16 STUDY OVERSIGHT

Oversight of studies conducted by the Microbicide Trials Network (MTN) occurs at numerous levels and begins early in the development process with an evaluation of each proposed study concept by the Network Principal Investigator (PI) to ensure it falls within the research mission of the Network. Once approved by the Network PI, discussion, review and approval/disapproval by the voting members of the Network Executive Committee follows. (See Section 10.1 of this manual.)

Subsequent MTN protocol development is accomplished through multidisciplinary collaboration among the various operational units of the Network and the study (product and financial) sponsors. Final review and approval of the protocol is provided by the study sponsors and documented according to MTN Good Documentation Policy. (See Sections 10 and 9.2 of this manual.)

Once a given protocol has been approved for implementation, the activities of pre-study activation and study execution are led by the MTN Leadership and Operations Center (LOC [FHI 360]) Clinical Research Manager (CRM). Several of these steps require collaborative work among Protocol Team and clinical research site (CRS) staff members, which the CRM must coordinate. (See Section 11 of this manual.)

Following successful IRB/IEC, regulatory, the Division of AIDS (DAIDS) and Network approval of each site to initiate the study, participant enrollment is initiated. Clinical Research Site personnel continually monitor study conduct, as outlined in the site's Clinical Quality Management Plan (CQMP). The Protocol Team (see Section 4.4 of this manual) monitors study conduct across all participating sites to identify and address emerging issues or problems.

The Statistical and Data Management Center (SDMC) monitors and ensures data quality during study implementation and prior to database lock through the development and implementation

of a study Data Management Plan (DMP). The plan includes specifications on automated data quality checks, as well as the Statistical Center for HIV/AIDS Research & Prevention (SCHARP) manual and safety data reviews.

MTN has established additional oversight procedures through the Networks' various operational components and resource committees (as discussed in following subsections). The U.S. National Institute of Allergy and Infectious Diseases (NIAID), the U.S. National Institute of Mental Health (NIMH) and the U.S. *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) sponsor MTN studies and, together with the specific product developer as applicable, have ultimate responsibility for overseeing MTN research.

The NIAID Division of AIDS (DAIDS) contracts with a Clinical Site Monitoring Group (CSMG), convenes independent Data and Safety Monitoring Board (DSMB) reviews, and provides general guidance and oversight to MTN studies. The following entities within DAIDS are also involved in study oversight: Prevention Sciences Program (PSP), Office of Clinical Site Oversight (OCSO), Regulatory Affairs Branch (RAB) and Pharmaceutical Affairs Branch (PAB).

16.1 Network Quality Statement and Policy

OUR MISSION:

To aid in the development and licensing of microbicide products that are safe and effective in the prevention of HIV transmission; that are acceptable and easy to use, inexpensive to manufacture, and readily available to those populations in greatest need, at little or no cost.

OUR GOAL:

To efficiently conduct high quality clinical trials within an NIH-funded grant structure to support the expeditious licensing of a safe and effective HIV-prevention product.

OUR GUIDING PRINCIPLES:

1. Quality
2. Productivity
3. Multi-disciplinary approach
4. Efficiency
5. Transparency
6. Flexibility
7. Innovation
8. Global and U.S. Perspective

OUR QUALITY POLICY:

To produce the highest quality research, conducted with the highest ethical standards.

16.2 Network Quality Management Plans

Each of the organizational components of the MTN follows a Quality Management Plan developed by the respective leadership of that operational unit (LOC [Pitt], LOC [FHI 360], LC and SDMC). These plans are overseen by DAIDS.

Each plan describes the proactive processes, by which the unit intends to meet the expectations set forth by:

- MTN Quality Statement and Policy
- U.S. federal regulations
- NIH and DAIDS institutional policies and procedures
- International Conference for Harmonisation Guideline for Good Clinical Practice (E6)
- MTN Manual of Operational Procedures

Each plan incorporates sound quality control and quality assurance principles and establishes procedures for internally reporting identified and/or potential failures to meet quality expectations. Each plan also incorporates procedures for establishing effective corrective and preventive actions to resolve identified and/or potential failures.

