14 SAFETY CONSIDERATIONS

Ensuring participant safety is critical to all HPTN trials. Close cooperation between the protocol chair(s), sites investigators, site staff, Division of AIDS (DAIDS) Medical Officers, Leadership and Operations Center (LOC) Clinical Research Manager (CRM), Statistical and Data Management Center (SDMC) Clinical Data Manager (CDM), Laboratory Center representative (LC), the protocol-specific Clinical Management Committee (CMC) (if applicable), and other members of the study team is necessary to closely monitor participant safety and to respond to occurrences of toxicity or social harms in a timely manner.

The requirements and procedures for identifying and reporting adverse events (AEs) and/or social impacts for each study will be specified in the protocol and Study-Specific Procedures (SSP) manuals. The study site investigators serve an important first line role in monitoring participant safety and are responsible for reporting AEs and/or social impacts according to the specified procedures. Instructions for site access to and use of the DAIDS Adverse Event Reporting System (DAERS) are found on the DAIDS Regulatory Support Center (DAIDS RSC) website.

The study protocol for clinical trials will describe the AE reporting requirements and procedures to be followed. Requirements for expedited reporting of adverse events are described in the Manual for Expedited Reporting of Adverse Events (EAE) to DAIDS, and the version to be used will be specified in the protocol. The protocol will also specify:

- The product or products considered to be under study
- The start and duration of AE reporting
- AE grading criteria (DAIDS Table for Grading of AEs version, any special grading scales)
- Any additional protocol-specific AE or EAE reporting requirements

Any exceptions to the procedures or requirements specified in the EAE Manual must be specified in the protocol. Alternative procedures for studies that do not involve investigational agents and for which there is no AE reporting (e.g., behavioral intervention trials), will be specified in the study protocol.

DAIDS has an internal process for review of AE reports submitted in an expedited manner to the DAIDS RSC by study sites. This process includes careful review by the responsible Medical Officer and a Regulatory Affairs Branch (RAB) Safety Specialist. Investigators are responsible for submitting additional information regarding AEs upon request by the RSC and as specified in the EAE Manual. When indicated, Investigational New Drug (IND) safety reports or other safety communications are prepared by the RSC and submitted to the appropriate regulatory bodies (e.g., United States (US) Food and Drug Administration [FDA]). Copies are provided to the investigators and are to be submitted to the responsible Institutional Review Boards/Ethics Committees (IRBs/ECs) as described below.

14.1 Safety Distributions to HPTN Investigators

Product safety information is provided to HPTN investigators and protocol teams of clinical trials involving study products by DAIDS prior to study initiation and during the course of a clinical trial, as needed. Product safety information is distributed in several forms including:

- Investigator’s brochures (IB) for investigational products
- Package inserts for licensed products
- IND safety reports
- Safety memoranda/updates

In addition to the documents listed above, Data and Safety Monitoring Board (DSMB) review summaries are also distributed to investigators and study teams by DAIDS for all studies monitored by the National Institute of Allergy and Infectious Disease (NIAID) DAIDS Data and Safety Monitoring Board (see Section 15.8). Investigator's Brochures (IBs) are electronically distributed to Site Leaders, Principal Investigators, Investigators of Record, CTU Coordinators and CRS Coordinators through the NIAID Clinical Research Management System (NIAID CRMS) EAE Reporting Module (DAERS). A guide for CRS leaders and coordinators for access to IBs is located here or on the RSC site: Safety Information Distribution | DAIDS Regulatory Support Center (RSC) (nih.gov).

Distributions of these documents to investigators and study teams include explicit instructions regarding the requirements for handling of the information. IBs, package inserts, IND safety reports, safety memos, other product information, and DSMB summaries must be submitted by the investigators to the relevant IRBs/ECs for informational purposes (not approval) as instructed by DAIDS.

For any study that will be conducted at more than one US site, all safety information listed above are submitted by the LOC for single Institutional Review Board review on behalf of all US sites.

To ensure that all intended recipients have received relevant safety distributions issued by DAIDS, monthly reports and periodic summaries of the distributions (such as Investigator's Brochure updates and IND safety reports) are also distributed by DAIDS through the RSC. Investigators and study coordinators are responsible for reviewing this information to verify that they have received all relevant correspondence and for ensuring that this information is submitted to the IRBs/ECs overseeing the study, as instructed by DAIDS.

The SSP manuals for each study will describe the types of safety information that investigators should expect to receive from DAIDS before and during study conduct and the requirements for IRB/EC submission of these. The types of safety information to be issued for each study will vary based on whether the study is solely behavioral or observational, whether a study product is being used, and whether it is being conducted under an IND with the US FDA.

