1. Introduction

1.1 Overview of Section 1

This section includes specifics on study conduct including the sources of procedural information available to HPTN 111 study site staff, the responsibilities of the site Investigators, and the process by which each site will be approved to implement HPTN 111.

1.2 Source of Procedural Information

All study procedures must be conducted in accordance with the study protocol and this study specific procedures (SSP) manual. Unless instructed by the HPTN Leadership and Operations Center (LOC), if there is inconsistency between this manual and the protocol, the specifications of the protocol take precedence. Please alert the HPTN Leadership and Operations Center (LOC) of any such inconsistencies.

In instances where there is an urgent need for a change to the SSP manual, and when a full revision of the SSP is not imminent, the LOC may distribute an email containing a "Notification of Interim Change" to the current version of the SSP manual. These interim changes will be considered an official part of the SSP manual and should be considered official by any monitoring agents.

Study site staff are encouraged to contact the HPTN LOC Clinical Research Managers

(CRMs) with all questions related to interpretation and proper implementation of the protocol. Questions related to community education and outreach should be directed to the HPTN LOC Community Program Managers. Questions related to data management and data collection should be directed to the HPTN Statistical and Data Management Center (SDMC) Clinical Data Manager(s). Questions related to the collection, processing, and storage of local and central lab specimens should be directed to the HPTN Laboratory Center (LC) study representatives. The persons to contact information for these types of questions are:

HPTN LOC Clinical Research Managers	Jayla Harris Clinical Research Manager Phone: 919-321-3866 Email: jharris@fhi360.org Shannon Hinds Clinician Trials Assistant Phone: 919-321-3474 Email: shinds@fhi360.org
HPTN LOC Community Program Manager	Maggie Albano Community Programs Associate Tel: 202-464-3753 Email: malbano@fhi360.org Molly Dyer Community Programs Associate Phone: 919-321-3851 Email: mdyer@fhi360.org
HPTN SDMC Clinical Data Manager	Paul Butler Title: Clinical Data Manager Tel: 206-667-7928 Email: pbutler@scharp.org Ian Bell Title: Clinical Data Manager Tel: 206-667-7061 Email: ibell@scharp.org
HPTN Laboratory Center (LC) Representatives	Estelle Piwowar-Manning Title: HPTN Lab Center Deputy Director Tel: 410 614 6736 Email: epiwowa@jhmi.edu

Contact information for all other HPTN 111 protocol team members can be found in the protocol roster in the HPTN 111 protocol.

1.3 Sites Participating in HPTN 111

Clinical Research Site (CRSs) that will participate in HPTN 111 are:

Table 1-2
Participating HPTN 111 Site

	CRS ID	CRS Name	Location
1	30293	MU-JHU Research Collaboration (MUJHU CARE LTD) CRS	Kampala, Uganda

1.4 Investigator Responsibilities

HPTN 111 must be conducted in accordance with the US Code of Federal Regulations (CFR) and the International Conference on Harmonization (ICH) Consolidated Guideline for Good Clinical Practice (GCP). Copies of the regulations governing the conduct of this study (45 CFR 46 and 21 CFR 11, 50, 54, 56, and 312) and the ICH guideline can be requested from the HPTN LOC or found online. The DAIDS Policy for Requirements for Essential Documents and Source Documentation can be found in the Division of AIDS (DAIDS) Site Clinical Operations and Research Essentials (SCORE) Manual .

HPTN 111 also must be conducted in accordance with all local regulations, policies, and guidelines applicable to human subjects research in general and/or the conduct of study procedures in particular.

The Investigator of Record (IoR) at each site is the person responsible for the conduct of the clinical trial at the clinical research site. This person is the signatory for the DAIDS Investigator of Record Form which must be signed prior to site activation, to formally indicate his/her agreement to conduct the study in accordance with the protocol; this SSP manual; all applicable US and in country regulations, policies, and guidelines; and HPTN policies. Additionally, site investigators must promptly report to their local IRB/EC and any other local regulatory bodies any changes in the study and must comply with the requirements of 45 CFR 46.108(a)(4) and 21 CFR 56.108(b) for promptly reporting the following: unanticipated problems involving risks to participants or others; serious or continuing noncompliance with applicable regulations or the requirements or determinations of the IRB; and any suspension or termination of IRB approval.

Investigators may delegate work involved in conducting the study to other study staff members; however, delegation does not relieve the Investigator of their ultimate responsibility for all study procedures performed and all study data collected. Additional guidance can be found in the US Food and Drug Administration's Information Sheet Guidance: Information Sheet Guidance for Institutional Review Boards (IRBs), Clinical Investigators, and Sponsors.

1.5 Study Activation Process

Prior to undertaking any study procedures, the study site must obtain approval to conduct the study from the Institutional Review Board that will be responsible for this study. Thereafter, sites must complete Protocol Registration with the DAIDS Regulatory Support Center (RSC), as well as Study Activation procedures with the HPTN LOC. These procedures are also described in the HPTN Manual of Operations (MOP) available at: https://www.hptn.org/resources/manual-of-operations. HPTN 111 study procedures may not be conducted prior to completing all of these steps and receipt of a site-specific study activation notice from the HPTN LOC.

1.5.1 Protocol Distribution

The HPTN 111 Clinical Research Manager will distribute the final implementation version of the protocol electronically to the study site.

1.5.2 Development and HPTN LOC Review of Site-Specific Informed Consent Forms: English Language Versions

Site staff will adapt the sample informed consent forms appended to the study protocol to reflect local procedures and IRB requirements and forward the forms for review by the HPTN LOC CRM prior to submission for IRB approval.

1.5.3 Development and HPTN LOC Review of Site-Specific Informed Consent Forms: Local Language Version(s) and Back-translation(s)

For the initial version of the protocol, after incorporating review comments from the HPTN LOC CRM, site staff will translate the informed consent forms into all applicable local languages and then submit the translated forms, back-translations of the forms, and a certificate of translation for review by the HPTN LOC. The HPTN LOC CRM will provide review comments to site staff as quickly as possible. The back-translation need not be completed by a certified translator; however, it is recommended that two different individuals translate the document(s) and then review each other's work to prepare a composite. The back-translation should be completed by an individual who did not participate in the translation process.

1.5.4 IRB Review

The study site is responsible for submitting their site-specific documents, including ICF, current curriculum vitae (CV) of the IoR and any other study-related materials, to the local IRB for approval.