Issues affecting or with the potential to affect the confidentiality, safety and/or wellbeing of the study participants; the scientific validity of the study; and/or the validity and/or integrity of the study data are reported to the relevant study Protocol Chair(s)/Co-Chairs(s), LOC [FHI 360] and LOC [Pitt]. The communication and management of such issues complies with the MTN Good Documentation Policy (see Section 9.2.1 of this manual).

16.3 Clinical Quality Management Plans

According to the DAIDS policy *Requirements for Clinical Quality Management Plans at DAIDS-Funded and/or Supported Clinical Research Sites,* each study site is required to establish and implement a CQMP. This requirement is based on the following goals:

- Proper planning for study implementation
- Compliance with regulations, sponsors and MTN requirements
- Verification of the accuracy of data submitted to SDMC
- Identification of areas in need of corrective action and follow-up
- Avoidance of costly corrective action and duplication of effort
- Continuous quality improvement of study conduct and documentation
- Assurance of a constant state of readiness for monitoring visits and external audits.

The DAIDS policy *Requirements for Clinical Quality Management Plans at DAIDS-Funded and/or Supported Clinical Research Sites* can be accessed at the following website: https://www.niaid.nih.gov/sites/default/files/qmppolicy.pdf.

The Clinical Trials Unit (CTU) PI is responsible for the overall CQMP process and its implementation at each of the CTU's affiliated clinical research sites (CRSs). Each site's initial CQMP is reviewed and approved by the DAIDS OCSO Program Officer (PO) assigned to the CTU/CRSs. Quality Assurance (QA) findings are reported to DAIDS bi-annually using the CRS QA Summary Report template. At DAIDS discretion, QA reporting may be required more frequently based on site performance. The CTU/CRS evaluates the CQMP after each QA

review to ensure it adequately addresses current issues and/or trends. The designated CTU Quality Assurance/Quality Control (QA/QC) Coordinator is responsible for the day-to-day implementation of the CQMP. The CSMG will periodically assess the CQMP implementation and note his/her findings in the monitoring report described in Section 17 of this manual. A copy of the CQMP and documentation of its activities must be maintained on site.

16.4 Site Visits by the LOC, SDMC and LC

Staff from the LOC (FHI 360 and University of Pittsburgh [Pitt]), SDMC and LC makes routine visits to MTN CTUs/CRSs. The purpose of these visits is to:

- Assess the quality of study implementation and documentation
- Identify strengths and weaknesses in study implementation
- Troubleshoot and provide technical assistance and/or retraining related to implementation issues and problems
- Share information on successful implementation strategies identified at other sites
- Identify action items as needed to address study implementation issues and problems.

Staff members from the LOC, SDMC and LC generally contact site staff at least two to four weeks in advance to schedule and plan visits. Planned visits are announced during routine team calls to allow for input from study management regarding visit activities. While on site, the LOC, SDMC and LC staff perform assessments and provide technical assistance and/or training, as needed. Each organization conducts and documents visits according to its own standard operating procedures.

When the MTN LOC (FHI 360) Clinical Research Managers (CRM) conduct site assessment visits, all or some of the following aspects of study conduct may be reviewed: staffing levels, participant charts, recruitment and retention systems, and clinical processes. At least one week prior to the assessment visit, the FHI 360 CRM will contact the MTN SDMC Clinical Data Manager (CDM) and request copies of Participant ID (PTID)-specific electronic casebooks, which contain participant electronic Case Report Form (CRF) data, to review while on site. The CRM may request casebooks for certain PTIDs or may request a random sample. During the visit, or immediately following the visit, the CRM may request additional casebooks to review a chart of interest or if needed to identify trends in participants' charts. . During the visit, the CRM may conduct a full or targeted review of participant charts, including CRFs, from the SDMC-provided casebooks. Any findings or concerns related to documentation on CRFs or data entry will be forwarded directly to the CDM during or immediately after the visit. The CDM will review the findings/concerns and place data queries as needed in the study clinical (RF database; ideally, within 2 weeks of receipt of the findings/concerns from the CRM. The CDM will then work directly with the site to review and correct data entry errors, submit missing data, and provide refresher training to site staff, if needed. In addition, the CRM will make every effort to invite the CDM to any site debriefing meeting that includes a discussion about data management. Any serious findings identified during an assessment visit are reported immediately to the Protocol Chair(s) by the CRM visiting the site.

