3. Document Requirements

3.1 Overview of Section 3

This section contains a listing of required administrative and regulatory documentation, commonly referred to as "Essential Documents", which each study site must maintain and keep current throughout the study, as well as procedures for establishing adequate and accurate study participant source documentation records.

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/daids-essentialdocpolicy.pdf* and its appendix: *https://www.niaid.nih.gov/sites/default/files/essentialdocappndx.pdf*) and *ICH E6 Good Clinical Practice: Consolidated Guidance* (*http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf*) 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 094. 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.

- Protocol (implementation version and any subsequent amendments, letters of amendment and clarification memos)
- Informed Consent Forms (all IRB -approved versions, all signed and dated forms from screened/enrolled study participants), as well as any "Dear Participant" Letters (all IRB -approved versions) for all screened/enrolled participants
- Signed and dated FDA Form 1572, 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
- Note to file that sIRB roster held at LOC
- All correspondence to and from the IRB, including documentation of all submissions, reviews and approvals and copies of site-specific interim and annual reports
- All 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 listed in the FDA Form 1572
- 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
- Product Safety Information/Reports/Memos (IND Safety Reports provided by DAIDS)
- Current Truvada® (TDF/FTC) package insert and subsequent updates
- Current Descovy® (FTC/TAF) package insert and subsequent updates
- Current Biktarvy® (BIC/TAF/FTC) package insert and subsequent updates
- All study product accountability records

- Local laboratory normal values/reference ranges for protocol-specified testing
- Key study-related correspondence with the HPTN LOC, HPTN SDMC, HPTN Laboratory Center (LC), NIDA 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 094 and all subsequent updates
- Note to file that the following DAIDS reference materials are found in the DAIDS SCORE Manual:
    - 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/daids-sourcedocpolicy.pdf and its appendix: https://www.niaid.nih.gov/sites/default/files/sourcedocappndx.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/daids-essentialdocpolicy.pdf and its appendix: https://www.niaid.nih.gov/sites/default/files/essentialdocappndx.pdf) and subsequent updates; and
    - DAIDS Protocol Registration Policy and Procedures Manual: (https://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-manual).
- Study specific procedures (SSP) manual, original versions and all updates, bulletins, clarifications, and communiqués
- Monitoring visit log, reports, and site response to visit findings. Sites should print PPD visit reports for their files from the DAIDS website for Clinical Research Management System (https://ncrms.niaid.nih.gov/NCRMS/Main/Login.aspx)
- 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 shipping 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). (See DAIDS SCORE Manual)

3.3.1 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. (See DAIDS SCORE Manual)

For HPTN 094, participant source documents will consist of narrative chart notes, visit checklists, medical records, laboratory reports, pharmacy records and CRFs and other items as defined by each participating site. As a condition for study activation, each site must establish an SOP for source documentation that specifies the use of these documents as source documents.

HPTN 094 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 first collected by entering directly into a computer, the electronic data in the computer becomes the source document**. If data are first written down on paper, the paper record is 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, clinical management committee (CMC), CRS investigators to study nurses, etc.)
3. IRB correspondence pertaining to a participant or the study
4. Computer-Assisted Self-Interview (CASI) questionnaires

Each electronic record needs to be associated with an originator type, otherwise known as an authorized data originator. In HPTN 094, 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 each 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. Consulting services (e.g., a radiologist reporting on a computed tomography (CT) scan)
4. Medical devices (e.g., electrocardiograph (ECG) machine and other medical instruments such as a blood pressure machine)
5. Electronic health records (EHRs)
6. Automated laboratory reporting systems (e.g., from central laboratories)
7. Other technology

3.3.2 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 (see SSP Section 4 Tables 4-1 and 4-2) 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 the participant's exposure to the study product
- A record of any SAEs 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 injection reaction)
    - Data ascertained by study staff (e.g., exam and lab findings)
    - Data obtained from non-study sources (e.g., medical records)

In general, according to DAIDS, sites should apply ALCOA+ to achieve data quality.

- **A**ttributable: Is it traceable to a person and date?
- **L**egible: Is it clear enough to read?
- **C**ontemporaneous: Was it recorded as it happened?
- **O**riginal: Is it the first place data is recorded?
- **A**ccurate: Are all the details correct?