1.5.5 Protocol Registration

Note: *Additional details on the protocol registration process can be found in the Division of AIDS (DAIDS) Protocol Registration Policy and Procedure Manual (located at* https://www.niaid.nih.gov/sites/default/files/prmanual.pdf *) and the HPTN MOP.*

Upon obtaining approval from the responsible IRB, site staff will submit the following documents to the Protocol Registration Office (PRO) at the RSC. These documents may be sent electronically to protocol@tech-res.com. Site staff will also submit a copy of the submission documents to the HPTN LOC:

- Current, signed, and dated CV of the IoR, in English
- Documentation of approval from the responsible IRB, and local regulatory authority if applicable, of the study protocol and the informed consent forms.

Note: *Documentation of IRB must reference the exact protocol number, title, version number, and date as listed on the cover page of the protocol.*

- A copy of the approved site-specific informed consent forms including local language translations, back-translations and a certificate of translation (if appropriate).

Some sites may have additional site-specific documents to be included with the protocol registration package (e.g., additional information requested by DAIDS). These documents should be submitted to the DAIDS RSC, and a copy should be submitted to HPTN LOC.

If the site deletes or makes any substantive change to basic and/or additional elements as presented in the ICFs, the IoR must provide written documentation to explain the deletions/change(s) at the time of initial protocol registration with the DAIDS RSC.

DAIDS regulatory staff will communicate their review findings to the site staff, who will coordinate any required re-submissions.

1.5.6 Study Activation

The HPTN has specified certain requirements that must be met in order to activate HPTN study operations. The activation requirements for HPTN 111 are outlined in the HPTN 111 Activation checklist which is distributed the site in advance of expected study activation. General HPTN study-specific site activation requirements can be found in Table 1 of Section 10 of the HPTN MOP.

If there is an inconsistency between the items in this SSP manual and the HPTN MOP for study-specific site activation, contact the HPTN 111 CRM for clarification.

1.5.7 Abbreviated Study Activation for Protocol Amendments

When a full protocol amendment is implemented, the site is not required to repeat the entire site-specific study activation process. However, a subset of these activities must be conducted in order to prepare for the changes to study conduct based on full protocol amendments. The list below outlines the required activities and/or items that must be in place before a site can begin study conduct under a full protocol amendment. Not all items will apply for each amendment. The site should submit for DAIDS protocol

registration within 14 days after receiving IRB approval for the protocol and site specific-ICFs. The list below applies to any version after Version 1.0.

- Approvals from the responsible IRB for the protocol and site-specific ICFs
- Sites should review, and if necessary revise, the CV for the IoR, the CRF and Eligibility Source Documentation Tables, and all study-related SOPs.
- Completion of study-specific training (remote or on site) for the latest version of the protocol, if necessary
- The site must have a current IATA specimen shipping certification for at least one study staff member
- If any of the following laboratory-related SOPs are revised, they must be reviewed and approved by the network laboratory.
    - SOP for laboratory QA/QC procedures
    - SOP for chain of custody related to testing primary study endpoints
    - SOP for local laboratory back-up arrangements

1.6 Continuing Review

Throughout the course of the study, all sites are required to submit annual progress reports to the IRB overseeing study conduct and receive annual approval. Documentation of this approval must be submitted to the RSC. See https://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-manual for more information.

Additional information and guidance about continuing review can be found at the Office of Human Research Protection (OHRP) website: http://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-continuing-review-2010/.

2. Protocol

2.1 Overview of Section 2

The table below documents the history of the HPTN 111 protocol along with Clarification Memos, Letters of Amendment, and Full Amendments. These documents are considered Essential Documents. A copy of each document should be available to staff and a copy should be maintained in the central files.

Document	Date
HPTN 111 Protocol, Version 1.0	**18 September 2023**
Letter of Amendment # 1 to HPTN 111 Protocol Version 1.0	**05 February 2024**
Letter of Amendment # 2 to HPTN 111 Protocol Version 1.0	**16 July 2024**
Letter of Amendment #3 to HPTN 111 Protocol Version 1.0	**31 October 2024**
HPTN 111 Protocol, Version 2.0	**27 January 2025**

Note: Clarification Memos and Letters of Amendment are incorporated into subsequent full versions of the protocol. A Clarification Memo may also be incorporated into a subsequent Letter of Amendment.

3. Document Requirements

3.1 Overview

3.2 Essential Documents

The DAIDS Policy for *Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials* (*https://www.niaid.nih.gov/sites/default/files/score-essential-documents.pdf* and its appendix: *https://www.niaid.nih.gov/sites/default/files/essentialdocappndx.pdf*) and *ICH E6 Good Clinical Practice: Consolidated Guidance* (*https://www.fda.gov/media/93884/download*) specify the administrative and regulatory documents that HPTN study sites must maintain for DAIDS-sponsored studies. Based on this DAIDS Policy, the documentation listed below must be maintained for HPTN 111. When required documents are modified or updated, the original and modified/updated versions must be maintained. Although all required documentation must be available for inspection at any time, all documents need not be stored together in one location. In HPTN 111, essential documents may be stored at the clinic site in Kalangala or at MU-JHU in Kampala. The study team is responsible for maintaining a listing of where all essential documents are located.

- Protocol (implementation version and any subsequent amendments, letters of amendment and clarification memos)

- Informed Consent Forms (IRB, all signed and dated forms from screened/enrolled study participants), as well as any "Dear Participant" Letters (IRB-approved versions) for all screened/enrolled participants.
- Signed and dated DAIDS Investigator of Record Form, original and subsequent versions
- Documentation of approved protocol registration from DAIDS, original protocol registration and for all subsequent protocol modifications
- Documentation of study activation from HPTN LOC
- Documentation of local regulatory authority correspondence, authorization, and/or approval of the protocol
- Federal Wide Assurance (FWA) number(s) and expiration date
- All correspondence to and from the IRB, including documentation of all submissions, reviews and approvals and copies of site-specific interim and annual reports.
- IRB-approved participant informational/educational materials and advertisements for participant recruitment, as well as subsequent updates
- Screening and enrollment logs
- Participant identification code list (if applicable)
- Study staff roster, signature sheet, and delegation of duties, including Investigator responsibilities.
- Signed and dated CV for each study staff member, current within the last two years
- Financial disclosure forms from all key staff
- Documentation of staff members' current human subjects training (within 3 years)
- Documentation of staff members' study-specific training, including training on all official revisions/amendments/regulatory actions related to the protocol.
- Documentation of staff members' current GCP training (within 3 years)
- Documentation of staff members' current GCLP training
- Local laboratory accreditations/certifications
- Local laboratory normal values/reference ranges for protocol-specified testing

