15 SAFETY CONSIDERATIONS

Ensuring participant safety is of utmost importance in all Microbicide Trials Network (MTN) studies. Monitoring participants' safety and responding to occurrences of potential harm (such as toxicity or social harms) in a timely manner requires close cooperation among all members of the protocol team. Participant safety is the collective responsibility of study site investigators; site staff; Medical Officers (MOs) from the National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS) and/or other institutes of the National Institutes of Health (NIH); the DAIDS Safety Pharmacovigilance Team (SPT); Leadership and Operations Center (LOC) staff, including Protocol Safety Physicians (PSP) and FHI 360 Clinical Research Managers (CRM); the Statistical Data Management Center (SDMC) Clinical Data Managers (CDM) and Clinical Safety Associate (CSA); and other members of the protocol team.

Study site investigators represent the first tier in monitoring participants' safety and are responsible for reporting adverse events (AE) and/or social harms according to protocol-specified procedures. Each study protocol and Study-Specific Procedures (SSP) manual specifies the requirements and procedures for identifying and reporting occurrences and severity of AEs and/or social harms for that particular study. Study protocols and SSP manuals provide details for safety monitoring to protect human subjects and capturing data for safety analyses. Study protocols also describe requirements and procedures for expedited reporting to the DAIDS Safety Office (delegated via contract to the Regulatory Support Center [RSC]). Unless otherwise specified in MTN study protocols, expedited reporting will follow the current version of the *Manual for Expedited Reporting of Adverse Events to DAIDS*, which is available on the RSC website: http://rsc.tech-res.com/clinical-research-sites/safety-reporting.

As required by DAIDS, each study protocol must also specify the following:

- Product(s) considered investigational in the study
- The level of expedited reporting to be implemented (such as standard, intensive or targeted)
- The duration of expedited reporting
- Any additional protocol-specific reporting requirements, as applicable

Any exceptions to the procedures or requirements specified in the *Manual for Expedited Reporting of Adverse Events to DAIDS* must be approved by DAIDS. Alternate reporting procedures will be specified in the study protocol.

DAIDS has an internal process for reviewing expedited reports submitted to the DAIDS RSC. This process includes a careful review by the DAIDS MO and sign-off by the head of the SPT. Once an expedited AE has been reported, site investigators must respond promptly to RSC queries. Site investigators are obligated to follow all AEs to resolution or until the condition is stable and to submit additional information about the reported event when available (or from active investigation) in a timely manner. When indicated, the RSC prepares Investigational New Drug (IND) safety reports or other safety communications, which DAIDS submits to the U.S. Food and Drug Administration. Copies are provided to site investigators for on-site review, filing and submission to Institutional Review Boards/Independent Ethics Committees (IRB/IECs) and local drug-regulatory authorities as described below.

15.1 Safety Distributions to Microbicide Trials Network Investigators

DAIDS will supply product safety information to MTN site investigators and protocol teams prior to study initiation and during the course of a study, as needed. In instances in which DAIDS does not hold the IND, the IND holder will supply this information, unless otherwise specified by a study's Clinical Trial Agreement. Product safety information is provided in several forms, including (but not limited to) the following:

- Investigator’s Brochures (IB) for study products
- Package Inserts for licensed products
- IND safety reports
- Safety memoranda/updates
- Data and Safety Monitoring Board (DSMB) review summaries

Site investigators must submit all safety information to the relevant IRB/IEC for informational purposes (that is, not for approval) as instructed by DAIDS and according to local IRB/IEC requirements. Safety-related documents may be distributed via email or by express mail. Safety-related distributions include explicit instructions regarding the requirements for handling the information.

To ensure that all intended recipients (that is, site investigators) have received all relevant safety information from DAIDS, the DAIDS RSC sends out periodic summaries of distributions (for example, IB updates and IND safety reports). Site investigators must review this information to verify that they have received all relevant distributions and ensure that this information is submitted to all responsible IRBs/IECs as instructed by DAIDS. The site is obligated to receive and process safety distributions (for example, to submit them to IRBs/IECs) from the time the site is registered for the protocol by the DAIDS Protocol Registration Office until the time the site is de-registered from the protocol.

The SSP manual for each study describes the types of safety information that investigators should expect to receive from DAIDS before and during study conduct and instructions for submitting the information to IRBs/IECs. The types of safety information for each study depend on various considerations (for example, whether the study involves an investigational product and/or is being conducted under an IND).

15.2 Clinical and Laboratory Safety Data Review for Biomedical Clinical Trials

In addition to the internal DAIDS process for review and regulatory reporting of expedited AEs, MTN uses a three-tiered approach to monitor and review safety data. The approach is designed to identify potential safety concerns in a timely manner and ensure the quality and accuracy of data that are reported and analyzed in MTN studies (such as clinical, laboratory and social harm data). In this approach, individual and aggregate safety data are reviewed and evaluated (after enrollment has begun) by qualified personnel in a consistent and methodical process.