Site staff are required to allow the LOC, SDMC and LC staff to access study facilities and inspect specimen storage and documentation (for example, informed-consent forms [ICFs], clinic and laboratory records, other source documents and CRFs) as well as to observe the performance of study procedures, if applicable. Site staff are encouraged to share information on study implementation successes, issues and problems with the LOC, SDMC and LC staff

during these visits. The LOC, SDMC and LC staff will make every effort to minimize the impact of their visits on day-to-day study operations.

The LOC, SDMC and LC staff will document the visit activities and findings in a Site Visit Assessment report. Within days of the visit, the LOC (FHI 360) will provide any findings from PTID binders to the site study coordinator to review and correct any errors and, within three weeks of the visit, the LOC (FHI 360) will distribute the full report to the site and study leadership. The report will include a table outlining action items which the site is responsible for completing; all items should be completed within the timeline set by the CRM (approximately two weeks from the time of report distribution). A copy of the report and confirmation of completed action items is stored at the site and in the LOC (FHI 360) records.

16.5 Protocol Team Oversight

Protocol teams are responsible for actively monitoring a study's conduct and progress, largely by reviewing data reports that the SDMC developed and issued in accordance with the study reporting plan generated for each study. (See Section 13.5 of this manual). The Protocol Chair(s) may visit study sites as well. When these visits occur, the Protocol Chair(s) should notify the LOC, SDMC, LC and DAIDS staff approximately two to four weeks in advance of the visit and subsequently document the visit in a brief report describing its purpose, findings and recommendations. Issues identified during site visits and/or in monitoring reports may also be brought to the attention of the protocol team for review and action. The Protocol Chair(s) is responsible for ensuring that the team discusses issues and problems in a timely manner and that corrective action is taken, as needed. If issues cannot be resolved within the protocol team, the Protocol Chair(s) or other team members may refer issues to the MTN Leadership.

16.6 Oversight of Reportable Protocol Deviations

The U.S. Food and Drug Administration's (FDA) Compliance Program Guidance Manual, Inspectional Chapter, Section D3, defines a protocol deviation (PD) as "generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change." A PD can occur for many reasons, some of which are unforeseen. Every clinical researcher should anticipate that deviations will occur and have a policy in place to address them as they arise. A comprehensive MTN Protocol Deviation policy, in compliance with U.S. federal regulations, is a key component of study conduct oversight.

The DAIDS Policy on Source Documentation Requirements Appendix (https://www.niaid.nih.gov/sites/default/files/sourcedocappndx.pdf), Policy number DWD-POL-CL-04.00A1, states the following:

> *All protocol departures/deviations/violations must be recorded in the subject's research record. If pertinent, reasons for the departures and/or attempts to prevent or correct the departures are to be included in the documentation…. Examples of departures and appropriate documentation: a) a missed visit needs a note stating it is a missed visit and the site's attempts to locate the subject to request that he/she come in to make up that visit.… Departures from protocol also include incomplete laboratory evaluations, physical assessments, questionnaires, etc. If the vital status of a subject is known during the time period that a visit was missed, that information and the means by which it was obtained*

(e.g., telephone contact, conversation with relative, or other medical records, etc.) should be reflected in the subject's research record.

Pervasive and persistent trends in PDs as well as other performance metrics could result in the temporary suspension of the study at the site by OCSO/DAIDS. (See *Office of Clinical Site Oversight Standard Operating Procedure for Temporary Suspension of Clinical Research Site Activities*, Number OCS-014 [https://www.hanc.info/resources/Documents/Forms/AllItems.aspx].) Persistent trends in PDs could also result in FDA or another regulatory body electing not to use site study data in its consideration of the product's approval. Early identification of PD trends allows for swift corrective and preventive actions and better ensures overall good study conduct and good quality data to support potential licensure of the product.