- Key study-related correspondence with the HPTN LOC, HPTN SDMC, HPTN Laboratory Center (LC), DAIDS PAB or DAIDS, as well as other study-related communication

- Documentation of study-related conference calls and meetings

- Applicable local public health reporting requirements pertinent to study procedures

- Final, approved version of each local site- and study-specific SOPs that will be used for HPTN 111 and all subsequent updates

- DAIDS reference materials including:

    - DAIDS Policy for Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (DWD-POL-CL-04.00 (https://www.niaid.nih.gov/sites/default/files/score-source-documentation.pdf and its appendix:https://www.niaid.nih.gov/sites/default/files/score-source-documentation-requirements.pdf)) and subsequent updates,

    - DAIDS Policy for Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials (DWD-POL-RA-03.00 (https://www.niaid.nih.gov/sites/default/files/score-essential-documents.pdf)) and subsequent updates; and

    - DAIDS Protocol Registration Policy (https://www.niaid.nih.gov/sites/default/files/protocolregpolicy.pdf) and the Protocol Registration Manual, Version 3.0, dated April 2015 (https://www.niaid.nih.gov/sites/default/files/prmanual.pdf) and any subsequent updates.

- Study specific procedures (SSP) manual, original versions and all updates, bulletins, clarifications, and communiqués

- Monitoring visit log, reports, and site response to visit findings (for HPTN LOC, SDMC, LC, and other site visits). Sites should print visit reports for their files.

- A complete, blank copy of the electronic case report forms (CRFs) (original and all revisions – these will be provided by the HPTN SDMC). Sites may choose to print the forms and file as part of their essential documents, or they may choose to file electronically.

- All completed CRFs, which will include electronic initials and dates per the electronic data capture system (these will be provided by the HPTN SDMC at the end of the study)

- Record of stored specimens and transport logs.

- Site specific Source Documentation Table (Table 3-1a or 3-1b) and Source Documentation for Eligibility Criteria (Table 3-2)

- Source documents
- Signed agreements related to the study (e.g., between Investigator and affiliated sites)

3.3 Investigator Responsibilities

Study sites must maintain an accurate and complete participant research record containing all information pertinent to the study for each study participant. As defined by the *DAIDS Policy for Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (DWD-POL-CL-04.00)*, the research record consists of the following: original subject-signed informed consent form(s), participant source documents, and case report forms (CRFs).

3.4 Concept of Source Documentation

A source document is defined as the first document on which study-related information is recorded. Study sites must adhere to the standards of source documentation specified in the *DAIDS Policy for Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (DWD-POL-CL-04.00)* and the standards outlined in this manual.

For HPTN 111, participant source documents will consist of narrative chart notes, visit checklists, medical records, laboratory reports, CRFs, and other items as defined by the site. As a condition for study activation, the site must establish an SOP for source documentation that specifies the use of these documents as source documents.

HPTN 111 will use an electronic data capture system. Electronic records are any combination of text, graphics, data, audio, pictorial, or other information in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system (21 CFR 11.3). **When data are entered directly into a computer, the electronic data in the computer becomes the source document**. A paper record (printout/hard copy/ "print screen") of the electronic data is considered to be a copy. Requirements for documentation, record keeping, and record retention apply to electronic records the same as they do for paper systems.

Examples of electronic records include but are not limited to:

1. Participant data, reports, and/or results
2. E-mail communications pertaining to a participant or protocol management (e.g., directives from protocol chairs, CRS investigators to study nurses, etc.)
3. IRB correspondence pertaining to a participant or the study
4. Audio Computer-Assisted Self-Interview (ACASI) questionnaires

Each electronic record needs to be associated with an originator type, otherwise known as an authorized data originator. In HPTN 111, the authorized data originator is most likely going to be a person; however, it can also be a computer system, a device, or an instrument that is authorized to enter, change, or transmit data into the electronic record.

Sites must develop and maintain a list of all authorized data originators. This list must be made available for study-related monitoring, audits, IRB review, and regulatory inspection by authorized individuals at the clinical research site. Examples of data originators include, but are not limited to:

1. Clinical investigator(s) and delegated clinical study staff
2. Participants or their legally authorized representatives
3. Medical devices (e.g., medical instruments such as a blood pressure machine)
4. Automated laboratory reporting systems (e.g., from central laboratories)
5. Other technology

3.5 Source Documentation

Participant source documentation should contain all of the following elements:

- Participant ID number (PTID) assignment.
- Documentation that the participant provided written informed consent to participate in the study prior to the conduct of any study procedures, including an Informed Consent Assessment tool to verify comprehension.
- Documentation that the participant met the study's eligibility criteria.
- A record of all contacts, and attempted contacts, with the participant.
- A record of all procedures performed by study staff during the study.
- A record of any AEs and Social Impacts reported by participants.
- Study-related information on the participant's condition before, during, and after the study, including:
    - Data obtained directly from the participant (e.g., self-report of social harm)
    - Data ascertained by study staff (e.g., exam and lab findings)
    - Data obtained from non-study sources (e.g., medical records documenting circumcision procedure)

In general, sites should apply ALCOA* to achieve data quality.

- **A**ttributable: is it obvious who wrote it?
- **L**egible: can it be read?
- **C**ontemporaneous: is the information current and in the correct time frame?
- **O**riginal: is it a copy; has it been altered?
- **A**ccurate: are conflicting data recorded elsewhere?

*Source: "The Facts About Source Documents" by Stan W. Woollen, Presented at the 1999 DIA Annual Meeting

3.6 Examples of Source Documentation

3.6.1 Clinic Notes

Study staff must document contacts with a study participant where data and pertinent study information are collected in a signed and dated clinic note specifying the date, type, purpose, location of the contact, and the general status of the participant. Routine study visit reminders may be documented per local site SOPs and requirements). Clinic notes also must be used to document the following:

- The informed consent process and/or coversheets
- Procedures performed that are not recorded on other source documents.
- Pertinent data about the participant that are not recorded on other source documents.
- Protocol deviations that are not otherwise captured on other source documents (such as the Protocol Deviation Form). Note that the *DAIDS Policy for Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* (DWD-POL-CL-04.00) requires that all protocol deviations be recorded in participants' study records, along with reasons for the deviations and/or attempts to prevent or correct the deviations if applicable.

