Section 2: Document Requirements

2.1 Overview of Section 2

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.

2.2 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 091. 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/EC-approved versions, all signed and dated forms from screened/enrolled study participants), as well as any "Dear Participant" Letters (all IRB/EC-approved versions) for all screened/enrolled participants

- Signed and dated DAIDS IoR 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 (Applicable for Brazil site; US sites are using a central IRB, Advarra, and information is kept at LOC)
- IRB/EC roster(s) (Applicable for Brazil site; US sites are using a central IRB, Advarra, and information is kept at LOC)
- All correspondence to and from the local IRB/EC, 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 (Applicable for Brazil site. For US sites, general documents such as the study protocol, ICF template, educational and recruitment materials templates, ACASI surveys, IDI guides, and any other materials centrally generated will be submitted by FHI 360 to Advarra on behalf of the sites. Sites will submit any site-specific document (e.g., site-specific ICF and recruitment materials) to Advarra as part of their IRB submission.)
- 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 key staff (e.g., IoR, sub-investigators)
- 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® (TAF/FTC) Package Insert and subsequent updates (for US Sites only)
- Current Package Insert for all Gender Affirming Hormonal Therapy (GAHT) and subsequent updates provided to participants during study participation
- 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), DAIDS PAB or DAIDS, as well as other study-related communication
- Documentation of participation in 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 091 and all subsequent updates
- DAIDS reference materials including:
    - The DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual: https://www.niaid.nih.gov/research/daids-score-manual; 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, communiqués, and any communication providing guidance or updates that may impact study procedures or implementation
- Monitoring visit log, reports, and site response to visit findings (for PPD, HPTN LOC, SDMC, LC, PAB, and other site visits). 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
- Protocol Signature Page for current and all subsequent protocol versions.

2.3 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 Site Clinical Operations and Research Essentials (SCORE) Manual*, the research record consists of the following: original subject-signed informed consent form(s), participant source documents, and case report forms (CRFs).

2.4 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 Site Clinical Operations and Research Essentials (SCORE) Manual* and the standards outlined in this manual.

For HPTN 091, 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 091 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, clinical management committee (CMC), CRS investigators to study nurses, etc.)
3. IRB/EC 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 091, 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/EC 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

2.4.1 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 4.12.3 Table 4.5to 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 study products
- 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 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, 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

2.4.2 Examples of Source Documentation

Clinic Notes

2.4.2.1 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 (and a site may wish to include this information in the retention SOP). 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 Site Clinical Operations and Research Essentials (SCORE) Manual* 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 they are feeling or their symptoms. For example, how they are sleeping or eating or if they are 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 clinic notes using the SOAP method:

Sample Clinic Note for a Screening Visit:

26 October 2021: Participant presented for HPTN 091 screening at Bridge HIV CRS Clinic obtained written informed consent for screening/enrollment before initiating any procedures; HIPAA consent reviewed and signed. Copies of signed documents were provided to the participant. All of 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 infection. Participant was assigned male at birth, identifies as a woman, and met all behavioral risk criteria (see checklist). The participant has never participated in an HIV prevention or vaccine trial.

O: BP 126/54. Exam entirely WNL. HBV immune.

A: Healthy participant that may be eligible for HPTN 091.

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

{staff signature/date}

2.4.2.2 Visit Checklists

The checklists are provided as a study document to 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. 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 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.

2.4.2.3 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 2-1 (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 2-1 should be modified to

accurately reflect the source documentation for each CRF item at the site. Table 2-1 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 2-1 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 2-1a and 2-1b: HPTN 091 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 3-1b below are listed in alphabetical order 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.

Table 2-1b: For each CRF listed below, add which elements of the form serves as the source document for study procedure/evaluation.

Table 2-1a: HPTN 091 Source Documentation Template

Evaluation/Procedure	Source Document(s)
ADMINISTRATIVE, BEHAVIORAL AND REGULATORY	
Obtain Informed consent(s)	*Example: Signed and Dated Informed Consent form, Informed Consent Coversheet (or chart note)*
Demographic information	
Locator information	
Randomization	
ACASI	
HIV prevention counseling (Offer condoms and lubricant)	
Provision of PrEP	
PrEP counseling and support	
Provision of GAHT	
GAHT counseling and support	
Peer Health Navigation using Strengths-Based Case Management	
CLINICAL	
Complete Medical History (including bleeding history at Screening), physical	*Example: Medical History Questionnaires, Pre-Existing Conditions CRF, and/or chart notes*
Symptom-directed physical exam	
Interim medical history (including STI symptoms)	
Concomitant medications	
Blood collection	
Urine collection for urinalysis	
Urine collection for GC/CT testing	
Rectal (& pharyngeal) swab for GC/CT testing	
STI treatment, if indicated	
Hepatitis B vaccination or decline of vaccination	
LABORATORY	
HIV testing	*Example: Lab result report or other site-specific form*
HBV testing (HBsAg, HBsAb, HBcAb-Total)	
HCV testing	
CBC with differential	
Chemistry testing (BUN or urea, albumin and potassium)	
Fasting lipid profile	
Syphilis serologic testing	
GC/CT testing for NAAT (rectal, urine, pharyngeal)	
Dipstick urinalysis (protein and glucose)	
Plasma storage	
DBS storage	
LFTs (AST, ALT, TBili, alkaline phosphatase)	
Creatinine clearance	
Estradiol and total testosterone testing	