15.2.1 Tier One

The first tier of review for clinical and laboratory safety data involves study-site clinicians and LOC PSP; the DAIDS MOs, RSC, SPT and Regulatory Affairs Branch (RAB); and SDMC personnel. Site clinicians are responsible for assessing participants' safety, reporting relevant clinical and laboratory data via case report forms (CRFs), and for reporting AEs that meet the criteria for expedited reporting to the DAIDS RSC.

The SDMC generates and reviews protocol-specific reports on a routine basis. Depending on protocol-specific needs, these reports may include individual participant-level or aggregate data from AEs, laboratory results, product hold/discontinuations, pregnancy report and history, and pregnancy outcome CRFs. The SDMC is also responsible for applying clinical quality control notes (queries) to data that require confirmation, clarification or follow-up by site clinicians.

15.2.2 Tier Two

Unless otherwise determined, a Protocol Safety Review Team (PSRT) will be established for each MTN study that involves an investigational agent or otherwise requires AE reporting. This team should include at least one LOC PSP, the DAIDS MO, the Protocol Chair(s), and others, depending on the protocol design and safety considerations. The SDMC CSA serves as the point person between the SDMC and the study PSRT. S/he provides the PSRT with safety updates as needed, and facilitates communication between the PSRT and site staff, including placing clinical queries as needed. The LOC (FHI 360) CRM and SDMC CDM may also facilitate and participate in PSRT reviews and other communications.

For each study, the PSRT conducts routine reviews (typically by conference call) of the safety-data reports that the SDMC produces and distributes. The PSRT also convenes by conference call as needed to discuss any potential safety concerns. These meetings are documented by the LOC PSP according to MTN Good Documentation Policy (see section 9.2.1 of this manual). The frequency of PSRT reviews should be agreed upon in advance of each study and adjusted as needed as the study progresses (within protocol specifications). Depending on the nature of the study, the PSRT may have additional roles, such as eligibility consultation, clinical consultation, decision making on AE reporting, toxicity management and management of study-product use. For studies in which the PSRT serves in a consultative role, the LOC PSP will receive all queries, formulate PSRT responses to the queries and circulate them to the rest of the PSRT; issue consensus PSRT responses to the queries; and maintain documentation (see section 9.2.1 of this manual) of the query process. The LOC PSPs will make every effort to forward final responses to queries within 72 business hours.

In support of PSRT functions, the LOC PSP reviews all safety-data reports. Based on this review, the LOC PSP works closely with the SDMC CSA to query the study sites for accurate, complete and consistent AE reporting. The LOC PSP chairs PSRT calls and leads discussions regarding potential safety concerns. In the event that PSRT discussions raise questions about

reported safety data, the LOC PSP will coordinate with the SDMC CSA to query the site for additional information. Site investigators are responsible for providing additional information to the PSRT, when requested. When applicable, the LOC PSP will communicate consensus PSRT opinions or guidance to site investigators regarding safety-data reporting, toxicity management and/or the management of study-product use. All such communication will be documented and placed on file according to MTN Good Documentation Policy.

15.2.3 Tier Three

An independent DSMB, chartered by DAIDS/NIAID, reviews Phase IIb and Phase III studies of the MTN, as described in Section 16.12 of this manual. (The DSMB is responsible for the review of other NIAID-funded studies as well.) DSMB reviews are conducted at least annually to examine a study's accumulated endpoint and safety data, including unblinded data. Based on the DSMB's review of both open and closed reports, and the observed beneficial or adverse effects attributable to the product(s) under study, the DSMB may recommend that: (i) the study continue with no changes, (ii) the study continue with modifications, or (iii) a study arm or the entire study stop altogether. NIAID leadership in turn decides whether to accept the DSMB's recommendation. Protocol Chair(s) are expected to participate in the open session of these reviews. DAIDS or the DSMB may request other protocol team members to participate. Protocol statisticians may take part in open and closed DSMB sessions, as requested by the DSMB. However, for blinded studies, only the unblinded statisticians are in attendance when interim analyses of unblinded data are presented.

For randomized or multi-cohort studies not subject to DSMB review, the Study Monitoring Committee (SMC) reviews participant safety data as described in Section 16.8 of this manual. Studies are typically reviewed at intervals determined by the SMC Chair and in consultation with other SMC members. At least one SMC review is performed for trials being conducted under an IND. Some SMC reviews may include a closed safety-data review.

Observational and/or ancillary studies that are subject to neither DSMB nor SMC reviews may undergo Interim Study Reviews (ISR) as needed to assess operational and other study-related issues. In some instances, unblinded endpoint and safety data may be reviewed in closed session by external experts serving on an ISR committee in conjunction with the Protocol Statistician. Interim Study Reviews are described in Section 16.9 of this manual.

All DSMB, SMC and ISR reviews will be documented and placed on file according to MTN Good Documentation Policy (see section 9.2.1 of this manual). For further information, see Sections 16.12, 16.8 and 16.9, respectively.