One way that clinic notes can be structured is by using the SOAP method. The acronym SOAP stands for Subjective, Objective, Assessment, and Plan and the following information is included in each section:

S: Subjective information that includes what the patient tells you about how heis feeling or his symptoms. For example, if he is experiencing pain or having trouble urinating.

O: Objective information including vital signs, pertinent physical exam findings, and the most recent laboratory test results.

A: The assessment describes your diagnosis of the symptoms. The assessment also includes a summary of how the patient is doing and what has changed from the previous visit.

P: The plan includes how each diagnosis or problem will be addressed. This section will include information about new or changes to existing relevant medication (e.g., STI treatment), laboratory tests to order, or consults to obtain.

Below is an example of clinic notes using the SOAP method:

Sample Clinic Note for a Screening Visit:

26 October 2016: Participant presented for HPTN 111 screening at Kalangala Health Center. Obtained written informed consent for screening/enrollment before initiating any procedures; Copies of signed documents provided to participant. All the participant's questions were answered. Screening procedures were completed per the visit checklist and site SOPs.

S: Participant reported no current health problems and shows no signs of acute HIV infection. Participant is a heterosexual man and met all behavioral risk criteria (see checklist). The participant has never participated in an HIV prevention or vaccine trial.

O: BP 126/54. HIV rapid tests negative/nonreactive.

A: Healthy participant that may be eligible for HPTN 111.

P: Proceed to enrollment; call participant with syphilis test results.

{staff signature/date}

3.7 Visit Checklists

The checklists provided in Section 6 of the Accrual, Follow-up, and Retention SSP section may be used as a convenient tool for study staff to ensure that all study procedures are performed at each visit. The checklists as designed may not be able to serve as source documentation – see Section 6 (Accrual, Follow-up, and Retention SSP section) for further information about this. If a site modifies the checklists to serve partly or wholly as source documents, individual study staff members must initial *only* those procedures that they complete to fulfill the source documentation requirement of identifying responsibility. In addition, if procedures listed on a single checklist are completed across multiple dates or by more than one person, the date upon which each procedure is completed must be clearly noted and initialed.

Even with modification, the checklists alone may not be sufficient for documenting all procedures. For example, chart notes may be required to document procedures performed at unscheduled study visits or to explain why procedures in addition to those specified on a checklist have been performed. Chart notes may also be required to document the content of discussions with participants (*e.g.*, issues related to barbershop services and HIV counseling). Sites are encouraged to contact the HPTN LOC with any questions about which checklists to use and/or how to modify them for site specific purposes.

3.8 Case Report Forms

As mentioned above, the study will utilize an electronic data capture system. Each study site must document the source documentation for each electronic CRF item by completing Table 3-1 (which may be modified to suit a site's needs), submitting a copy to

the HPTN LOC, and maintaining the original document in the site's administrative and regulatory files. The comments section of Table 3-1 should be modified to accurately reflect the source documentation for each CRF item at the site. Table 3-1 will be finalized and signed at each site prior to site activation. Site staff must follow the designations in Table 3-1 consistently for all study participants throughout the study.

In the event that it is not possible to record data directly onto forms designated as source documents, the following procedures should be followed:

- Record the data onto an alternative source document.
- Enter the alternative source document into the participant's study chart.
- Transcribe the data from the alternative source document onto the appropriate case report form.
- Enter a chart note stating the relevant study visit, date, and the reason why an alternative source document was used.

Tables 3-1a and 3-1b: HPTN 111 Source Documentation TEMPLATES

NOTE: These tables are provided as example documents. Each site must complete a site-specific source documentation table based on their individual needs and policies. The CRFs in table 2-1b below are listed in in order of respective data level (i.e., participant, barber, and barbershop) and not necessarily in the order in which procedures are performed.

Table 2-1a: For each procedure listed below, add the source documents for each study procedure/evaluation.

Evaluation /Procedure	Source Document(s)
PARTICIPANT	
ADMINISTRATIVE, BEHAVIORAL AND REGULATORY	
Pre-screening assessment	Pre-screening checklist
Informed consent(s)	Signed and Dated Informed Consent form. Informed Consent Coversheet (or chart note)
Locator information	Participant contact information form
Demographic information	See Table 3-1b: re: Demographics CRF
Social impacts assessment	Chart notes
Socio-behavioral assessment	ACASI data collection for these items; See Table 3-1b re: Sexual Behavior CRF and GEMS CRF
Disclose study group (intervention or control) to participant	Chart notes
Intervention acceptability assessment	See Table 3-1b re: Barbershop Services Acceptability CRF
HIV self-testing assessment	See Table 3-1b re: HIV Prevention Services CRF and Interim HIV testing Log
HIV counseling and testing	HIV Testing Counseling Worksheet. For test results see Table 3-1b re: HIV Test Results CRF (or laboratory results log form)
Provide information about recommended HIV testing schedule	Chart notes
Offer condoms	Chart notes
In-depth interviews	Qualitative data Database
CLINICAL	
Complete Medical History	Chart notes
Targeted Medical History	Chart notes
Symptom directed physical exam	See Table 3-1b re: Physical Exam CRF
Concomitant drug use	Chart notes
Blood collection	Laboratory requisition form
Urine collection	Laboratory requisition form
HIV prevention services care referral	Chart note
STI Treatment	See Table 3-1b re: Physical Exam CRF or STI Test Results CRF and chart notes
LABORATORY	
HIV diagnostic testing	*Laboratory results log form*
STI testing: blood for syphilis	*Laboratory results log form*
STI testing: urine NAAT for gonorrhea and chlamydia	NAAT machine results page
Blood storage for LL QC	LL Storage form

Evaluation /Procedure	Source Document(s)
BARBER	
ADMINISTRATIVE, BEHAVIORAL AND REGUATORY	
Informed Consent	Signed and Dated Informed Consent form. Informed Consent Coversheet
Memorandum of understanding	Signed and Dated Memorandum of understanding
Locator information	Locator form
Collect barber demographics	See Table 3-1b Barber CRFs re: Demographics CRF
Collect barbershop details	See Table 3-1b Barbershop CRFs re: Pre-baseline Information
Training on study and recruitment procedures	Training Logs
Training on barbershop-based intervention procedures	Training Logs
Social impacts assessment	See Table 3-1b Barber CRFs re: Social Impact Log
Intervention acceptability and feasibility assessment	See Table 3-1b Barber CRFs re: Barbershop Intervention Acceptability
Social harms assessment	Chart notes
In-depth interviews	Qualitative data database
BARBER LED-PROCEDURES	
Record number of clients referred to study	Barbershop Recruitment Log
Provide HIV education	Intervention Delivery tracking log
Provide HIVST kits	Intervention Delivery tracking log
Record number of HIVST kits distributed and services provided	Intervention Delivery tracking log
HIV prevention services referral	Intervention Delivery tracking log
Lead group sessions	See Table 3-1b Barber CRFs re: Group Session Log