- Complete: Is the data whole?
- Consistent: Is data repeatable and traceable?
- Enduring: Will the data last over time?
- Available: Is the data easily accessible? Will it remain easily accessible over time?

In addition, the European Medicines agency (EMA) suggests adding for electronic source documentation:

- Credible: Is the data trustworthy?
- Corroborated: Can you confirm the data?

3.3.3 Examples of Source Documentation

3.3.3.1 Clinical Notes

Study staff must document contacts with a study participant where data and pertinent study information are collected in a signed and dated clinical 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 (and a site may wish to include this information in the retention SOP). Clinical 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 clinical 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 he/she is feeling or his/her symptoms. For example, how he/she is sleeping or eating or if he/she is experiencing pain or having trouble urinating or defecating.

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 medication, laboratory tests to order, and consults to obtain.

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

Sample Clinical Note for a Screening Visit:

03 March 2021: Participant presented for HPTN 094 screening at UCLA Vine Street Mobile Unit. Obtained written informed consent for screening/enrollment before initiating any procedures; HIPAA consent reviewed and signed. Copies of signed documents provided to participant. All of the participant's questions were answered. Screening procedures were completed per the visit checklist and site SOPs.

S: . Participant was born male. Participant states willingness to start MOUD. The participant has never taken PrEP. Confirmed sharing of equipment.

O: BP 126/54. Participant shows signs of recent injection opioid use and urine positive for opioids. Meets criteria for OUD as defined by DSM-5. Exam entirely WNL. HCV negative as of 3 months prior; HBV immune.

A: Participant that may be eligible for HPTN 094.

P: Schedule follow-up with participant to review lab results and confirm eligibility.

{staff signature/date}

3.3.3.2 Visit Checklists

The checklists provided in Section 6 of this SSP manual 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 6.0 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 care visits, interim 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 study product adherence 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.

3.3.3.3 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 study activation (submission to the HPTN LOC of subsequent updates to the table is not required once the study has been implemented). 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, or dosing visit, date and the reason why an alternative source document was used.

Tables 3-1a and 3-1b: HPTN 094 Source Documentation TEMPLATES

These tables are provided as example documents. Each site must complete a site-specific source documentation table based on their individual needs and policies. Sites should refer to the Division of AIDS (DAIDS) Site Clinical Operations and Research Essentials (SCORE) Manual to ensure they are meeting sponsor requirements for source documentation.

For each procedure listed below in Table 3.1a, add the source documents for each study procedure/evaluation.

Table 3-1a: Source Documentation for Study Evaluations and Procedures

Evaluation /Procedure	Source Document(s)
ADMINISTRATIVE, BEHAVIORAL AND REGULATORY	
Obtain 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*
Randomization	*See Table 3-1b re: Randomization CRF*
MOUD Counseling	*Chart note*
HIV risk reduction counseling and test results	*Chart note for counseling. For test results see Table 3-1b re: HIV Test Results CRF*
Provide/facilitate harm reduction	*Chart note*
Offer condoms and lubricant	*Chart note*
Behavioral data collection	*ACASI data collection system for these items; See Table 3-1b re: Behavioral Questionnaire CRFs,*
Introduction to peer navigator	*Chart note*
Conclusion of peer navigation	*Navigator progress notes*
CLINICAL	
Assessment for COVID-19	*Chart notes*
Assessment for OUD & recent injection drug use (track marks)	*'Tool for Diagnosis of Opioid Use Disorder per DSM-V' from SSP Section 9 for OUD, Chart notes for recent injection drug use*
Targeted medical history including MOUD treatment, HIV risk behaviors, participation in other research studies	*See Table 3-1b re: Medical History and Medication for Opioid Use Disorder CRFs*
Basic physical (wellness) exam	*Chart notes*
Screen for mental health needs and refer for services as indicated	*Screening: Behavioral Questionnaire CRFs for alcoholism, anxiety disorder, depression and PTSD; chart notes for any other screenings. Referrals: chart notes.*
PrEP initiation (intervention arm) or referral (active control arm)	*PrEP initiation: See Table 3-1b re: Pre-exposure Prophylaxis CRF. Referral: chart notes*
ART initiation (intervention arm) or referral (active control arm)	*See Table 3-1b re: Antiretroviral Treatment Regimen CRF for ART initiation*
COWS assessment and initiate mobile unit-based MOUD treatment program (intervention arm only)	*Chart notes*
Provide clinical management of MOUD and PrEP or HIV infection, including medication or prescription dispensation, as indicated	*See Table 3-1b re: Antiretroviral Treatment Regimen, Medication for Opioid Use Disorder, and Pre-exposure Prophylaxis CRFs*

