

MTN Manual of Operational Procedures (MOP)

Section 17: Monitoring

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17 MONITORING

In compliance with U.S. federal regulations and International Council for Harmonisation (ICH) E6(R2) Good Clinical Practice (GCP) guidelines, the study sponsor of a clinical trial (defined as the party which takes responsibility for the initiation, management and/or financing of the trial) is responsible for ensuring that the trial is adequately monitored. In the past, the U.S. National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS) has assumed regulatory responsibility for overseeing all Microbicide Trials Network (MTN) clinical research studies that it funds. However, effective October 2017, DAIDS contractors will only monitor those studies where DAIDS is the regulatory sponsor (IND holder).

The purpose of monitoring clinical research studies is to verify that the:

- Rights and well-being of human subjects are protected.
- Reported study data are attributable, legible, contemporaneous, original, accurate, complete and verifiable from source documents.
- Study conduct follows the currently approved study protocol/amendment(s), guidelines for GCP and applicable regulatory requirements.

The remainder of this section describes how DAIDS monitors MTN studies.

Additional details on the DAIDS site monitoring is available in the DAIDS SCORE Manual: <https://www.niaid.nih.gov/sites/default/files/crs-site-visits.pdf>.

17.1 Monitoring Clinical Research Sites

Every clinical research site (CRS) that conducts an MTN study is periodically monitored by DAIDS or by another sponsor, depending on the study being conducted at that site. The frequency of monitoring visits is based on the risk, size and complexity of the study. Prior to each monitoring visit, the monitors will contact site staff to schedule the visit, confirm the visit dates and specify the items to be monitored during the visit.

Monitoring visits may be study-specific (focusing on a single study at the site), site-specific (assessing all studies and procedures at one site) or targeted (such as monitoring laboratories). The Protocol Specific Monitoring Plan (PSMP), which may include the Targeted Source Documentation Verification (TSDV) worksheet and corresponding list of eCRFs to be monitored (if using Medidata Rave), will be developed in conjunction with the Office for Clinical Site Oversight (OCSO) Liaison, DAIDS Medical Officer, Statistical Data Management Center (SDMC) and FHI Pharmaceutical Product Manager (when applicable). The types of activities performed and the documents reviewed during each study monitoring visit may include the following:

- Assessment of the study initiation
- Assessment of the adequacy of a site's clinic, pharmacy, laboratory and other facilities
- Review of regulatory and other essential document files
- Review of DAIDS-required standard operating procedures
- Review of informed consent forms and eligibility
- Review of select eCRFs in Medidata Rave for targeted source documentation verification (if applicable)
- Review of participant study records
- Review of study procedures and documentation to assess compliance with study protocols, GCP guidelines and applicable regulatory requirements
- Verification of source documents to ensure the accuracy and completeness of study data
- Verification of the proper collection and storage of biological specimens
- Verification of the proper storage, dispensing and accountability of investigational study products
- Assessment of the implementation and documentation of the site's clinical quality management procedures
- Assessment of the site's staff training needs
- Assessment of the study close-out

Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose by NIAID. Remote monitoring visits may be performed in place of, or in addition to, onsite visits to ensure the safety of study participants and data integrity. The site will make available study documents for site monitors to review utilizing a secure platform that is HIPAA and 21 CFR Part 11 compliant. Selected platforms must be confirmed with the DAIDS Office of Clinical Site Oversight (OCSO) in advance.

During on-site monitoring visits, the Investigator of Record (IoR) or designee arranges for the monitor to meet with the appropriate study staff and ensures that all documentation is readily accessible. The site must identify an appropriate place for the monitor to work during the visit. Access to the internet is required; access to a telephone and a copy machine is recommended but not required. Toward the end of the visit (typically, on the last day), the monitor holds a debriefing to review the visit's findings with the site staff. The monitor may leave a list of pertinent findings with the IoR or designee at the end of the visit to expedite any corrective action, if applicable. The monitor prepares a report documenting each monitoring visit as described below. Sites must maintain monitoring logs/sign in sheets as part of the study essential documents.

