1. Clinical/Counseling Considerations

1.1 Overview of Section 1

This section provides guidance on counseling and clinical considerations for the HPTN 111 protocol.

1.2 HIV Counseling and Testing

1.2.1 During Scheduled Study Visits

HIV testing is required at each scheduled HPTN 111 study visit as per the schedule of events. All counseling should be conducted following the standard-of-care, in accordance with the Uganda Ministry of Health guidelines for provider-initiated HIV counseling & testing. This will include pre- and post-test counseling and status-dependent referrals for prevention or care services.

1.2.2 Between Study Visits

All enrolled participants will be advised about the recommended HIV testing schedule for persons behaviorally vulnerable to HIV (every three months). For participants in the intervention group, they will be reminded that they can access HIV self-test kits from their barber or from local health facilities, where they can also access provider-based testing. For participants in the control group, they will be advised that they can access provider-based or HIV self-test kits at local health facilities.

All participants, in both the intervention group and control group, will be asked to contact the

study team if they complete an HIV test between study visits. The study team will document the contact and results of the test in the study database and chart notes and will provide any necessary recommendations or referrals for subsequent testing or care. If a client reports a positive/reactive HIV test, they will be requested to come to the study clinic for confirmatory HIV testing and referral to HIV care (if needed).

1.2.3 Linkage to care for participants who acquire HIV during the study

If a participant has a positive/reactive test during the study, testing will follow the HIV testing algorithm (SSP Section 1 of the Lab Considerations Manual). Once a participant has been confirmed to be living with HIV, the study team will make every effort to link the participant to HIV treatment/care in the community. The site may further explain linkage procedures in a site-specific SOP.

Participants who acquire HIV during the study should be counseled that they can remain in the study for study visits and to receive the intervention from the barber (if in the intervention group).

1.3 STI Management

Participants will undergo STI testing as per the schedule of events. If a participant has a positive STI result (syphilis, gonorrhea, or chlamydia), the participant will be contacted and requested to return to the study clinic for treatment, provided by the study team. The study team will attempt to contact a participant with a positive STI result within two business days of receiving the positive test result. The treatment regimen provided will be consistent with local guidelines. If for any reason the study team cannot provide treatment or additional follow-up testing is required, the participant will be linked to testing/treatment at a local health facility.

1.4 Medical History/Events

Since this protocol is minimal risk and does not involve a drug or device intervention, medical history and events will not be recorded in the study database. Additional details about adverse event reporting are in SSP Section 1 of the Study Reporting Plan Manual.

1.5 Symptom-directed Physical Exams

Targeted physical exams will be performed at study visits, as needed, based on participant report of symptoms of clinician observation of care needs. The reason for the physical exam will be recorded in the study database/participant chart.

1.6 Alcohol and Drug Use

Participants will be asked about their alcohol and drug use and each scheduled visit. At enrollment, they will be asked the Alcohol Use Disorders Identification Test (AUDIT)-C questionnaire which can be used to help identify if a participant has alcohol use disorder. Responses on these screening questions should be scored and should inform discussions with the participant, and referrals as appropriate.

1.6.1 Scoring the AUDIT-C

The AUDIT-C is a screening tool for alcohol use disorders. It has 3 questions and is scored on a scale of 0-12. Each question has 5 answer choices valued from 0 points to 4 points. In men, a combined score of 4 or more is considered positive, optimal for identifying hazardous drinking or active alcohol use disorders. Generally, the higher the score, the more likely it is that a person's drinking is affecting their safety.

1.7 Clinical Referrals

If for any reason the study team feels a participant needs a referral for clinical care or testing beyond the scope of the HPTN 111 protocol, the team will provide a referral consistent with local standard-of-care.

1.8 Social Harms Counseling and Management

Participants will be asked about any potential social impacts associated with their participation in the study. If a participant reports a social harm, this will be documented in the study database and chart notes. The social harm should be followed until resolution or the end of the study. The study team will be knowledgeable about local services that can be used for referral services (e.g. mental health counseling).

Prior to study initiation, study staff teams at the site should discuss as a group, and with community representatives, what issues and problems are most likely to be encountered by participants and barbers and should agree upon how these issues and problems should be handled if reported. Roles and responsibilities should be defined for all staff members, such that each staff member is aware of what actions he/she can appropriately take, and what actions should be referred to other members of the team. During study implementation, the site team should continue to discuss actual participant experiences, successful and unsuccessful response strategies, and other lessons learned among themselves and with community representatives. Based on these discussions and lessons learned, procedures for responding to issues and problems should be reassessed and updated as needed throughout the study.

2. Study Reporting and Monitoring

2.1 Overview of Section 2

This section provides guidance on study reporting and monitoring procedures for HPTN 111.

