: UM Cancer Center

• Protocol Review Committee (PRC)
  o Provides oversight of the scientific aspects of all cancer clinical research at UM
  o A DSMP must be submitted as part of the application
  o https://sites.google.com/a/umich.edu/prc/home

• Data Safety Monitoring Committee (DSMC):
  o Monitors safety and data integrity for all cancer clinical trials not already having a rigorous monitoring body in place
  o Monitoring requirements are based on study risk
  o https://sites.google.com/a/umich.edu/dsmb_site/home
Completing eResearch Application

7.1.10 Will the study have a Data and Safety Monitoring Plan (DSMP)? [Require Section 32]

- Yes
- No

A DSMP is required for:

- FDA-regulated research,
- Research where adverse events (AEs) are expected e.g., physical, social, psychological, confidentiality/privacy, etc., and
- NIH-sponsored research involving human subjects.

Note: For Dental School Applications, see Help for more information.

Completing eResearch Application

eResearch self-populates questions based on previous responses

32.2 Data Safety and Monitoring Plan - Monitoring the Study

32.2.1 Indicate the frequency with which the study team will conduct scheduled assessments of study recruitment, data integrity and quality, adverse events, withdrawals, and compliance with protocol plan.

32.2.2 Study oversight and safety monitoring may be required based on the nature, size, and complexity of the study. Indicate the responsible entities. Select all that apply:

32.2.2.1 Additional monitoring activities will be conducted.

32.2.3 If a DSMB or DSC charter exists, upload it here.

32.2.3.1 Monitoring reports will be provided to:

- Organization
- Reporting Mechanism
When to Submit Monitoring Report

Follow the timetable as indicated in your approved eResearch application / protocol

Image from [https://blog.udemy.com/javascript-submit-form/](https://blog.udemy.com/javascript-submit-form/)

IRBMED Standard Timetable

From [https://az.research.umich.edu/medschool/guidance/other-reportable-information-or-occurrence-orio](https://az.research.umich.edu/medschool/guidance/other-reportable-information-or-occurrence-orio)

<table>
<thead>
<tr>
<th>TYPE OF EVENT OR INFORMATION</th>
<th>REPORTING MECHANISM AND TIMEFRAME for INFORMATION AND OCCURRENCES (NON-AE)</th>
<th>Report as part of SCHEDULED CONTINUING REVIEW (SCR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Report as an ORIO within 7 CALENDAR DAYS of becoming aware of the event or information</td>
<td>NOTE: These events or reports do not require a separate ORIO submission. They should be uploaded into field 4.1 of the Scheduled Continuing Review (SCR) application, and discussed within the SCR field 1.2.</td>
</tr>
</tbody>
</table>

**Report(s) to or from oversight entity**

- OMB/OSMC reports with findings that yield implications for the conduct of the study (issues of safety, data validity or regulatory compliance)
- Routine monitoring reports with implications for the conduct of the study (issues of safety, data validity or regulatory compliance)

This includes reports from sponsor or contract review organization (CRO) monitoring visits, and internal monitoring committees such as ORES, ARCH, and QMRC

- Reports of internal or external audits
- Reports on Drug or Device recalls or safety notices from the sponsor
- Study holds or suspensions that are not built into the study design
- Study completed or enrollment closed/completed notifications with safety or regulatory concerns
- Any other reports from sponsor, oversight entity or other sources with safety or regulatory concerns

*NOT REQUIRED TO SUBMIT*: Routine monitoring reports (interim monitoring reports, or other) without issues impacting safety, data validity, or regulatory compliance. These must be retained by the study team and available upon request.

This includes reports from sponsor or CRO monitoring visits, and internal monitoring committees such as ORES, ARCH, and QMRC

Upload these reports individually into SCR submission or separately as required by the Sponsor’s protocol or contract.