17.2 Monitoring Reports

Within 15 working days after completing a monitoring visit at a U.S. site, or within 21 days for an international site, the monitor will prepare two types of reports: a Site Monitoring Report (SMR) and a Pharmacy Monitoring Report. These reports will be made available through the electronic Clinical Site Monitoring (CSM) system, via the DAIDS Enterprise System (ES) Module within the Clinical Research Management System (CRMS)

(<https://ncrms.niaid.nih.gov/NCRMS/Main/Login.aspx>). Additional details on the CSM system may be found in the following DAIDS reference guide:

<http://www.mtnstopshiv.org/sites/default/files/attachments/Clinical20Site20Monitoring20Reference20Guide20-20Sites.pdf>.

The FHI Pharmaceutical Product Manager accesses the Pharmacy Assessment Reports through the DAIDS electronic CSM system and contacts the CRS Pharmacist of Record (PoR) in writing if issues are identified, as described in Section 17.3.

Site monitoring reports are available through the CSM system to the Clinical Trials Unit (CTU) Principal Investigator (PI), CRS Site Leader, CRS PoR and appropriate staff from the MTN Leadership and Operations Center (LOC), SDMC, Laboratory Center (LC) and Network Evaluation Committee (NEC).

The CTU/CRS laboratories are monitored routinely as described in Section 14.5 of this manual. Members of the DAIDS Clinical Laboratory Oversight Team (DCLOT) request monitoring visits. Monitors from the Clinical Safety Monitoring Group (CSMG) visit the CTU/CRS laboratories and clinics and provide written reports to DCLOT. The reports are provided to the MTN LC for review and follow-up, if necessary.

17.3 Site Response to Monitoring Reports

When monitoring reports are made available, the DAIDS OCSO Program Officer (PO) acknowledges the SMR, provides comments on the report, identifies issues that need resolution and requests corrective action through the CSM system. Next, the CTU PI or delegated site staff respond via the CSM system. After the PO is satisfied with the site responses, he or she tags the issues as resolved in the CSM system. A similar process is followed for the Pharmacy Monitoring Reports.

Typically, the DAIDS OCSO PO and the FHI Pharmaceutical Product Manager acknowledge monitoring reports and enter issues for resolution in the CSM system within 15 working days of the report being issued. Site staff are expected to acknowledge reports and resolve issues identified by DAIDS within 15 working days of receiving resolution requests through the CSM system. Sites should contact their DAIDS OCSO PO for assistance if they experience problems accessing and/or using the CSM system, which in turn could delay their response.

The FHI Pharmaceutical Product manager reviews the Pharmacy Monitoring Reports for MTN studies. The process is as follows:

- The FHI Pharmaceutical Manager acknowledges a Pharmacy Monitoring Report within 15 working days of receipt.

- If issues are identified that need resolution, the FHI Pharmaceutical Product Manager contacts the CRS PoR in writing. The FHI Pharmaceutical Product Manager may also contact the CTU PI if deemed necessary.
- The CRS PoR must provide written responses.
- Site pharmacy staff must acknowledge the Pharmacy Monitoring Report(s) and resolve identified issues within 15 working days.
- The FHI Pharmaceutical Product Manager will forward this information to the DAIDS OCSO PO.

If site staff disagree with or have questions regarding any monitoring findings cited in the SMR and/or the way the monitoring visit was conducted, the site's IoR should contact their assigned DAIDS OCSO PO. As appropriate, the DAIDS OCSO PO will work with the site and the monitors to resolve any issues. Likewise, if pharmacy staff disagree with or have any questions regarding any monitoring findings cited in the Pharmacy Monitoring Report, the PoR should contact the FHI Pharmaceutical Product Manager. As appropriate, the FHI Pharmaceutical Product Manager will work with the site pharmacy staff and the monitor to resolve any issues.

17.4 Temporary Suspension of Clinical Research Site Activities

Serious and/or persistent non-compliance with protocol, regulatory, or grant requirements may result in temporary suspension of a site's study-specific activities, network-specific activities or all DAIDS-sponsored research being conducted at the site. A temporary suspension may be initiated by the OCSO PO in consultation with the DAIDS Prevention Sciences Program, Clinical Microbicide Research Branch personnel and MTN PI in the following circumstances:

- Serious and/or persistent non-compliance identified by monitors during a site visit or through internal QC/QA processes at the site.
- Significant concerns are communicated by site staff or participants to DAIDS and/or the network.
- A failure to comply with regulatory requirements is identified.