For each MTN study that opened to accrual on or after June 1, 2012, PDs will be reported to the SDMC via a CRF. Questions will be fielded by the study FHI 360 CRM and the MTN Regulatory Group, and the study management team will routinely review the reported PDs.

Central reporting of all PDs will provide:

- The ability to identify areas for retraining or other corrective and preventive actions
- The ability to identify areas of the protocol that may need to be clarified
- Information that will allow MTN to fulfill reporting obligations to Investigational New Drug (IND) sponsors for their submissions to FDA and other regulatory bodies

The PD policy stipulates the following:

1. All deviations from the protocol will be reported to the SDMC within the time frame and according to the specifications included in the Study Specific Procedures (SSP) Manual for that protocol. Most PDs will be reported on a PD CRF, but others (such as missed visits and study regimen non-adherence) may be reported on other specific CRFs.
2. Sites must document one PD for each participant and/or study visit affected by any given deviation. For example, if the same study procedure was not performed for a participant across several study visits, a PD would be reported for each occurrence. Reporting in this way makes it easier to track PDs and identify their frequency without having to read the free text entries of all deviations. Any questions from sites about PDs should be sent to the FHI 360 CRM for the study, who will consult with the MTN Regulatory Group (mtnregulatory@mtnstopshiv.org) as needed.
3. The study management team may request a Corrective and Prevention Action (CAPA) plan from the study site for deviations that are more significant in nature. The CAPA will provide more detail than what is documented on the CRF. This request is determined on a case by case basis.
4. Some, but not all PDs, may be considered critical events, per the DAIDS policy *Identification and Classification of Critical Events; Site Responsibilities* [https://www.niaid.nih.gov/sites/default/files/cesiteresp.pdf]. As per that policy, sites are required to confer with their OCSO representative on determination of a critical event, and to promptly report critical events directly to DAIDS and to their local IRB/IEC.
5. Per the FDA and International Conference on Harmonisation (ICH) E6 Good Clinical Practice (GCP) regulations, PDs occur without prior sponsor and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval, *only when the need arises to eliminate*

apparent immediate hazards to study participants (ICH GCP Guidance for Industry Section 4.5.2, 4.5.4; 21 CFR 312.66; 21 CFR 812.35[a] [2]). Although allowable, these PDs must be reported to both the study sponsor and the site's local IRB/IEC within a specified amount of time and per local institutional policies.

6. Questions regarding potential anticipated protocol deviations due to participant noncompliance, such as an upcoming study visit that a participant does not expect to be able to attend, should be referred to the MTN Regulatory Group unless directives for managing this have already been provided in the protocol or SSP Manual.
7. Sites are to follow local requirements regarding reporting PDs to local regulatory bodies.
8. Each site must maintain a central file of deviations and make it available to the MTN Leadership, DAIDS, protocol teams, the Network Evaluation Committee (NEC) and other MTN groups upon request. The SDMC will maintain on ATLAS (an online interface maintained by the SDMC that provides secure access to data, reports and analysis tools) a summary listing and table of PDs, including missed visits (reported on a separate CRF) for each study.
9. On a monthly basis, the study management team, protocol chair(s), and DAIDS representative will review the ATLAS reports of PDs and related CAPAs. Documentation of these reviews will be included in meeting summaries. The FHI 360 CRM, Protocol Chair(s) or other study management team member will communicate with any site regarding suggested modifications to CAPAs, and will notify the study team of any trends identified.

16.7 Study Operations Group Oversight

The Study Operations Group is composed of representatives from the LOC (FHI 360 and Pitt), SDMC, LC and DAIDS. The purview of the group includes studies for which the protocol development process has been completed (that is, final version 1.0 of the protocol has been approved), studies that are in active implementation, and studies that are transitioning to closeout.

