

NIAID, DMID Safety Oversight Guidelines

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The Fundamentals of International Clinical
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DMID/ICSSC

The Need for Oversight

- Ethical responsibility to study participants
- Responsible parties:
 - Investigators
 - Study Team
 - Sponsors
 - Institutions
 - IRBs
 - Independent Safety Oversight (Monitoring)

Safety Oversight Overview

- NIH requires that

- Each Institute and Center have a system for appropriate oversight and monitoring of the conduct of clinical trials and integrity of data
- Safety monitoring should be commensurate with risks and with size and complexity of trials

Purpose of Safety Monitoring

- Provide an independent and objective review in timely fashion
- Monitor safety, study conduct, study progress, and when appropriate, interim analysis of efficacy data

DMID's requirements

- DMID's policy is that safety monitoring be in place for all clinical research beyond minimal risk
- The safety monitoring must be independent

What is an “independent” monitor?

- Someone not directly involved with the trial
- Someone not under the investigator’s supervision
- Preferably from a different organizational group
- No financial, intellectual, proprietary or professional interest in outcome of trial

High Standard of Independence Required

- OCRA confirms that no conflict exists prior to every review or meeting
- “Conflict or appearance of a conflict”
- Any potential conflicts must be discussed with DMID and resolved with OCRA
 - Unmanageable? Nonvoting member?
 - Full disclosure?
- Note that COI statement mentions \$10,000 in financial interest or assets as ceiling

Setting up Oversight Structure

- For an step-by-step outline of the process, go to:

<http://www.dmidctm.com/partners/home.htm>

- “Resources and Guidelines” Tab
- “Quick References” Tab
- “Safety Oversight” Tab

Which Oversight Structure? ISM, SMC, DSMB FORM FOLLOWS FUNCTION

- Is the primary focus of monitoring participant safety?
- Phase I trial with low risk intervention?
- Will rapid enrollment impact ability to analyze efficacy data in interim analysis?
- Phase III Trials have an NIH requirement for DSMB review

Independent Safety Monitor ISM

- Safety responsibility is primary
- Typically used in early phase, low risk trials such as PK and immunogenicity studies
- Availability in real time
- No conflicts of interest, impartiality is critical to independent decision making
- Particular emphasis on “serious and unexpected” events
- Communication with DMID primarily through the Clinical Protocol Manager (CPM)



Safety Monitoring Committee SMC

- Group of experts with primary responsibility of participant safety
- Typically used in Phase I and Phase II studies
- ISM should be a member of SMC
- At least three voting members
- Ad hoc members as appropriate
- Must be able to meet on an Ad hoc basis when safety issues arise



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Data and Safety Monitoring Board DSMB

- Monitors efficacy data in addition to safety oversight
- Required for all Phase III trials
- May be required for complicated Phase II and Phase I trials (multi-centered, blinded, high risk populations, etc.)
- More formal structure and plan (Open, closed sessions)
- Members include a statistician and individuals with sophistication in design of clinical trials that test efficacy



Roles and Responsibilities

Membership

- DMID Clinical Protocol Manager has primary responsibility for assignment of safety monitor or formation of safety oversight committee
- Investigators and Industrial collaborators should be consulted and can recommend members
- OCRA has approval responsibilities for members, safety monitoring structure and plans and conflict of interest resolution

Roles and Responsibilities

Findings and Recommendations

- Safety Monitoring Individuals and Groups provide opinions to DMID
- Consensus among members not required
- Individual opinions should be expressed
- Recommendations are given careful consideration, but are not binding
- DMID has ultimate responsibility for implementing recommendations

Roles and Responsibilities

Study Team Responsibilities

- Primarily responsible for safety oversight
- Provide necessary documents, monitoring plans, safety, and interim reports
- Participate in monitoring meetings as appropriate
- Transmit summary of findings and recommendations to the appropriate IRBs
- Work with DMID to respond to all recommendations

Summary

- What is independent?
- Form follows function
- Roles and responsibility
- <http://www3.niaid.nih.gov/LabsAndResources/resources/DMIDClinRsrch/>



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