Evaluation /Procedure	Source Document(s)
HAV vaccination referral	*See Table 3-1b re: Hepatitis Test Results CRF*
HBV vaccination referral	*See Table 3-1b re: Hepatitis Test Results CRF*
HBV treatment/treatment referral	*See Table 3-1b re: Hepatitis Test Results CRF*
HCV treatment referral	*See Table 3-1b re: Hepatitis Test Results CRF*
Development of a clinical plan	*Chart notes*
Empiric treatment of STIs (if symptomatic)	*See Table 3-1b re: STI Test Results CRF*
Lab-based STI results provided and, if indicated, treatment (intervention arm) or referral (active control arm)	*See Table 3-1b re: STI Test Results CRF*
Provide clinical assessment and management or referral for other medical conditions	*Chart notes*
Blood collection	*See Table 3-1b re: Specimen Collection CRF*
Urine collection	*See Table 3-1b re: Specimen Collection and Urine Dipstick CRF*
Swabs for STI testing	*See Table 3-1b re: STI Test Results CRF*
LABORATORY	
HIV rapid testing	*See Table 3-1b re: HIV Test Results CRF*
Laboratory-based HIV testing (see SSP Manual)	*See Table 3-1b re: HIV Test Results CRF*
MOUD testing (urine dip stick)	*See Table 3-1b re: Urine Dipstick Test Result CRF*
Substance use testing (urine)	*See Table 3-1b re: Urine Dipstick Test Result & Chemistry CRFs*
Pregnancy testing (urine)	*See Table 3-1b re: Pregnancy Test Results CRF*
STI testing (syphilis, GC/CT NAAT)	*See Table 3-1b re: STI Test Results CRF*
HIV viral load testing	*See Table 3-1b re: CD4 Test Results/Viral Load CRF*
CD4 cell count	*See Table 3-1b re: CD4 Test Results/Viral Load CRF*
HCV Ab testing	*See Table 3-1b re: Hepatitis Test Results CRF*
HCV RNA (viral load)	*See Table 3-1b re: Hepatitis Test Results CRF*
HBV testing (HBsAg, HBsAb, HBcAb)	*See Table 3-1b re: Hepatitis Test Results CRF*
Other HBV-related testing	*See Table 3-1b re: Hepatitis Test Results CRF*
HAV testing (HAV IgG)	*See Table 3-1b re: Hepatitis Test Results CRF*
COVID-19 testing	*HPTN Laboratory Center instrument test results*
Heme/Chem testing	*See Table 3-1b re: Chemistry and Hematology Test Results CRFs*
Plasma storage	*See Table 3-1b re: Specimen Collection CRF*
Urine storage	*See Table 3-1b re: Specimen Collection CRF*
DBS storage	*See Table 3-1b re: Specimen Collection CRF*
Serum storage for SARS-CoV-2 testing	*See Table 3-1b re: Specimen Collection CRF*

Signature, Investigator of Record **Date**

Table 3-1b: For each CRF listed below, note what the source document is for each of the questions/elements of the form.

Note that for many items where it is suggested below that chart notes will be source, sites may opt instead to enter data directly into the eCRF. This is acceptable; the site needs only revise the notation below and double check the how "Source: Yes, No, Mixed" is checked.

Table 3-1b: Source Documentation of CRF Elements

*For items where the CRF is the source document, please describe whether the source data are captured directly into Medidata Rave, directly into a locally-produced electronic database that reflects the CRFs exactly, or onto a paper copy of the CRFs.*_____