Table 3-1b: Elements of each CRF that are considered source documentation

CRF Name	Source			Comments
	Yes	No	Mixed	
Participant CRFs				
Demographics			*X*	*CRF is source for all items except age/DOB which is recorded in chart notes*
Inclusion Exclusion Criteria		*X*		*Eligibility Checklist is source for all items*
Informed Consent		*X*		*Informed consent forms are source for all items.*
Enrollment	*X*			*CRF is source for all items*
Physical Exam		*X*		*Chart notes are source for all items*
HIV Lab Test Results		*X*		*Lab reports are source for all items except 1) specimen collection date for which the lab requisition is source and 2) final HIV status, for which chart notes are source.*
Interim HIV testing log		*X*		*Chart notes are source for all items*
STI Results		*X*		*Lab requisition is source for sample collection date. Chart note is source for not done/not collects, and actions taken. Lab reports are source for results.*
Social Impact Log		*X*		*Chart notes are source for all items*
Protocol Deviation Log		*X*		*Chart notes or QA/QC reports or monitoring/auditing/inspection reports are source for all items.*
Alcohol and Drug Use	*X*			*CRF is source for all items*
Barbershop Services Received	*X*			*CRF is source for all items*
Barbershop transfer form			*X*	*Chart notes or CRF is source for information about last completed contact. CRF source for all other items.*
Gender Equitable Men Scale (GEMS)	*X*			*CRF is source for all items*
Barbershop Services Acceptability	*X*			*CRF is source for all items*
HIV Prevention Services	*X*			*CRF is source for all items*
Self-efficacy	*X*			*CRF is source for all items*
Sexual Behavior	*X*			*ACASI/CRF is source for all items*
Seroconversion Follow-up	*X*			*CRF is source for all items*
Termination		*X*		*Chart notes are source for all items.*
Barber CRFs				
Demographics	*X*			*CRF is source for all items.*
Enrollment/Informed Consent		*X*		*Informed consent forms are source of all items*
Inclusion Exclusion Criteria		*X*		*Eligibility Checklist is source for all items*

CRF Name	Source			Comments
	Yes	No	Mixed	
Barbershop Intervention Acceptability	*X*			*CRF is source for all items.*
Group Session Log			*X*	*CRF or physical group session log form is source for all items*
Social Impact Log		*X*		*Chart notes are source for all items*
Protocol Deviation Log		*X*		*Chart notes or QA/QC reports or monitoring/auditing/inspection reports are source for all items.*
Barbershop Transfer			*X*	*Chart notes or CRF is source for information about last completed contact. CRF source for all other items.*
Barbershop Level CRFs				
Pre-baseline Information		*X*		*Barbershop Collection Criteria document*
Recruitment Log Form		*X*		*Barbershop Recruitment Log*
Services Provided Log		*X*		*Intervention Delivery tracking log*
Barbershop Activation		*X*		*Shop activation memo for activation date; final randomization list for randomized study group*
Barbershop Withdrawal		*X*		*Chart notes*

3.9 Eligibility Criteria

It is essential that source documentation be provided to demonstrate that each inclusion and exclusion criterion contained in the protocol has been met before enrolling a participant. **Failure to document that each of the criteria has been met may result in an enrollment violation.** Sites are encouraged, but not required, to use Table 2-2 to show how they will document that all eligibility criteria have been met for each enrolled participant. As with Table 2-1, Table 2-2 should be modified to accurately reflect the source documentation being used at the site. The site may choose to develop their own site-specific documentation to specify the source for each eligibility criterion. This table is required prior to site activation.

If a site chooses to use Table 2-2, it should be signed and dated by the Investigator of Record, included in the regulatory files, and followed consistently for all participants throughout the study.

Sites are required to use either the local modified version of the *Participant Eligibility Verification Checklist* Template found in Section 6 of the Accrual, Follow-up, and Retention section of the HPTN 111 SSP manual (which includes instructions for who is responsibility for sign-off), Section 6, or a local-modified version that includes all the required elements found in the provided template, to verify the eligibility of each participant prior to enrollment in HPTN 111. Use of this checklist ensures that the Investigator of Record at the site (or designee) has reviewed the eligibility of that participant and confirmed that the criteria have been met. The site may modify the checklist to be site-specific before using it. Whichever approach the site uses, the investigator signature component must be retained on the checklist. Sites are encouraged to contact the HPTN LOC for help with the task of modifying the checklist. See Section 6 (Accrual, Follow-up, and Retention SSP Section) of this manual for additional information on requirements for completing this checklist.

For each participant, the site is required to use the Participant Eligibility Verification Checklist to verify each enrollment criterion for the appropriate group checking “yes” or “no” to indicate whether the requirement was met. The staff member verifying eligibility will sign and date the form where indicated. If more than one staff member is involved in completing verification of the participant’s eligibility, then each eligibility criterion must be individually initialed and dated by the staff member performing the confirmation. It is important that each item on the checklist is completed. No item should be left blank. For example, if there are no applicable comments to include in the comment section, please write “N/A” to indicate that that section was not omitted by accident. If an item on the checklist is left blank, it will be considered incomplete. For this study, the eligibility checklist will be the first place that eligibility confirmation will be captured for the majority of criteria. This will make the eligibility checklist the source documentation for that item. In these cases, the checklist is listed as source on the Source Documentation for Eligibility Criteria Tables (Table 3-2).

Once the Eligibility Checklist has been completed for new enrollments, the completed checklist must be kept in the participant chart. The participant is considered enrolled in the study once the eligibility checklist has been completed and the participant has confirmed their willingness to enroll in the study.

Table 3-2: HPTN 111: Source Documentation for Eligibility Criteria (EXAMPLE)
(NOTE: This table is an <u>example</u> document. If a site chooses not to use this document, they must complete a site-specific table based on their individual needs and local SOPs prior to site activation.)