LOC (FHI 360) compiles a study operations report each month for review by the Study Operations Group. The report includes a standard study accrual and retention summary generated by the SDMC, a summary of laboratory issues prepared by the LC and narrative reports prepared by the LOC (FHI 360). The narrative reports include information on current study status and any issues and problems with implementation. Studies remain in the purview of the Study Operations Group until the last participant visit is completed for the study. The final study report will include the date of the last follow-up visit for each site. Thereafter, the group may opt to discontinue oversight of the study or to continue oversight until key study closeout milestones have been achieved. After completion of the last participant study visit and concurrent with the Study Operations Group oversight of the operational aspect of study closeout, the Manuscript Review Committee assumes responsibility for ensuring the timely preparation of study presentations and publications.

The Study Operations Group does not meet routinely, but may meet by conference call in response to a request from DAIDS or other group members to address issues or problems identified in the monthly study operations report. The Study Operations Group identifies issues or problems that require attention to ensure high-quality study conduct. The group documents the issue or problem, makes recommendations for resolving it and forwards this information to the appropriate parties for follow-up. These include group members, study site Investigators of

Record (IoR), Protocol Chair(s), the Study Monitoring Committee (SMC) and the MTN Executive Committee (EC). In cases where the issue or problem identifies a need for an MTN (that is, network-wide) policy or procedure, group members refer the issue to the MTN Manual of Operational Procedures Task Force.

16.8 Study Monitoring Committee Oversight

The SMC is comprised of the SMC Chair and staff from the LOC (FHI 360), LC, SDMC and DAIDS. In addition, external expert(s) (i.e., individual[s] not affiliated with the study or with the MTN who have relevant subject-matter expertise related to the study) may also be asked to join the committee if requested by the SMC and/or Protocol Chair(s). The Protocol Chair(s) and SMC Chair (on behalf of the SMC members) must agree that the chosen expert(s) possess the professional experience and educational credentials to evaluate clinical processes and data key to the operational, endpoint and safety assessments for the study.

The SMC provides peer review of the conduct of most MTN studies, with an emphasis on key performance indicators such as participant accrual and retention, protocol and intervention adherence, data quality and laboratory quality. Requirements for the SMC review are contained within each study protocol. For studies not subject to DSMB review, the SMC also reviews participant safety data. Studies are typically reviewed at an interval determined in accordance with the SMC Chair and in consultation with other SMC members, unless the SMC Chair waives review; however at least one SMC review is conducted for every IND trial. The schedule is based on several factors, including the study design, duration of participant accrual and follow-up periods and prior review findings. For studies subject to DSMB review, an SMC review will take place prior to the DSMB review and, when possible, will consider the same data to be reviewed by the DSMB except it will be blinded to treatment assignment. Ad hoc SMC consultations and/or reviews also may take place to address operational issues or concerns at the request of protocol teams, the Study Operations Group and/or the MTN EC.

SMC oversight is based on several factors, including the duration of participant accrual and follow-up periods. Typically, the SMC reviews take place via conference call. The SDMC schedules SMC reviews and prepares study-specific data reports for review by the SMC (see section 13.5.6 of this manual). The SDMC and/or LOC (FHI 360) may prepare and submit additional written materials in consultation with other protocol team members for the SMC's consideration, as needed. Study-site investigators do not prepare materials for submission to the SMC unless requested to by the SMC, SDMC or LOC (FHI 360).

In addition to voting SMC members, certain individuals designated as *authorized observers* may participate in SMC reviews. All SMC members and observers are required to maintain the confidentiality of SMC reviews pending release of the written summary of each review. Authorized observers may include the following:

- Protocol team members from the LOC (FHI 360 and Pitt), SDMC, LC and DAIDS PSP
- The DAIDS Medical Officer (MO), and/ or the OCSO PO involved in the oversight of MTN studies
- Study IND holder
- Study-site investigators

SMC reviews that take place via conference call may be conducted in closed and/or open sessions:

- In a closed session, SMC members discuss the SMC report and other materials submitted for review.
- In an open session, the Protocol Chair(s), and authorized observers, join the SMC to clarify issues and answer questions. Other protocol team representatives (such as study site IoRs) may be invited to join an open session, if requested by the SMC Chair or Protocol Chair(s).

For some studies, the SMC review may take place through ATLAS, an online interface maintained by SDMC that provides secure access to data, reports and analysis tools. In this case, all reviewers will document the completion of their review of the SMC report, any questions or comments regarding the contents of the report and whether a formal conference call is required.

