10. Adverse Event Reporting and Safety Monitoring

10.1 Overview of Section 10

This section presents information related to adverse event (AE) reporting and safety monitoring in HPTN 094. The following resources are relevant to AE reporting:

- DAIDS Table for Grading Adult and Pediatric Adverse Events, dated July 2017
- Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0 (DAIDS EAE Manual, dated January 2010)
- Section 7.0 of the HPTN 094 protocol (Version 1.0, dated 15 JUL 2020)

10.2 Adverse Event - Definition

The standard definition of an adverse event is any untoward medical occurrence in a clinical research participant administered an investigational product and which does not necessarily have a causal relationship with the investigational product. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the product. In this study, in which the intervention does not involve an investigational product, we define an AE as any untoward medical occurrence in a research participant who has been a recipient of at least one component of the study intervention (either peer navigation or provision of medical care from the mobile health unit) which does not necessarily have a causal relationship to the participant's receipt of the study intervention. This definition applies to all participants from the time a participant is randomized through when they terminate from the study.

10.3 Serious Adverse Events (SAEs) - Definition

ICH-E6 defines a serious adverse event (SAE) as any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
  NOTE: *The term "life threatening" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. A grade 4 severity grading on the Toxicity Table does not necessarily mean that an event is life-threatening. When determining whether a grade 4 event meets the ICH definition of "life threatening", consider the event in the context of any related symptoms the participant may have experienced.*
- Requires in-patient hospitalization or prolongs an existing hospitalization. The following types of hospitalizations <u>are not</u> considered adverse events, serious or otherwise:
  - Any admission unrelated to an AE (e.g., for cosmetic procedures)
  - Admission for diagnosis or therapy of a condition that existed before randomization AND has not increased in severity or frequency since baseline.
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly/birth defect, or
- Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the outcomes listed above.

ICH guidance (E2A) states that medical and scientific judgment should be exercised in deciding whether other adverse events not listed above should be considered serious.

SAEs are a subset of all AEs. For each AE identified, an authorized study clinician must determine whether the AE meets the ICH definition of "serious". When assessing whether an AE meets the definition of serious, note that <u>seriousness is not the same as severity</u>, which is based on the intensity of the AE.

10.4 Documenting Adverse Events

Study site staff are responsible for documenting all AEs reported or observed in study participants in the study source documentation according to the site's SOP for source documentation. Source documentation for all AEs should minimally include the following:

- AE term/diagnosis
- Severity grade
- Onset date

- Outcome
- Outcome date
- Treatment for the AE (if any)

Whenever possible, a final diagnosis, rather than individual signs and symptoms, should be documented. If a diagnosis is not possible, each individual sign and symptom should be identified and documented as an individual AE. Additional information and tips may be found in the HPTN 094 Study Specific Training Materials.

Further tips and guidelines for assigning AE terms include:

- Use specific medical terms whenever possible (e.g., "ulcers" instead of "sores")
- Use correct spelling for all terms; and,
- Do not use abbreviations.

When reporting an AE that is associated with an underlying condition, include the underlying condition in the AE term or description. For example, if a participant is experiencing pain related to an underlying arthritic condition, include the arthritis diagnosis in the AE term or description, as in, "joint pain related to rheumatoid arthritis."

Clinical site staff identified in the delegation of duties log will grade all AEs for severity according to the DAIDS Table for Grading Adult and Pediatric Adverse Events, dated July 2017 (referred to herein in this section as the "DAIDS Toxicity Table". This table will be used throughout the entire study, and can be downloaded at: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf

The term severity is used to describe the intensity of an AE. The severity of all AEs identified in HPTN 094 must be graded on a five-point scale:
Grade 1 = Mild
Grade 2 = Moderate
Grade 3 = Severe
Grade 4 = Potentially life-threatening
Grade 5 = Death

Severity is not the same as seriousness, which is based on the outcome or action associated with an event. AEs not listed in the DAIDS Toxicity Table should be graded according to the "estimating severity grade" row of the following table:

Grade 1 **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Potentially** **Life-Threatening**
Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social and functional activities	Symptoms causing inability to perform usual social and functional activities	Symptoms causing inability to perform basic self-care functions OR Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death

10.5 Documenting Serious Adverse Events

For every AE identified, clinical site staff identified in the delegation of duties log will assess the event for seriousness. Serious Adverse Events (SAEs) are defined by ICH E2A, as described in Version 2 (January 2010) of the DAIDS EAE Manual, section 2.1, Seriousness. An SAE is any untoward medical occurrence that:

- Results in death,
- Is life-threatening, (The term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe, nor does it refer to grade 4 events as graded using the DAIDS Toxicity Table unless they are thought to be truly life-threatening.)
- Requires inpatient hospitalization or prolongation of existing hospitalization, (Per ICH SAE definition, hospitalization itself is not an AE, but is an outcome of the event.) The following types of hospitalization do not require expedited reporting to DAIDS:
    - Any admission unrelated to an AE (e.g., for labor/delivery, cosmetic surgery, administrative or social admission for temporary placement for lack of a place to sleep),
    - Admission for diagnosis or therapy of a condition that existed before receipt of study agent(s) and has not increased in severity or frequency as judged by the clinical investigator. (NOTE: A new AIDS-defining event in a subject already known to be HIV-infected would be considered an increase in severity of a pre-existing condition [HIV infection] and would therefore be reportable.)
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect,
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples include the following: intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; etc.

Site staff will record assessment of seriousness in source documentation. Source documentation may include CRFs for reporting SAEs to the study database, and this should be spelled out in the site's SOP for source documentation.

For every SAE identified, study staff will assess relatedness to the study intervention. For this study, relatedness means whether there is a reasonable possibility that the participant's receipt of peer navigation services or receipt of medical care in the mobile health delivery unit caused or contributed to the SAE.

The relationship assessment, based on clinical judgment, often relies on the following:

- A temporal relationship between the event and the participant's receipt of the navigation or medical care in the mobile unit
- A plausible biological mechanism for the receipt of navigation or medical care on the mobile unit to cause the AE
- Another possible etiology for the AE

- Previous reports of similar AEs associated with receipt of navigation or medical care from a mobile unit

The terms used to assess the relationship of an event to the study intervention are:

- Related - there is a reasonable possibility that the AE may be related to the participant's receipt of navigation and/or medical care from the mobile unit.
- Not Related - There is not a reasonable possibility that the AE is related to the participant's receipt of navigation and/or medical care from the mobile unit.

Note that when an SAE is assessed as "not related", an alternative etiology or explanation should be provided in the 'Comments' section of the CRF. If new information becomes available, the relationship assessment of any SAE should be reviewed again and updated as required.

10.6 Reporting of Adverse Events, Serious Adverse Events and SUSARs

This study will not report non-serious AEs into the study database. As well, there will be no expedited reporting of AEs to DAIDS for this study.

Site teams are expected to routinely review the clinical events that occur among participants and report to the study Clinical Monitoring Committee (CMC) any individual incidents or trends that raise concern about study conduct or the risk posed to study participants by the trial. Sites should also report all SAEs to the CMC.

Site teams will report SAEs into the study database using the Serious Adverse Event CRF. Sites should submit the SAE report within 72 hours after becoming aware of the SAE. Do not hold the forms in anticipation of receiving additional information at a later date. If additional information is received at a later date, update the forms in the database before the end of the next business day after receiving the new information.