Table 2-1b: HPTN 091 Source Documentation Template

CRF Name	Source			Comments
	Yes	No	Mixed	
ACASI Tracking				
Additional Study Procedures				
Adverse Event			*X*	*Example: Form is source for Alternate etiology information. For all other items, source will be based on the type of AE, including chart notes, lab report/testing log, medical questionnaires.*
CD4/Viral Load Results				
Chemistry Panel				
Concomitant Medications				
Counseling				
Date of Visit				
Date of Visit - Seroconverter Schedule				
Demographics				
Enrollment				
Fasting Lipid Test Results				
Gender Affirming Hormone Therapy Log				
Hematology				
Hepatitis B Vaccination				
Hepatitis Test Results				
HIV Test Results				
Hormone Tests				
Inclusion/Exclusion Criteria				
Informed Consent				
Interim Visit				
Medical History				
Missed Visit				
Participant Identifier				
Participant Receipt				
Participant Transfer				
Patient Health Questionnaire				
Peer Health Navigation Tracking				
Physical Exam				
PK Dose Time				
PK Specimen Collection				

CRF Name	Source			Comments
	Yes	No	Mixed	
Pre-exposure Prophylaxis Log				
Protocol Deviation				
Randomization				
Screening Date of Visit				
Social Impact Assessment Log				
Specimen Collection and Storage				
STI Tests				
Study Termination				
Supplemental HIV Results				
Urinalysis				
Vital Signs				

2.5 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.

Sites are required to use either the local modified version of the *Eligibility Checklist* Template (which includes instructions for who is responsibility for sign-off), 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 091. 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. Sites should modify the checklist to be site-specific before using them. 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 3.5 of this manual for additional information on requirements for completing this checklist.

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. 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 the source on the Source Documentation for Eligibility Criteria Tables (Table 3-2).

Risk-related behavior criteria as outlined in Section 4.1 – Inclusion Criteria – of the protocol (e.g., Any anal or vaginal sex with one or more sexual partners in the previous 3 months, regardless of condom use) needs to be documented at screening and should be re-verified prior to randomization. This is particularly important for participants who take the full 30 days to complete their screening process.

Table 2-2: HPTN 091: 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
Inclusion Criteria	
Assigned male at birth, identifies as a woman or on the transfeminine spectrum, 18 years or older at the time of screening	Chart Notes/Eligibility Checklist
Provides informed consent for the study	Informed Consent Form
Interest in receiving oral PrEP (Defined as participant expressing a desire in using oral PrEP (either for the first time or to continue oral PrEP use) or learn more about it.)	Chart Notes/Eligibility Checklist
Non-reactive HIV test results at Screening and at least one non-reactive test result at Enrollment.	Lab Results
Available to return for all study visits and within site catchment area	Chart Notes/Eligibility Checklist

At high risk of sexually acquiring HIV per at least one of the following: • Any anal or vaginal sex with one or more sexual partners in the previous 3 months, regardless of condom use. • Anal or vaginal sex in exchange for money, food, shelter, or other goods or favors in the previous 3 months. • History of STI(s) in the past 6 months.	Chart Notes/Eligibility Checklist
Willing to undergo all required study procedures	Chart Notes/Eligibility Checklist
General good health, as evidenced by the following laboratory values: ❒ Calculated creatinine clearance ≥ 60 mL/minute using the Cockcroft-Gault equation. ❒ Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and total bilirubin < 2.5 times the upper limit of normal (ULN.) (with the exception of Gilbert's syndrome). ❒ HBV surface antigen (HBsAg) negative.	Lab Results
Exclusion Criteria	
Any reactive or positive HIV test result at Screening or at least one reactive/positive HIV test result at Enrollment, even if HIV infection is not confirmed.	Lab Results
Plans to move away from the site area within the next 18 months.	Chart Notes/Eligibility Checklist
Co-enrollment in any other concurrent study which may interfere with this study. Exceptions may be made after consultation with the Clinical Management Committee (CMC).	Chart Notes/Eligibility Checklist
Significant hepatic dysfunction or end-stage liver disease, per the opinion of the site investigator and in consultation with the CMC. For participants using cyproterone acetate, please consult the CMC for any evidence of liver abnormalities.	Chart Notes/Eligibility Checklist
History of deep vein thrombosis, pulmonary embolism, and/or clotting disorder.	Chart Notes/Eligibility Checklist
Active or planned use of medications with significant drug interactions as described in the Package Insert for Truvada® or Descovy®.	Chart Notes/Eligibility Checklist/ConMed CRF
Any other condition, including but not limited to alcohol or substance abuse and uncontrolled medical condition and/or allergies, that, in the opinion of the Investigator of Record (IoR)/designee, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives would make the patient unsuitable for the study or unable/unwilling to comply with the study requirements.	Chart Notes/Eligibility Checklist