Eligibility Requirements	Source Document	Eligible (Yes/No/NA)	Initials/Date
All responses must be "YES" to be eligible for study participation			
Identifies as heterosexual male	Eligibility checklist		
Participant is 16 years or older	Chart note		
If 16 – 17 years old, is an emancipated or mature minor (mark all that apply) ☐ Drug or alcohol dependency ☐ Sexually transmitted infection ☐ Have a pregnant partner ☐ Married ☐ Have a child ☐ Cater for their own livelihood	Eligibility checklist		
Willing and able to provide informed consent to take part in the study	Informed Consent Form		
Behaviorally vulnerable to HIV in the last three months (mark all that apply): ☐ Had condomless sex with a partner of unknown HIV status or a person living with HIV ☐ Had more than one sexual partner	Eligibility checklist or chart notes		
Non-reactive/negative HIV test results at screening, as defined in the SSP Manual	Lab Results		
Regular customer at participating barbershop (3 haircut visits at the shop)	Eligibility checklist or chart notes		
Planning to stay in the study catchment area in the next 12 months.	Eligibility checklist or chart notes		
There are no other conditions that in the opinion of the IoR would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.	Eligibility checklist or chart notes		

_____ _____

Signature of Investigator of Record or designee Date

3.10 Document Organization

Study staff must make every effort to keep all research records - both individual participant records as well as logs and documents pertaining to all participants – confidential and secure. All records should be securely stored in an area with access limited to authorized staff only.

All study-specific documents and biological specimens that are transmitted to an off-site location, including copies of electronic CRFs, and all biological specimens processed in any way by non-study staff or transferred to an off-site location must be identified only by the participant's study identification number (PTID) to maintain confidentiality. The site must ensure that any document sent by email or other communication methods does NOT contain any participant identifiers. If a document has participant identifiers, the identifying information must not be visible or legible prior to sending. Inclusion of more than one identifier on other study records that are accessible only to authorized study staff is not prohibited by DAIDS, however, such records must be stored securely with limited access. Regardless of whether the participant identifier on a particular document is the participant's name or PTID number, the original identifier may not be obliterated or altered in any way, even if another identifier is added. When necessary to maintain confidentiality, identifiers may be obliterated or altered on **copies** of original source documents. For example, if supporting documentation of study eligibility is to be submitted to the HPTN LOC, such as chart notes or lab reports, contain a participant's name, this should be obliterated/redacted on the copy transmitted off-site, but not on the original.

All local databases will be secured with password-protected access systems.

Logbooks, appointment books, and any other listings that link PTIDs to participant names or other personal identifiers should never be left unattended or easily accessible to unauthorized individuals.

3.11 Document storage at coordinating site (MU-JHU, Kampala)

After participant follow-up is completed, study staff will re-locate participant signed informed consent forms and all other study documentation to the central coordinating site in Kampala, where document storage will follow the guidelines above and any relevant site requirements and SOPs.

All documentation will be transported in sealed files/boxes.

3.12 Record Retention Requirements

For studies not under IND such as HPTN 111, investigators must retain study records for a minimum of three years after completion of the research, or longer if needed to comply with local regulations.

Completion of a clinical research study occurs when the following activities have been completed:

- All research-related interventions or interactions with human subjects (e.g., when all participants are off study)
- All protocol-required data collection of identifiable private information described in the IRB-approved research plan.
- All analysis of identifiable private information described in the IRB-approved research plan.

The study-related records include but are not limited to the following:

- Study management information, including the protocol, clarifications, letters of amendment, protocol amendments, the SSP manual and associated errata, addenda, and bulletins.
- Signed informed consent forms for each study participant.
- Electronic CRFs for each study participant labeled by PTID.
- Source documents such as clinic notes, pharmacy records, and laboratory result reports.

3.13 Study Publications

All manuscripts, abstracts, posters, or presentations based on the results or conduct of HPTN 111 must be prepared in accordance with the HPTN MOP Section 21 (https://www.hptn.org/sites/default/files/inline-files/Section%2021%20-%20Publications%20and%20Data%20Sharing%20-%20Final%20-%201%20August%202022_0.pdf) and HPTN 111 Protocol Publications Committee.

4. Study Location

4.1 Overview of Section 4

This section includes specifics on the study location, including the barbershops and satellite study clinic participating in HPTN 111. The coordinating study site, responsible for conducting all study procedures, is MU-JHU (Kampala, Uganda).

4.2 Study Barbershops

HPTN 111 is a cluster-randomized trial, with barbershops in the Kalangala district of Uganda being randomized. The protocol team will identify 18 barbershops to participate in the study based on the criteria provided in Section 1.2.1 of the Study Management Overview SSP Section.

4.2.1 Selection criteria for barbershops

The protocol team is responsible for documenting and reviewing possible barbershops for inclusion in the study. Information about each potential shop is recorded in a Barbershop Selection Document. The information collected is provided in Appendix A. The protocol team reviews all potential shops for inclusion and comes to consensus on which shops should be included based on the selection criteria as defined in the protocol.

If there are multiple shops located within 5 km of each other, the protocol team determines which shop will be selected to participate and which shop(s) may be considered back-up in case the first selected shop is unable to participate or must be replaced during the study (as defined in Protocol Sections 3.1 and 4.3 (Accrual, Follow-up, and Retention section) and SSP Section 4.5 below). The reason for selecting the

primary shop is documented in the barbershop selection document and may include reasons such as number of weekly clients or enthusiasm of the barber to participate.

If the barbershop has multiple barbers, each barber is assessed separately to determine if they meet the inclusion criteria. A minimum of one barber at each barbershop must be willing and able to participate in the study. If the barber is not the owner of the shop, the protocol team will confirm acceptability of barber participation with the owner and provide general study sensitization. Other barbers at the shop who are not able or do not want to participate will be sensitized about the study but not expected to participate in recruiting participants or delivering the intervention. If a barber changes their mind and would like to participate in the study, they can be included in the study following procedures defined in Section 4 of the Accrual, Follow-up, and Retention Manual (Barbershop-based interventions).

4.2.2 Randomization

4.2.2.1. Study Design

HPTN 111 is a cluster-randomized trial with two arms. Study barbershops will be randomized 2:1 to either the intervention or control group. There are 18 participating barbershops, so 12 will be allocated to treatment, and six to standard-of-care.