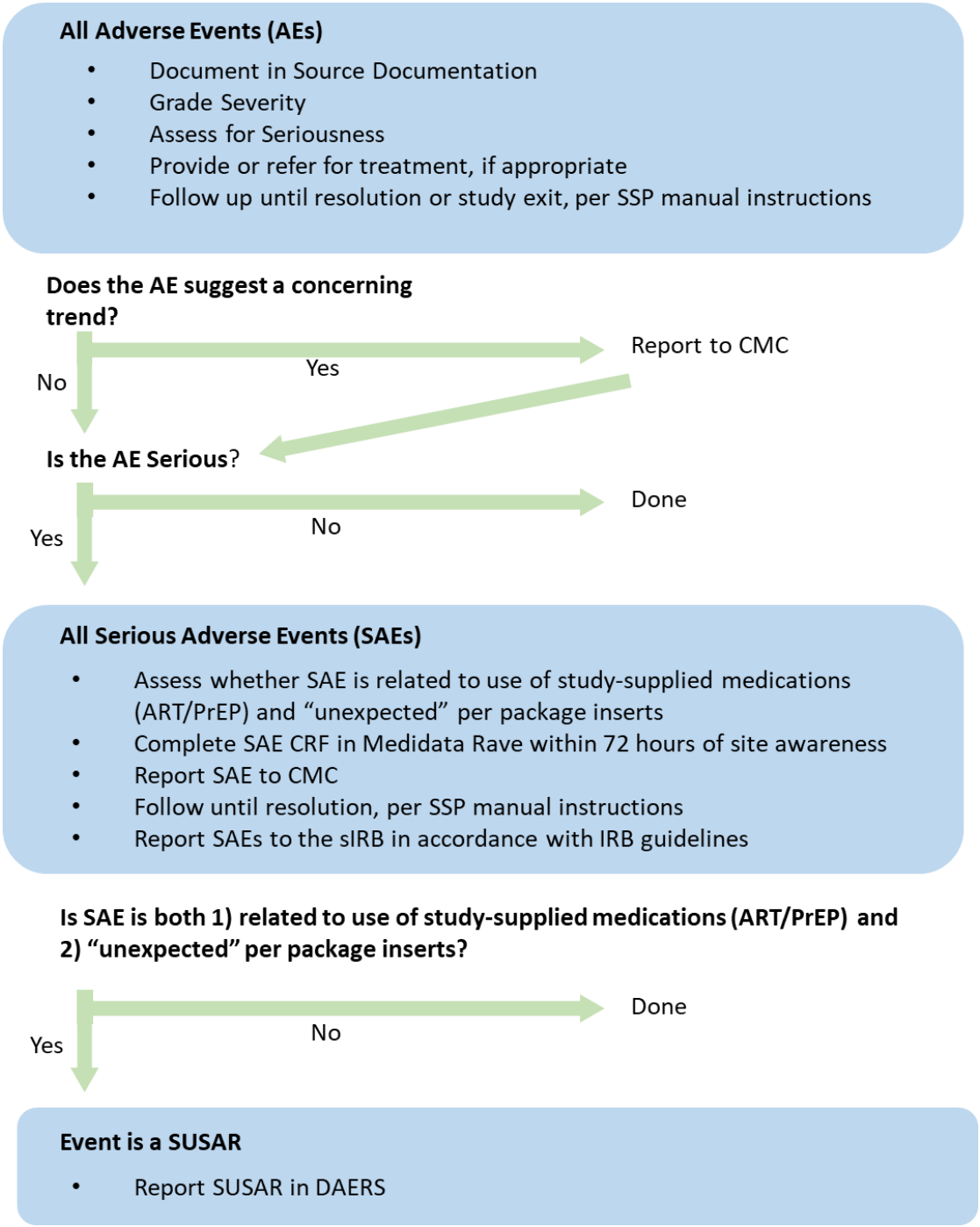
An SAE with onset after exposure to study-supplied medication(s) (ART or PrEP) will be reported as a SUSAR if the SAE is deemed both related and unexpected to any of the study-supplied medications. These assessments for relatedness and unexpectedness shall be made by a site study clinician. SUSAR assessment will be as specified in Version 2.0, January 2010 (or most current version) of the Manual for Expedited Reporting of Adverse Events (EAE) Reporting to DAIDS.

Sites are responsible for notifying the IRB of all SAEs according to the IRB's requirements.

This reporting is required for all participants from the time they are enrolled until their participation in the study ends. After this time, sites must report SAEs if the study site becomes aware of the event on a passive basis, i.e., from publicly available information.

Figure 10-1 provides an overview of SAE and SUSAR reporting for HPTN 094.

Figure 10-1: HPTN 094 AE, SAE and SUSAR Documentation and Reporting



10.7 Timeline for Following and Reporting AEs, SAEs and SUSARs

Non-serious adverse events do not need to be followed beyond the planned participation termination date. However, site clinicians must follow all SAEs until they become clinically stable or resolve. In addition, GCP requires that source documents include information about all follow-up activities as well as information concerning resolution.

For all SUSARs as defined above, each site will use the DAIDS internet-based reporting system, DAERS (DAIDS Adverse Experience Reporting System), to report all AEs that require expedited reporting to DAIDS. DAERS can be accessed at https://ncrms.niaid.nih.gov/NCRMS/Main/Login.aspx. In the event of system outages or technical difficulties,
EAEs may be submitted via the DAIDS EAE form (paper format). This form is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting.For questions about
DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov. Site queries may also be sent with the DAERS application itself. For questions about EAE reporting, please contact the RSC at DAIDSRSCSafetyOffice@tech-res.com. All SUSARS must be reported within 3 reporting days (see Manual of Expedited Reporting of Adverse Events to DAIDS, version 2.0, January 2010).