2.2 Safety Monitoring and Oversight

Section 7.0 of the HPTN 111 Protocol outlines the measures to monitor and safeguard participant safety. Safety monitoring of study participants is primarily the responsibility of study staff, under the direction of the IoR.

The IoR and designated study staff are responsible for submitting required forms to the HPTN SDMC and reporting the following to the study reporting team:

- Any social harm reported by a participant or barber
- Any participant death
- Any event deemed important, by the IoR, to the conduct of the study or participant safety

The study reporting team will include the protocol chairs, study site coordinator, and the HPTN CRMs. The email alias (111reporting@hptn.org) can be used to alert this group. The HPTN CRMs will be responsible for escalating any concerns to the DAIDS MO or other protocol team members (e.g. community working group or ethics working group representatives) if necessary.

Protocol deviations will follow separate reporting requirements, as outlined below.

2.3 DAIDS monitoring

Based on the risk level of HPTN 111, the DAIDS Monitoring Operations Branch has determined that DAIDS, nor any non-DAIDS entity, will not monitor HPTN 111.

2.4 Protocol Deviations

All deviations must be documented in the participant charts and any other pertinent source documents. A subset of deviations is also considered reportable per the HPTN and are described in the HPTN MOP Section 12 and in the HANC Cross-Network Protocol Deviation Reporting Guide. The HPTN has established a process for staff at HPTN study sites, the LOC, the LC and the SDMC to document the occurrence of protocol deviations that are considered reportable and to report them to the sponsor (DAIDS).

Full documentation of all protocol deviations – including reportable deviations as defined above - should be maintained at the site and reported as required to the IRB according to their requirements.

2.5 Reportable Protocol Deviations

Reportable deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of key study data or that may significantly affect a participant's rights, safety, or well-being.

Examples of reportable protocol deviations are:

- Enrollment of an ineligible participant or prior to confirming eligibility. This also includes situations when ineligibility is found after the fact.
- Informed consent not obtained prior to performing protocol-specified procedures.
- Any situation when any of the HPTN 111 HIV testing algorithms were not followed as per protocol and Section 11 of the SSP. This is applicable even if the error or omission was made by a commercial or external laboratory.
- A trend showing that protocol-specified procedures are not followed by site staff. For example, if a site forgets to provide or document collection/review of locator information for multiple participants and/or multiple visits, this would be considered a reportable protocol deviation.
- Breach of participant confidentiality
- A protocol-specified laboratory assay consistently not being performed (a single missed assay during one participant visit would not be considered a reportable protocol deviation).

- A site-specific laboratory assay is deliberately added to protocol requirements by the investigator to be conducted for all participants.

Participant non-compliance with the study protocol (e.g., not attending study visits, declining answering questionnaires) is not considered to be a reportable protocol deviation but should be discussed by the protocol team.

The Clinical Site Monitor (e.g., PPD) identifies protocol non-adherence events and violations in their monitoring reports, and some of these may also be reportable protocol deviations; however, there is not a one-to-one correlation between events reported by the Clinical Site Monitor and those to be reported through the HPTN protocol deviation reporting system. The Clinical Site Monitor may report protocol non-adherence events and violations that encompass every infraction of the protocol. For example, if a blood specimen is drawn for syphilis testing, but is not processed by the laboratory, it is a non-adherence event according to the Clinical Site Monitor. This would be considered a deviation, but not one that meets the HPTN definition of a reportable protocol deviation. If, however, syphilis testing is meant to be completed at each participant screening visit and is not being done at all, this would be a reportable protocol deviation as defined by the HPTN, because a trend of this error has been identified.

2.6 Protocol Deviation Reporting

If a site believes a protocol deviation has occurred, the following steps should be followed:

1. Contact the HPTN111 reporting alias (111reporting@hptn.org) as soon as possible (within 24 hours) but no more than 3 business days once a site becomes aware of a deviation. The reporting group will determine whether a deviation meets the above criteria or are otherwise deemed by the protocol team to be reportable deviations before they are reported in the electronic data capture system.
2. If it is determined the deviation does <u>not</u> meet the definition of reportable deviation, sites are asked to document the deviation as part of their study documents and report to the IRB per their policy.
3. If it is determined that the deviation does meet the definition of reportable deviation, sites must complete the following steps:

    a. Complete the Protocol Deviation eCRF; responses must be concise and clear when describing the event. The eCRF must be submitted within 5 reporting days, with Day 1 being the first business day that site personnel became aware of a PD that meets reporting criteria.

        One Protocol Deviation Log eCRF should be completed for each participant affected by the deviation. If the deviation occurred over a period of time, report the date the deviation first started and when it ended; if it is ongoing at the time the report is submitted, include this information as part of the description of the deviation.