Some SMC reviews include a closed safety-data review. Typically, this type of review is conducted for randomized and/or multi-cohort studies that are not subject to DSMB review. Closed safety-data reviews are scheduled by the SDMC to take place immediately preceding open sessions of full SMC reviews and are restricted to voting SMC members and the Protocol Statistician. The SDMC distributes the closed safety-data report to voting SMC members just prior to the SMC review. No written summary of the closed portion of the safety-data review is prepared; however, the SMC Chair communicates review findings to protocol team representatives during the open session of the full SMC review and these findings are summarized in the written summary of the full SMC review. For non-randomized and single cohort studies that are not subject to DSMB review, safety data should be included in the main (open) SMC report and reviewed as part of the full SMC review (with SMC members and authorized observers present).

In addition to the above, some SMC reviews include a confidential study-endpoint review. Typically, this type of review is conducted for Phase IIb and Phase III studies in which HIV infection is a primary study endpoint. The purpose of this review is to monitor study progress toward achieving the targeted number of endpoints per protocol specifications. Endpoint reviews are scheduled by the SDMC to take place immediately preceding full SMC reviews and are restricted to voting SMC members and protocol statisticians. Prior to the endpoint review, the SDMC distributes an endpoint data report to voting SMC members only. No written summary of the endpoint review is prepared; however, the SMC Chair communicates review findings to protocol team representatives during the open session of the full SMC review. This discussion is summarized in the written summary of the full SMC review.

The LOC (FHI 360) prepares the written summary of each SMC review (see Section 9.2 of this manual) as soon as possible after the review. In addition to including the minutes of the open session, it will document any verbal report made by the SMC Chair that the study data had been reviewed in closed session and include a summary of the major findings, if any. Following review by the SMC Chair, and subsequently, all SMC members, the LOC (FHI 360) distributes the summary to the protocol team. SMC summaries are stored in sites' regulatory files and at FHI 360. The MTN EC is informed of the SMC review outcomes, typically during routine EC conference calls. SMC recommendations that involve substantive changes to study implementation and/or cost are subject to EC approval. In addition, if a protocol team does not agree with the SMC's findings or recommendations, the Protocol Chair(s) may refer the disputed issues to the EC for discussion and resolution.

16.9 Interim Study Review Oversight

Designated MTN observational and/or ancillary studies that are not subject to the DSMB or SMC review may undergo an Interim Study Review (ISR) as needed to assess trial operations. External experts serving on the ISR in conjunction with the Protocol Statistician may review unblinded endpoint and safety data in a closed session.

ISR reviews may be scheduled by either the SDMC or LOC (FHI 360). The SDMC distributes the closed safety-data report to voting ISR members just prior to the ISR review. No written summary of the safety review is prepared. The ISR Chair, however, does communicate review findings (while maintaining study blinding) to protocol team representatives during the open session of the full ISR review. Safety data will be included in an open ISR report and be reviewed as part of the full ISR review (with ISR members and authorized observers present). Findings deemed relevant to safety or endpoint attainment in other MTN protocols will be documented and shared with the relevant Protocol Chair(s) as well as the DSMB and/or the SMC charged with the protocol's oversight.

The LOC (FHI 360) prepares the written summary of each ISR review as soon as possible after the review. Following review by the ISR Chair and, subsequently, all ISR members, LOC (FHI 360) distributes the summary to the protocol team. The MTN EC is informed of ISR review outcomes, typically during routine EC conference calls. ISR recommendations that involve substantive changes to study implementation and/or cost are subject to EC approval. In addition, if a protocol team does not agree with the ISR's findings or recommendations, the Protocol Chair(s) may refer the disputed issues to the EC.

16.10 MTN Executive Committee Oversight

Based on reports it receives from all Network organizations, teams, groups and committees, the MTN EC monitors MTN studies regarding the timeliness and quality of protocol development, study implementation and data analysis and reporting. All critical findings from monitoring and NEC CRS Evaluation Reports are reported to the EC. Most EC monitoring activity takes place during routine EC conference calls, but all studies are reviewed at least annually by the EC during a face-to-face meeting.