- OMB/OSMC (formally charged oversight entity) reports without any action items or safety issues
- FDA annual reports
  - For U-M held IND and/or IDE
  - For industry-sponsored IDE, per FDA guidance
- Temporary hold notifications as indicated in the approved protocol and limited to activities not impacting subject safety, such as routine interim data analysis
- Study completed or enrollment closed/completed notifications without safety or regulatory concerns
Report as an ORIO within **7 CALENDAR DAYS** of becoming aware of the event or information

- DSMB/DSMC reports with implications for the conduct of the study (issues of safety, data validity or regulatory compliance)
- Routine monitoring reports with implications for the conduct of the study (issues of safety, data validity or regulatory compliance)
- Reports of internal or external audits with implications for the conduct of the study (issues of safety, data validity or regulatory compliance)
- Reports on Drug or Device recalls or safety notices from the sponsor
- Study holds or suspensions that are not built into the study design
- Study completed or enrollment closed/completed notifications with safety or regulatory concerns
- Any other reports from sponsor, oversight entity or other sources with safety or regulatory concerns

Report as part of SCHEDULED CONTINUING REVIEW – These reports do not need a separate ORIO

- DSMB/DSMC (formally charged oversight entity) reports without any action items or safety issues
- Temporary hold notifications as indicated in the approved protocol and limited to activities not impacting subject safety, such as routine interim data analyses
- Study completed or enrollment closed/completed notifications without safety or regulatory concerns
- FDA annual reports
IRBMED Standard Timetable

NOT REQUIRED TO SUBMIT routine monitoring reports **without** issues impacting safety, data validity, or regulatory compliance. These must be made available upon request.

- This includes routine monitoring reports from sponsor, CRO monitoring visits, and internal monitoring committees such as **ORCR, MICHR, and QARC**

Other Reporting Timetables

**Commensurate with the risk level, complexity, and the size of the study**

- Industry studies
- National groups (eg, National Clinical Trials Network)
- External Consortia
- Investigator initiated

**Follow the IRB-approved protocol**
For new, previously unreported Adverse Events identified through monitoring, report per IRBMED-approved reporting plan:

32.1.2 Indicate the AE reporting timetable that will be used to report adverse events to the IRB:
Standard IRBMED AE reporting timetable

32.1.2.2 Provide the study specific AE reporting plan. If the study specific AE reporting plan is included in the previously uploaded scientific protocol, indicate section:

<table>
<thead>
<tr>
<th>Name</th>
<th>Version</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

There are no items to display

Indicate specific protocol section here:

Per Protocol Sec 8 PI must report all events meeting the criteria & definition of SAE to local IRB per current local standards. SAEs will be reported to UM via IRBMED Standard AE Reporting Guidelines.

For detail on IRBMED Adverse Reporting guidance, go to https://az.research.umich.edu/medschool/guidance/adverse-event-reporting

For reports that must be submitted within 7 days, use ‘ORIO’ via eResearch:

1.1 Type of Report—choose one
Other Reportable Information or Occurrence (ORIO)

1.2.1 Other Reportable Information or Occurrences (ORIO) types:
Report(s) to or from oversight entity

10.7 Supporting Documentation:
Name Version
How to submit reports to the IRB

For reports submitted as part of Continuing Review, use ‘Continuing Review’ via eResearch:

Discuss within 1.2

1.2 Describe any significant new findings or information developed during the course of this research or other associated research that may relate to a subject’s willingness to continue participation. Provide literature citations and/or links to publications. This field may also be used to communicate additional information to the IRB that is pertinent to the review of this SCR.

Upload into 4.1

4.1 Please upload any additional documents provided or required by the sponsor (for example, memos from sponsors, and CIRB specific documents). Do NOT upload any documents that require IRB review and approval (for example, informed consent, recruitment materials, and survey instruments).

Thank you!

If in doubt, reach out to the IRBMED for guidance

• Contact assigned regulatory staff (as identified for each HUM within eResearch)

  -or-

• Use the IRBMED’s email / phone number
  o irbmed@umich.edu / (734) 763-4768
Additional slide provided by Office of Regulatory Affairs in response to discussion during Q&A.

Thank you.

May 4, 2021