If 5 or more participants are involved in the same protocol deviation, report the deviation for each individual PTID in a separate eCRF, and include in the description of the deviation the number of PTIDs impacted by the deviation. Please note, when reporting trends (meaning a deviation that impacted 5 or more PTIDs), the information on eCRFs must be identical for all impacted PTIDs (with the exception of participant-specific information such as PTID and applicable dates).

b. Complete a Corrective and Preventive Action (CAPA) Form. The CAPA does not need to be completed within the 5-day reporting period.

c. Download the Protocol Deviation eCRF from REDCap Cloud, and email it (or multiple CRFs if there is more than one) to the HPTN 111 reporting email alias at 111reporting@hptn.org indicating that a deviation has occurred and the date it was submitted to the REDCap Cloud database system. If the deviation is the same for multiple PTIDs, only append one Protocol Deviation e-CRF to the email and indicate in the body of the email how many participants are impacted by the same deviation.

The HPTN 111 protocol deviation email alias includes the following individuals:

- Protocol Chair and Co-Chair
- LOC, LC, and SDMC protocol representatives
- DAIDS Protocol Medical Officer
- DAIDS HPTN Office of Clinical Site Oversight (OCSO) Program Officer Liaisons

When sending emails to the 111 Protocol Deviation email alias letting them know that a reportable deviation has occurred, please note:

- Site should also cc: the IoR, Study Coordinator, Site Regulatory Coordinator, and the site's DAIDS OCSO representative on the email (please note, the site's DAIDS OCSO representative is not the same as the Program Officer Liaisons).
- When reporting a deviation trend, please include one Protocol Deviation Log eCRF as part of the email sent to the 111 Protocol Deviation email alias and specify in the body of the email that a trend is being reported, and list of affected PTIDs and applicable dates for each. Individual eCRFs must be entered into REDCap Cloud for each affected PTID.

Please use the following format when sending an email to the 111 Protocol Deviation email alias:

Subject line: Include "111 PD: [PTID] – [One-line summary of reportable deviation]."
Body of the email:

1. Site name and number

2. Name of person submitting the reportable protocol deviation
3. Participant Identification number (PTID) and Week on Study (Use "Screen" if pre-enrollment)
4. Short summary of the reportable deviation

Email example:

Subject line: 111 PD: Participant 103-000012 – ICF error
Body of email:

- Site name and number: MU-JHU (30293)
- Person submitting query: Hedda Lettuce, Study Coordinator
- PTID and Week on Study: 103-000012, Screening
- Short Summary: Participant enrolled on February 1, 2024. During QC process after the participant left the study clinic, it was noticed the participant did not date the informed consent form. Participant was contacted to return to clinic and has promised to come tomorrow to rectify the form.

It also should be noted that DAIDS has a critical event policy that may overlap with events that are deemed as protocol deviations by the HPTN. Refer to the policy at this link: https://www.niaid.nih.gov/research/daids-clinical-research-event-reporting-safety-monitoring. The HPTN has a template available for sites to use to respond to the requirements of a critical event – it can be found at this link: https://hptn.org/resources/manual-of-operations (listed under "Other").

2.7 Adverse Events

Since HPTN 111 is a minimal risk study and does not involve a biomedical or clinical care intervention, standard adverse event reporting is not required. Medical history and adverse events will not be recorded in the study database. The study site will record and report adverse events according to local IRB/EC guidelines and GCP. The site may create internal SOPs or log forms to track adverse events for participants.

Any participant death should be reported to the study reporting team (111reporting@hptn.org) within three business days. Participant deaths and any other serious adverse events should be reported to local IRB/ECs as per their requirements. A Termination eCRF should document the participant death.

2.8 Social Harms

Participants or barbers in HPTN 111 may experience social harms. Study staff will discuss potential social impacts or harms during each study visit for participants or at the time of

quarterly questionnaire completion for barbers. Participants and barbers should also be counseled to contact study staff if they ever feel they have experienced a social impact due to their participation in the study.

Social impacts will be reported in the study database and the study team should alert the study reporting team (see SSP Section 2.6 above) within three business days of the initial report by the participant or barber. Additional information about management of participant and barber wellbeing related to social harms is available in the Clinical, Safety, and AE Management SSP Manual Section 1.

2.9 Anti-homosexuality Act, 2023 in Uganda

The Uganda Parliament passed a bill, signed into law by President Museveni in May 2023, that criminalizes same sex conduct. The Anti-Homosexuality Act of 2023 has been condemned as an extreme law that targets and oppresses LGBTQ+ Ugandans. While the protocol team has determined that the potential risk to participants, barbers, and study staff are minimal due to the nature of this study (heterosexual men), the HPTN 111 takes the safety of all participants very seriously. A risk mitigation plan has been developed to outline the context of the Act, discussions within the medical and research communities within Uganda, and details on how the HPTN 111 team will protect participants, barbers, and staff as it relates to the Act.