4.2.2.2. Restriction Criteria

We will use covariate-constrained randomization to balance three factors:

- The population of the village/town where the barbershop is located, based on Kalangala District government data.
- The number of clients the barber works on per day. If the shop has multiple barbers, this will be based on the lead barber. This is based on self-report by the participating barbers.
- The distance in kilometers from the barbershop to the nearest clinic that offers HIV testing. This is based on an estimate by study staff visiting barbershops.

The table below shows the barbershop characteristics that were used in the randomization.

Table 1: Characteristics of barbershops

Barbershop number	Town/village	Town/village population	Number of clients per day	Distance to clinic with HIV testing (km)*
1	Banga landing site	569	15	7
2	Beta village	1230	10	2
3	Bugoma village	1311	10	3

4	Bumangi town	466	5	2.5
5	Mutambala landing site	773	10	5
6	Bwendero town	1259	10	2
7	Dajje landing site	704	10	4
8	Kalangala town council	1835	25	0.1
9	Kasamba village	194	15	6
10	Kasekulo landing site	2114	15	7
11	Kasenyi landing site	580	10	2
12	Kazi-Malanga village	815	7	7
13	Kibale village	695	15	3
14	Kibanga maboga	704	10	6
15	Kyagalanyi	1558	12	1
16	Nakatiba village	988	10	3
17	Senero landing site	739	10	3
18	Buyiri landing site	379	10	7

*To standardize the precision of reported distances used in the restriction criteria, fractions were rounded up.

There are 18,564 different possible ways to allocate 18 shops to 2:1 arms. To accommodate a transparent randomization event (see below), we will use covariate-constrained randomization to create three equally sized groups. Then simple randomization will assign two of the groups to treatment and one to standard-of-care, creating the final 2:1 randomization. There are over two million different ways the shops could be allocated to three equal groups.

Restrictions on the allocation to three equal groups were defined as requiring, for all three characteristics, that the mean values among the treated shops was within a set distance of the mean value among the standard-of-care shops for all three possible ways of arranging three groups into 2:1 randomization. A range of restrictions were explored: average village population within 100-300 difference between arms; average number of clients per day within 1-4 difference between arms; and average distance to the nearest clinic within 0.5-1 km difference between arms.

To assess the validity of the randomization, the following checks were conducted. First, whether the number of possible 2:1 allocations to arm was reasonably large (at least five thousand). Second, that correlation between pairs of barber shops was not too strong: for candidate restriction criteria the number of times that each pair of shops was allocated to the same group of six was counted. To maintain validity, this number should be close to 30% of acceptable allocations for all (or almost all) pairs of shops.

Combinations of the restriction criteria listed above were evaluated against the two validity requirements. This assessment was done by statisticians from the Statistical Center for HIV/AIDS Research & Prevention (SCHARP). The protocol team selected one of the restriction criteria which passed the validity checks, based on relative strength of restriction for the three chosen factors. The final choice of restriction criteria to apply was: average village population within 300; average number of clients per day within 4; and average distance to the nearest clinic within 0.75 km. Of the 18,564 ways to allocate the shops to the 2:1 arms, 5,627 randomizations met these criteria.

4.2.2.3. Randomization Event

Barbershops are randomized at a public randomization event. The study team strives to have a representative from each participating barbershop attend the event. The event includes barbershop representatives, study staff, and local stakeholders.

The event allows the allocation process of the randomization to be conducted transparently with the study team, participating barbers, and the community. In the first stage of randomization, the shops are allocated to Groups A, B, and C. In the second stage of randomization, the groups are randomly allocated to study groups - intervention (two groups) or control (one group). Due to the restricted randomization process's complexity, the first stage will be done ahead of the public randomization event. This will be done by creating a list of all the ways to allocate 18 shops to three equal groups which meet the restriction criteria listed above, and randomly sampling one allocation. Statisticians from SCHARP will perform this randomization prior to the public randomization event. For example, the allocation below assigns shops 1, 6, and 7 to group 1, and so on.

Shop number	1	2	3	4	5	6	7	8	9	...
Group	1	2	3	2	3	1	1	2	3	...

Barbers/shop representatives participating in the public randomization event will be provided with an envelope specific to their shop; the envelope will contain a letter that indicates the Group (A, B, or C) to which they are included.

The letters will be generated by the HPTN LOC CRM and checked by the study statistician to ensure the Groups are accurately recorded per the first step of the randomization. The coordinating study site will be responsible for printing the letters and putting in an envelope that is labeled with the town/village name that matches the letter.

The second stage of randomization begins after barbers have been assigned to three groups of six (A, B, and C) and they have opened their shop-specific envelope. In this second stage, groups are assigned to intervention or control. There will be a large opaque sack/bag that includes three smaller bags within. In each of the small bags, there will be six balls (or other token item) and a label indicating intervention or control. The label will not be visible from the outside of the bags, and the three small bags will be indistinguishable. Two small bags will be labeled "intervention" and one bag will be labeled "control" to meet the 2:1 randomization requirement. One representative from each group will pick a small bag out of the large sack and the three representatives will be instructed to open their small bags at the same time. The label in the bag drawn by the representative of the group determines the arm assignment for all six barbershops in that group.

Study staff will be responsible for ensuring that the final randomization assignment is accurately recorded and provided electronically to the HPTN LOC CRM and protocol statistician. A template for the final randomization documentation can be found in Appendix B.

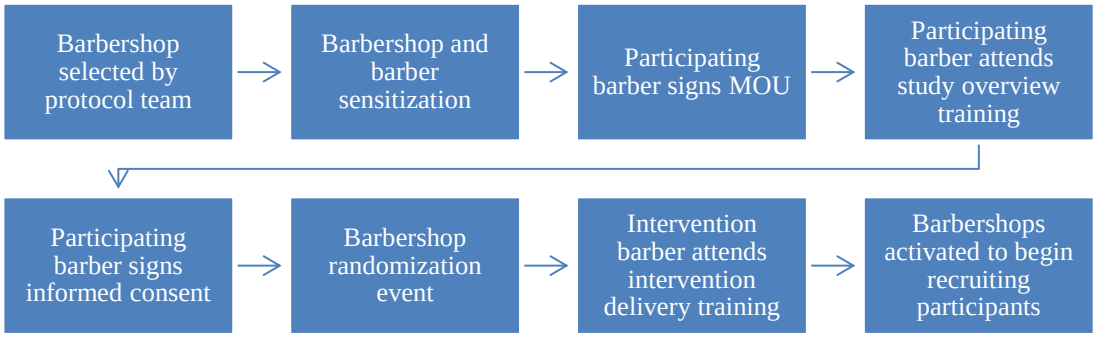
4.3 Satellite Study Clinics

There will be one satellite study clinic on Bugala Island where the 18 barbershops are located and where participants will attend their study visits. The study clinic will be co-located at the Kalangala Health Facility IV. The clinic has private space for all study procedures to occur and for study documentation to be kept confidential (in a lockable room and within lockable cabinets).