The EC also monitors resource allocation and use across studies and study sites. For example, the EC might assist DAIDS in determining the need for additional resources because of unexpected costs associated with study procedures, or in deciding whether to support ancillary studies endorsed by protocol teams.

16.11 DAIDS Oversight

As the network sponsor, DAIDS has a regulatory responsibility for overseeing and monitoring all MTN studies. DAIDS has delegated responsibility for on-site monitoring activities to a contractor, the CSMG; further details on site monitoring are in Section 17 of this manual. The DAIDS/OCSO staff play an active role in overseeing study implementation by ensuring that action is taken in response to monitoring reports and by working with other MTN collaborators (for example, LOC, SDMC or LC) to specify corrective action plans to site-specific study implementation issues or problems.

DAIDS staff plays an active role in approving study activation at each participating site and overseeing study implementation by contributing to MTN protocol teams and oversight groups and committees. They assign an MO to each MTN study. Other collaborating study co-sponsors, such as NICHD, may also assign an MO. The DAIDS MO contributes to the monitoring of participants' safety in MTN studies by:

- Working with protocol teams to specify adequate and appropriate plans for safety monitoring in study protocols
- Working with protocol teams to specify corrective action plans in response to issues and problems with study implementation
- Taking part in routine safety-data reviews conducted by a Protocol Safety Review Team (PSRT)
- Reviewing and assessing expedited adverse event (EAE) reports and reporting EAEs to drug regulatory authorities, when appropriate
- Informing PSRTs of all reported EAEs

DAIDS also provides oversight to MTN studies by convening DSMB reviews of MTN studies, as described below.

16.12 DSMB Oversight

An independent DSMB chartered by NIAID/DAIDS is responsible for reviewing safety and efficacy data as well as overall study conduct of all ongoing MTN Phase IIb and Phase III studies and other selected studies. The DSMB's purpose is to ensure the safety and welfare of participants by reviewing safety, efficacy and overall study conduct. The DSMB members are independent experts in a variety of fields — for example, biostatistics, medicine, clinical trial design and medical ethics. They have no conflicts of interest in the outcomes of the studies they review. *Ad hoc* members may be added for reviews of specific studies as circumstances require and/or to ensure appropriate country representation for non-U.S. studies. Appointments to the DSMB are made by NIAID. Additional information can be found in the NIAID policy on DSMB operations: https://www.niaid.nih.gov/sites/default/files/dsmb_charter.pdf.

The DSMB meets at periodic intervals (approximately every six months) during the course of a study to examine the study's accumulated endpoint and safety data, including unblinded data.

The SDMC prepares data reports for each DSMB review of an MTN study. (See Section 13.5.7 of this manual) Representatives of the protocol team (for example, the Protocol Chair(s), Statistician or DAIDS MO) may attend open sessions of DSMB reviews to discuss study progress and respond to questions. DSMB members then meet in a closed session and may subsequently share their recommendations of a routine nature with protocol team members and DAIDS representatives at the meeting. In circumstances when there is a major recommendation, the DSMB first communicates this to NIAID leadership, that is, the NIAID Director. In all cases, the NIAID Director makes the final decision whether to accept the DSMB's recommendations.

Based on its review of a study's ongoing conduct, the DSMB may recommend that the study proceed with no changes, modifications be made to the study, or that the study or part of the study (such as a study arm) be stopped. Reasons for recommending that the study or part of the study be stopped or modified include the following:

- The study objectives have been met earlier than originally planned (a clear finding that the product or intervention is effective or not effective).
- The study involves a risk to participants' safety.
- The study will not be able to answer the questions it was intended to answer because of, for example, low rates of participant accrual or retention, or lower-than-expected rates of primary outcomes or adherence to study product.
- The scientific question intended to be answered by the study is no longer relevant.

A written summary of each review is prepared (see Section 9.2 of this manual) and distributed to the protocol team as soon as possible after the review takes place. Each study site must submit this summary to its IRB/IEC and maintain copies in its Essential Documents files.