_____

CRF Name	Source			Comments
	Yes	No	Mixed	
Antiretroviral Treatment Regimen		*X*		*Chart notes are source for all items except for stop codes for which lab reports may be source, and drugs prescribed or dispensed by the site for which prescription is source.*
Behavioral Questionnaire Part A	*X*			*CRF is source for all items*
Behavioral Questionnaire Part B	*X*			*CRF is source for all items*
CASI Tracking		*X*		*The CASI system is source for CASI collection date and CASI ID. Chart notes are source for the other items.*
CD4 Test Results/Viral Load		*X*		*Lab reports are source for all items except for questions about whether a sample was collected and specimen collection date, for which the lab requisition is source.*
Chemistry Panel			*X*	*Lab reports are source for all items except: 1) questions about whether a sample was collected and specimen collection date, for which the lab requisition is source, and 2) comments section, for which the CRF is source.*
Clinical Care Visit			*X*	*Chart notes are source for all items except for the question of which other forms were completed at the visit, for which the other forms themselves are source for completed forms and for which this CRF is source for forms not completed.*
Couple Tracking	*X*			*CRF is source for all items*
Date of Visit			*X*	*Chart notes are source for whether the participant completed the visit, date of visit and whether participant exited the study. For the question of which other forms were completed at the visit, the*

				other forms themselves are source for completed forms and this CRF is source for forms not completed.
Demographics	*X*			*CRF is source for all items*
Hematology			*X*	*Lab reports are source for all items except: 1) questions about whether a sample was collected and specimen collection date for which the lab requisition is source, and 2) comments section, for which the CRF is source.*
Hepatitis Test Results			*X*	*Lab reports are source for all items except: 1) specimen collection date for which the lab requisition is source, 2) whether referral was made or treatment started, for which chart notes are source and 3) comments, for which the CRF is source.*
HIV 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 the chart notes are source.*
Informed Consent		*X*		*Informed consent forms are source of all items.*
Interim Visit			*X*	*Chart notes are source for all items except for:1) the question of which other forms were completed at the visit, for which the other forms themselves are source for completed forms and this CRF which is source for forms not completed, and 2) interim visit code for which this CRF is source.*
Medical History Y/N		*X*		*Chart notes are source for this item.*
Medical History		*X*		*Chart notes are source for all items unless medical records or lab reports are source for a medical condition/event.*
Medication for Opioid Use Disorder		*X*		*Chart notes are source for all items except for drugs prescribed or dispensed by the site for which prescription is source.*
Missed Visit		*X*		*The visit calendar is the source for target visit date. Chart notes are source for all other items.*
Navigation Session Y/N		*X*		*Navigation database is source for this item*
Navigation Session		*X*		*Navigation database is source for these items*
Participant Identifier	*X*			*CRF is source for all items.*
Participant Receipt			*X*	*CRF is source for names of sites. Informed consent is source for date of receipt of participant.*
Participant Transfer			*X*	*CRF is source for names of sites. Chart notes or CRFs are source for information about last completed contact. Shipping records are source for date of shipment of records to receiving site.*
Pre-exposure Prophylaxis		*X*		*Chart notes are source for all items except for stop codes for which lab reports may be source, and drugs prescribed or dispensed by the site for which*

				prescription is source.
Pregnancy Outcome	*X*			*CRF is source for all items unless a medical record is obtained, in which case the medical record will be source.*
Pregnancy Report		*X*		*Chart notes are source for all items.*
Pregnancy Test Results	*X*			*CRF is source for all items.*
Protocol Deviations Y/N		*X*		*Chart notes or QA/QC reports or monitoring/auditing/inspection reports are source for all items.*
Protocol Deviations		*X*		*Chart notes or QA/QC reports or monitoring/auditing/inspection reports are source for all items.*
Randomization	*X*			*CRF is source for all items.*
Screening and Enrollment			*X*	*Source for whether the participant has screened before, and prior PTID if so, is chart notes. Source for eligibility status is the eligibility checklist if enrolled, eligibility checklist and chart notes if eligible but not enrolled, eligibility checklist if ineligible, chart notes if incomplete screening. This CRF is source for enrollment date and study arm. Source for date and reason found to be "Eligible/Not Enrolled" or "Ineligible" is the eligibility checklist. For "Investigator Decision" chart notes are source.*
Serious Adverse Event Y/N		*X*		*Chart notes are source for this item.*
Serious Adverse Event		*X*		*Chart notes are source for all items unless a lab report is source for information about a laboratory SAE.*
Social Impact Log		*X*		*Chart notes are source for all items*
Specimen Collection		*X*		*Lab requisition is source for type of specimen collected, whether specimen was collected, collection date, time of collection. LDMS is source for whether specimen was stored. Chart note is source for why specimens were not collected.*
STI Test Results			*X*	*Lab requisition is source for sample collection date. Chart note is source for not done/not collected, and actions taken. Lab reports are source for results. CRF is source for comments.*
Study Termination		*X*		*Chart notes are source for all items.*
Urine Dipstick Test Result	*X*			*CRF is source for all items.*

Signature, Investigator of Record **Date**

3.3.3.4 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 3-2 to show how they will document that all eligibility criteria have been met for each enrolled participant. As with Table 3-1, Table 3-2 should be modified to accurately reflect the source documentation being used at the site. Sites may choose to develop their own site-specific documentation to specify the source for each eligibility criterion. Please note, this table is required prior to site activation.