_____ _____

Signature of Investigator of Record Date

2.6 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, EAE Report Forms, 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 supporting documentation of study eligibility is to be submitted to the HPTN LOC, such as chart notes or lab reports that 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.

2.7 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 091 deviation alias list. The process for reporting these types of deviations is described below.

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
- Informed consent not obtained prior to performing protocol-specified procedures
- Non-compliance with study randomization
- Provision of PrEP prior to availability and confirmation of negative/non-reactive HIV test results
- Any situation when any of the HPTN 091 HIV testing algorithms were not followed as per protocol and Section 8 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
- Use of prohibited medications as specified in Section 6.2.6.2 of the SSP, even when medication is administered by an outside source (e.g., primary care physician, hospital).

  Participant non-compliance with the study protocol, including treatment specifications or adherence to regimen, is not considered to be a reportable protocol deviation, but should be discussed by the protocol team.
- Participant overdose of study product. For purposes of reporting, a study product overdose is defined as three or more occasions of taking more than the specified dose of study product during a 30-day period.

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

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 ALT, 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.

When a site identifies a protocol deviation, they will determine if the deviation meets the criteria of a reportable deviation as described above. If a site is unsure, they must contact Kaila Gomez-Feliciano (kgomez@fhi360.org) and Busola Akingbade (bakingbade@fhi360.org), ideally within 3 business days of site awareness, to determine whether a deviation meets the above criteria are or is otherwise deemed by the protocol team to be reportable.

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

1. Complete the Protocol Deviation eCRF (please note there is a limit of 1,000 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.

   For HPTN 091, trend is defined as a deviation that impacts 5 or more PTIDs. 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, the information on eCRFs must be identical for all impacted PTIDs (with the exception of participant-specific information such as PTID and applicable dates).

   NOTE: If the deviation involves more than 10 PTIDs, please contact Kaila and Busola for specific instructions on how to complete the reporting documentation.

2. Download the Protocol Deviation e-CRF from the MediData system, and email it (or multiple CRFs if there is more than one and up to 10 as stated above) to the HPTN 083 Protocol Deviation email alias at 091PD@hptn.org indicating that a deviation has occurred and the date it was submitted to the MediData database system. If the deviation is the same for multiple PTIDs, only append one Protocol Deviation e-CRF to the email and indicate in the body of the email how many participants are impacted by the same deviation.

   The HPTN 091 protocol deviation email alias includes the following individuals:

- Protocol Chair and Co-Chair
- LOC, LC, and SDMC protocol representatives

- DAIDS Protocol Medical Officer
- DAIDS Protocol Pharmacist
- DAIDS HPTN Office of Clinical Site Oversight (OCSO) Program Officer Liaisons

  When sending emails to the 091 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 091 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 MediData Rave for each affected PTID.

Please use the following format when sending an email to the 091 Protocol Deviation email alias:

Subject line: Include "091 PD: [Insert PTID] – [One-line summary of reportable deviation – for example – "Enrollment 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

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

2.8 Record Retention Requirements

All study-related regulatory and administrative documentation as well as participant research records must be retained on-site throughout the study's period of performance and after the completion or termination of the trial. No records should be destroyed without first receiving authorization from DAIDS. Records may be moved to secure, long-term storage facilities after the study is complete and the database has been locked. A record of this storage (location and organizational structure) must be provided to DAIDS and the HPTN LOC prior to moving any records off-site.

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.

All documents listed in Section 2.3.2 of this manual.

2.9 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 (http://www.hptn.org/web%20documents/HPTNMOP/section17.pdf).

2.10 Study Publications

All manuscripts, abstracts, posters or presentations based on the results or conduct of HPTN 091 must be prepared in accordance with the HPTN MOP and HPTN 091 Protocol Publications Committee.