17 MONITORING

The U.S. National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS) has regulatory responsibility for overseeing the Microbicide Trials Network (MTN) clinical research studies that it funds. To fulfill this responsibility, DAIDS contractors monitor MTN studies. The purpose of monitoring clinical research studies is to verify the following:

- The rights and well-being of human subjects are protected.
- The reported study data are attributable, legible, contemporaneous, original, accurate and verifiable from source documents.
- The conduct of a study is in compliance with the study protocol, guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements.

Additional details on the DAIDS monitoring policy can be found at the following website: https://www.niaid.nih.gov/sites/default/files/onsitemonitor_reqs.pdf.

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

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. Monitoring is conducted during on-site visits. 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) developed in conjunction with the Office for Clinical Site Oversight (OCSO) liaison, DAIDS medical officer, SDMC, and MTN Director of Pharmacy Affairs (when applicable) details the types of activities performed and the percentage of documents reviewed during each study monitoring visit and 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
- 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

During 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.

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 MTN Director of Pharmacy Affairs accesses the Pharmacy Assessment Reports through the DAIDS electronic CSM system and provides feedback to the DAIDS OCSO. OCSO provides additional feedback to the site through the CSM system, as described in Section 17.3 of this manual.

In addition to DAIDS OCSO, monitoring reports are available through the CSM system to the Clinical Trials Unit (CTU) Principal Investigator (PI), CRS Site Leader, CRS Pharmacist of Record (PoR) and appropriate staff from the MTN Leadership and Operations Center (LOC), Statistical and Data Management Center (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 MTN Director of Pharmacy Affairs 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 MTN Director of Pharmacy Affairs reviews the Pharmacy Monitoring Reports for MTN studies. The process is as follows:

- The MTN Director of Pharmacy Affairs acknowledges a Pharmacy Monitoring Report within 15 working days of receipt.
- If issues are identified that need resolution, the MTN Director of Pharmacy Affairs contacts the CRS PoR in writing. The MTN Director of Pharmacy Affairs 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 MTN Director of Pharmacy Affairs 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 conduct of the monitoring visit, 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 MTN Director of Pharmacy Affairs. As appropriate, the MTN Director of Pharmacy 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 a site's temporary suspension of 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 Leadership Group 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.