If a site chooses to use Table 3-2, 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. This example table is reflective of the inclusion/exclusion criteria in Version 1.0 of the protocol.

For each participant, sites are 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 (see section 6.4). 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 may be the first place that eligibility confirmation will be captured for several 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). Whatever documents are source for the individual items on the checklist, the Participant Eligibility Verification Checklist itself is the source documentation of the study team's ascertainment that a participant is eligible or ineligible and so will be source for the Screening and Enrollment CFR as indicated in Table 3-2.

Risk-related behavior criteria as outlined in Section 3.1, Inclusion Criteria, of the protocol (e.g., self-reported sharing injection equipment and/or condomless sex in the last three months with partners of HIV-positive or unknown status) needs to be documented at screening and should be re-verified prior to randomization. This is particularly important for participants who take more than 30 days to complete their screening process.

Table 3-2: HPTN 094: Source Documentation for Eligibility Criteria (EXAMPLE)
NOTE: This table is an example 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.

NOTE: In cells below where it says "Chart Notes/Eligibility Checklist" the site must choose one option and eliminate the other (or replace with a third option). Site may not leave as written because these are two different options.

Eligibility Requirements	Source Document
Inclusion Criteria	
18 to 60 years at the time of screening	*Chart Notes/Eligibility Checklist*
Provides informed consent for the study	*See Table 3-1a "Obtain Informed Consent"*
Urine test positive for recent opioid use and with evidence of recent injection drug use ("track marks")	*See Table 3-1a "Substance use testing (urine)" and "Assessment for OUD & recent injection drug use (track marks)"*
Diagnosed with OUD per Diagnostic and Statistical Manual of Mental Disorders (DSM) 5	*See Table 3-1a "Assessment for OUD & recent injection drug use (track marks)"*
Willing to start MOUD treatment	*Chart Notes/Eligibility Checklist*
Able to successfully complete an Assessment of Understanding	*Chart Notes/Eligibility Checklist*
Self-reported sharing injection equipment and/or condomless sex in the last three months with partners of HIV-positive or unknown status	*Chart Notes/Eligibility Checklist*
Able to provide adequate locator information	*Chart Notes/Eligibility Checklist**
Confirmed HIV status, as defined in the HPTN 094 SSP Manual	*See Table 3-1b HIV Test Results CRF*
Exclusion Criteria	
Received MOUD in the 30 days prior to enrollment by self-report	Chart Notes/Eligibility Checklist
Co-enrollment in any other interventional study unless approved by the Clinical Management Committee (CMC)	Chart Notes/Eligibility Checklist

*Note that although the participant contact form/locator form will be source for the participant's information itself, the determination that the information collected is ***adequate*** must be recorded as a separate note or check box.

_____ _____

Signature of Investigator of Record Date

3.3.4 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. **Sites 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. When communicating via email between two institutions for transfers that do NOT include anyone external to the two institutions, sites must follow their local institution's policy for transmission of confidential information (e.g., encrypted email, redacted files, etc.). 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 chart notes or lab reports contain a participant's name, this should be obliterated 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 participant PTID numbers to participant names or other personal identifiers should never be left unattended or easily accessible to unauthorized individuals.

3.4 Reportable Protocol Deviations

All deviations must be documented in the participant charts and any other pertinent source documents. A subset of deviations may also be considered reportable per the HPTN. Deviations that meet the criteria to be considered reportable will be reported to the study database as well as to the HPTN 094 deviation alias list. The process for reporting these types of deviations is described below in section 3.4.1.