A site's obligation for receipt and processing (e.g., submission to the IRB/EC) of safety distributions begins when the site is registered to the protocol through the RSC and ends once a site is de-registered from the protocol.

14.2 Review of Safety Data for Clinical Trials

In addition to the internal DAIDS review process for AEs reported in an expedited fashion, the HPTN uses a three-tiered approach to safety data review designed to identify potential safety concerns in a timely manner and to ensure the quality and accuracy of clinical and laboratory data reported and analyzed in HPTN clinical trials. Through this system, once enrollment has begun, individual and aggregate safety data are reviewed and evaluated by qualified personnel through a consistent, methodical process.

14.2.1 Tier One

The first tier of clinical and laboratory data safety review involves study site clinicians, RSC, DAIDS, and SDMC personnel. Site clinicians are responsible for carefully assessing participant safety and reporting relevant clinical and laboratory data via case report forms (CRFs) submitted to the SDMC as well as the reporting of AEs that meet the criteria for expedited reporting to the RSC.

The SDMC staff generates and reviews protocol-specific standard reports on a routine basis to ensure that safety data is complete, accurate and timely. The SDMC clinical coding and safety and data management staff applies AE coding and clinical queries to data requiring confirmation, clarification, or follow-up.

For studies with pause criteria or rules, SDMC programmers create computer programs that alert SDMC staff when criteria for pausing the study may have been met and the protocol team may need to be notified. Pause criteria must be specified in the study protocol.

14.2.2Tier Two

Tier two of safety oversight of HPTN studies of a biomedical intervention includes a Clinical Management Committee and may also include regular review of safety data by independent safety reviewers. For some studies, especially those without DSMB oversight, the HPTN Study Monitoring Committee may also review reports of safety data.

Clinical Management Committee

For each study with a clinical component, a Clinical Management Committee (CMC) will be established, composed of appropriate protocol team clinicians (including an HPTN Safety Physician, as necessary), who will provide support to site clinicians regarding individual participant clinical management (toxicity management, clinical holds of study drug, study drug re-challenge, permanent discontinuations). Blinding will be maintained with regards to the individual participant discussion(s).

Independent Safety Reviewers

The SDMC may contract with clinicians to serve as independent safety reviewers (ISR) for studies of products that are not approved for any indication or for studies of products that need further safety evaluation. The ISR is responsible for reviewing regular reports of safety data along with the Medical Officer (MO). If there are any trends in the safety data noted the ISR or MO will notify the protocol statistician who will in turn notify the Study Monitoring Committee (SMC) or DSMB, as appropriate. The ISRs may also serve as members of the SMC, particularly for studies with no DSMB oversight.

For trials with no DSMB oversight, the HPTN SMC will also review safety data, either in aggregate or by arm. The SDMC will prepare routine study conduct and safety reports for the SMC, which will meet by conference call approximately every 6 months and will review safety data during a closed meeting. More frequent or *ad hoc* reviews of safety reports may be conducted by the SMC as needed.

A recommendation to stop the trial may be made by the SMC at any such time that the team agrees an unacceptable type and/or frequency of AEs has been observed. If at any time a decision is made to discontinue the study product in all participants, DAIDS will notify the site IoRs, who will notify the responsible IRBs expeditiously.

14.2.3Tier Three

Phase IIb and III HPTN trials are typically reviewed by a DAIDS Data and Safety Monitoring Board (DSMB) as described in Section 15.8. The DSMB examines the accumulated endpoint and safety data to make recommendations to DAIDS concerning continuation, termination, or other modifications of the trial based on the observed beneficial or adverse effects of the interventions under study. This includes a closed-session review of study data by arm, often triggered by an event specified in the protocol (e.g., number of participants enrolled, or number of endpoints attained). Reviews of Phase IIb and III trials are conducted at least annually for safety and accrual, even if events that might prompt a review of efficacy have not yet occurred. Protocol Chairs (or designee) are expected to participate in the open session of these reviews.

14.3 Social Impacts

In addition to medical safety concerns, participants in HPTN studies may also experience social impacts such as discrimination, stigma or legal problems as a result of their participation in the study. Only events that participants perceive to have negatively affected them due to study participation are considered reportable. The staff's interpretation of an event is not considered in determining whether an event is a social impact. Each HPTN protocol will indicate how social impacts will be reported and assessed. Sites are also responsible for reporting social impacts to the responsible IRBs/ECs as applicable locally.