4.4 Barbershop activation criteria

There are multiple requirements that must be met before barbers can begin recruiting participants and delivering the intervention. The general process and description are included below.

Figure 1. Barbershop/barber involvement and study activation



The study team will conduct sensitization activities with each selected barbershop following selection to participate and prior to training and randomization. Sensitization will occur with all barbers in the shop, even if some barbers are not participating in the study. Barbers who are participating in the study will sign a memorandum of understanding (MOU) that details the expectations of their involvement in recruiting participants and delivering the intervention (if randomized to the intervention group). The MOU will also include information about the ongoing support that will be provided to the barbers by study staff. Following completion of the MOU, all barbers will participate in a training that will provide information about the study, details of client recruitment, and confidentiality.

Prior to undertaking any study procedures, including barber informed consenting and barbershop randomization, the coordinating study site will obtain approval to conduct the study from the Institutional Review Board that is responsible for the study. Thereafter, the site will complete Protocol Registration with the DAIDS Regulatory Support Center (RSC), as well as Study Activation procedures with the HPTN LOC. These procedures are also described in the HPTN Manual of Operations (MOP). HPTN 111 study procedures may not be conducted prior to completing all of these steps and receipt of a study activation notice from the HPTN LOC. The study activation notice will signal the beginning of study procedures, including barber informed consenting, randomization, and study/intervention specific training.

Barbers will undergo informed consent prior to barbershop randomization so that they are informed of all study procedures in which they will be asked to participate and can complete baseline questionnaires/CRFs. Barbers and shop representatives will participate in a randomization event after the overview training, as described above. Participating barbers from shops that have been randomized to the intervention group will attend a subsequent training specific to delivery of the intervention. Details of this training are included in Section 4 of the Accrual, Follow-up, and Retention Manual.

A barbershop will be activated to begin recruiting participants once all study activation procedures have been completed for that shop (e.g. availability of lockable cabinet, enrolled and trained barber, study materials at shop, etc.). The coordinating study site will work closely with the LOC to ensure that all requirements have been met, prior to

activation of the shop. Study activation notices will be completed for each individual shop before the barbershop may begin recruiting participants. Barbershops do not need to be activated all at the same time, which will allow for multiple barber training sessions or additional community sensitization in specific shops if needed before study activation and participant recruitment begins. However, we will aim to activate at least one-half of all intervention barbershops within one week of the intervention training.

4.5 Discontinuation and Replacement of Barbershops

There may be instances where a barbershop is unable to continue participating in the study or additional shops need to be added. Barbershops may be withdrawn fully from the study for multiple reasons and should be discussed with the Protocol Team on a case-by-case basis:

- Barber or shop owner withdrawal of agreement to participate.
    - If a shop has multiple barbers participating in the study, the shop may continue even if one barber has withdrawn their agreement for participation.
- Barbershop permanently closes
- Investigator discretion for barber, participant, or staff safety, or any other reason.

If a shop is fully withdrawn from the study, participant recruitment and delivery of the intervention (if applicable) will cease at the shop. The reasons for discontinuation will be recorded by the protocol team and within the database. Participants recruited from the withdrawn shop will be notified by the study team that the barbershop is no longer participating in the study. Any study materials at the shop should be collected by the study team.

If a shop is withdrawn from the study or if the shop is unable to meet recruitment goals, an additional shop may be added to participate in the study. Shops that are unable to recruit any participants in the first month of enrollment or 5 participants within the first 3 months of enrollment will be reviewed by the protocol team. The protocol team may decide that a replacement barbershop is needed in order to meet the goals of the study and/or that recruitment should be stopped at the shop. If recruitment is stopped at a shop, the barber should continue to provide follow-up intervention information to their enrolled clients.

Replacement shops will be added from the same village/town and will be assigned to the same arm of the study as the shop they are replacing. Replacement shops must meet all eligibility criteria as outlined in the Protocol.

Participants who were recruited from a shop that is later withdrawn or replaced will continue with regular study visits.

4.6 Appendix A: Barbershop Selection Criteria

- What is your name (Barber)?
- What is your age? (in complete years)
- What is your level of education?
- What are your contact details? (phone)
- What is the name of your barbershop?
- In which village /town is your shop?
- Estimated distance from the nearest village
- For how long have you operated this barber shop in this area (months)?
- When did you start this barber shop?
- How many other barbers do you work with in this shop?
- Who are your most customers?
- What is the age range for most of your customers?
- How many customers on average, do you work on per day?
- How much money do you charge per head (in Ugandan shillings)?
- Where do most of your customers come from?
- When is your shop busy?
- What is the sitting capacity for your barbershop?
- Do you operate this shop fulltime or part time?
- What work, other than this, do you do?
- Do you plan to relocate this barbershop to a different place in the next two years?
- Do you plan to close this barber shop?
- How many other barber shops are in this area?
- What distance is it to the next nearest barber shop? (KM)
- Are you interested in the HIV prevention study?
- Would you be interested in attending HIV prevention trainings?
- Are you willing to talk to your clients about HIV prevention? If "No", state the reason.
- Do you think your clients would like to receive HIV Prevention information /services from you?
- Are there lockable cabinets in this barber shop?
- Is there space for lockable cabinets in this barber shop?
- Are there other organizations that work with barbers in this area?
- Are there programs specifically targeting men in this area? If yes, tell me about those programs?
- What is the estimated time to travel to the study clinic (minutes)?
- What is the nearest health facility in your area?
- What is the estimated travel distance to the nearest health facility? (KM)
- What are services offered at this facility?
- GPS location
- Make any relevant notes about the lead barber’s personality.
- Community feedback about the barber, if any.
- Name of the Interviewer
- Rank

4.7 Appendix B: Randomization Documentation

TRIM/HPTN 111 Final Randomization List

Stage 1: Assignment of shops to groups

Group A	Group B	Group C

Stage 2: Assignment of groups to intervention or standard-of-care

Group A	Group B	Group C

Final Randomization Assignment

Intervention Group		Standard-of-care Group

Completed By: _____ Date: _____