As outlined in the HPTN Manual of Operations, reportable protocol deviations are defined by the HPTN as individual incidents, trends or omissions that result in:

- Significant added risk to the participant
- Non-adherence to significant protocol requirements
- Significant non-adherence to GCP

Examples of reportable protocol deviations are:

- Enrollment of an ineligible participant or prior to confirming eligibility. This also includes accidentally randomizing the wrong PTID, and situations when ineligibility is found after the fact (e.g., participant did not report at baseline a history of seizures)
- Informed consent not obtained prior to performing protocol-specified procedures
- Non-compliance with study randomization and blinding procedures
- Any situation when any of the HPTN 094 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 is not considered to be a reportable protocol deviation, but should be discussed by the protocol team.

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

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 STI, 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, an ALT is to be drawn at each participant 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.

3.4.1 Identifying and Reporting Reportable Protocol Deviations

If a site believes a deviation has occurred that would be considered reportable, the following steps should be followed:

1. Contact the HPTN 094 CRMs as soon as possible (within 24 hours) but no more than 3 business days once a site becomes aware of a deviation to determine whether a deviation meets the above criteria or are otherwise deemed by the

protocol team to be reportable deviations before they are reported into the electronic data capture system.

Note: Clinical-related deviations may also be identified by the CMC. The CMC or the HPTN 094 CRMs will respond with directions regarding reporting of these deviations, which will follow the same steps as below.

2. If it is determined the deviation does meet the definition of a reportable deviation, sites must complete the following steps:

    a. Complete the Protocol Deviation eCRF (please note there is a limit of 600 characters each for Description, Plans to Address, and Plans to Prevent areas of the eCRF; therefore, sites are asked to be concise and clear when describing the event).

    One Protocol Deviation Log CRF 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. Download the Protocol Deviation eCRF from the Rave database and email it (or multiple CRFs if there is more than one) to the HPTN 094 Protocol Deviation email alias at 094PD@hptn.org indicating that a deviation has occurred and the date it was submitted to the Rave database. If the deviation is the same for multiple PTIDs, only append one Protocol Deviation eCRF to the email and indicate in the body of the email the PTIDs of the other participants impacted by the same deviation and applicable dates for those participants.

    The HPTN 094 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 094 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 Program Officer on the email (**please note, the site's DAIDS OCSO Program Officer is not the same as the HPTN Program Officer Liaisons**).

- When reporting a deviation trend, please include one Protocol Deviation Log eCRF as part of the email sent to the HPTN 094 Protocol Deviation email alias and specify in the body of the email that a trend is being reported, and a list of affected PTIDs and applicable dates for each. Individual eCRFs must be entered into Rave for each affected PTID.

Please use the following format when sending an email to the HPTN 094 Protocol Deviation email alias:

Subject line: Include "094PD: [Insert PTID] – [One-line summary of reportable deviation – for example – "Dispensing error."

Body of the email: Include the following information:

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 of email: 094 CMC: Participant 103-000012 – Enrollment Error
Body of email:

- Site name and number: Site 103 – University Prevention Clinic
- Person submitting query: Hedda Lettuce, Study Coordinator
- PTID and Week on Study: 103-000012, Enrollment/Week 0
- Short Summary: Participant randomized on February 20, 2021. During QC process, it was noticed the participant was under 18 years of age.

3.5 Record Retention Requirements

For studies not under an IND such as HPTN 094, 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 subjects 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, study drug shipment and supply, 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.

3.6 Ancillary Studies

Ancillary studies (also sometimes referred to as "sub-studies") are those investigations, conducted in conjunction with a primary or "main" HPTN study, that address scientific questions not identified as study objectives in the primary study protocol.

Ancillary studies may involve HPTN investigators and/or non-HPTN investigators and may be initiated by the primary study team or by individuals inside or outside of the study team. They may:

1) involve all sites participating in a primary HPTN study or a subset of sites;
2) involve the use of data, biological specimens, or other information obtained through a primary HPTN study;
3) be either prospective or retrospective in nature;
4) involve surveys or focus groups among primary study participants; and
5) contain laboratory-based investigations using specimens obtained from participants in a primary HPTN study.

The administrative and regulatory requirements for the conduct of ancillary studies can be found in the HPTN Manual of Operations (MOP) Section 17 (https://www.hptn.org/sites/default/files/2019-01/Section%2017%20FINAL%20DEC2018%281%29.pdf).

3.7 Study Publications

All manuscripts, abstracts, posters or presentations based on the results or conduct of HPTN 094 must be prepared in accordance with the HPTN MOP and HPTN 094 Protocol Publications Committee.