All EAEs must also be reported as SAEs on the SAE CRF and to be submitted to the HPTN SDMC within 72 hours of the site awareness date. When completing SAE CRFs and EAE forms, study clinicians should carefully review all documentation of the event to ensure accuracy, completeness, and consistency. All SAE descriptions and details (e.g., SAE term, onset date, severity grade, relationship to study product) must be recorded consistently across all documents. All EAE forms received at the DAIDS Safety Office will be compared with the SAE CRFs received at the HPTN SDMC to ensure that all key data elements are matched with consistent details.

At each follow-up visit, an authorized (per site delegation of duties roster) site clinician should review all previously identified ongoing SAEs in order to evaluate and document their current status. Outcomes must also be reported on a Serious Adverse Event CRF. In many cases, the final outcome of an AE will not be available when the Serious Adverse Event CRF is first completed in the database (for those AEs that are reportable in the databases). In such cases, the eCRF should be updated when the final outcome becomes known, or when other status changes occur.

When reporting an SAE on a Serious Adverse Event CRF, sites must only use one of the following options:

- Recovered/Resolved
- Recovering/Resolving
- Recovered/Resolved with sequelae
- Not recovered/Not resolved
- Fatal
- Severity/Frequency increased

As noted above, resolution of an SAE is generally defined as returning to the condition or severity grade that was present at baseline/randomization (i.e., pre-existing) and "stabilize" (SAE updates only) is defined as persistence at the same severity grade for an adequate period of time determined by the Site Investigator.

If an SAE increases in severity or frequency (worsens) by at least one grade after it has been reported on a Serious Adverse Event CRF, it must be reported as a new SAE, at the increased severity or frequency, on a new Serious Adverse Event CRF. In this case, the status outcome of the first SAE will be documented as "Severity/Frequency increased."

The status of the second SAE will be documented as "Recovering/Resolving ". The outcome date of the first SAE and the onset date of the new (worsened) SAE should be the date upon which the severity or frequency increased.

NOTE: The Safety Reports that are reviewed by the SMC always display the highest severity grade reported for any specific condition. Thus, it is important to remember that, if the condition worsens, the Status/Outcome should be updated to be "Severity/Frequency increased" and a new SAE documenting the higher severity grade should be submitted. However, do not resolve a higher severity grade SAE and then submit a lower grade AE for the condition as it is improving. Leave the highest grade SAE as "Recovering/Resolving" until it returns to baseline or resolves completely.

10.8 Reporting Adverse Events at a Final Study Visit

Sites should review with participants any remaining AEs, or SAEs marked "Not recovered/Not resolved" on the Serious Adverse Event CRF, in an attempt to determine whether they have resolved since the last visit. Non-Serious Adverse Events do not need to be followed past the final study visit. However, SAEs must be followed until they have resolved or become clinically stable.

If any test results from the last scheduled study visit meet SAE reporting criteria, or the participant reports a new SAE at the last scheduled study visit, a new Serious Adverse Event CRF must be completed in the database prior to or at the same time the Termination CRF. New Serious Adverse Event CRFs should be completed as follows:

- The "**Status/Outcome**" field is marked as "Not recovered/Not resolved" and the case must be followed until it is resolved or stabilized.
- The "**Onset Date**" field is completed with the date of the last scheduled study visit (or before if the participant reports as such.)
- The "**At which visit was this adverse event first reported**?" field is completed with the last regularly scheduled study visit code.

If an SAE is ongoing at the termination visit but is stable, the status/outcome of the SAE should be updated to "Not recovered/Not resolved" in the database.

Note: Any SAE that is not stable but ongoing must be followed until stable or resolved.

10.9 Reporting Recurrent Adverse Events

If an SAE that was previously reported on a Serious Adverse Event CRF resolves and then recurs at a later date, the second occurrence must be reported as a new SAE on a new Serious Adverse Event CRF.

If a SUSAR that was previously reported to the DAIDS RSC in an expedited manner resolves and then later recurs at a level requiring expedited reporting, the second occurrence must be reported as a new EAE report in DAERS.

10.10 Social Impact Reporting

In addition to medical AEs, participants in HPTN 094 may experience social impacts — participant reported non-medical adverse consequences— as a result of their participation in the study. For example, participants could experience difficulties in their personal relationships with partners, family members, and friends if they find out they are participating in the study. They also could experience stigma or discrimination from family members and members of their community. In the event that social impact occurs, study staff should fully document the issues or problems and make every effort to facilitate their resolution as described in this section. In addition, the social impact must be recorded on the Social Impact Log. As with medical AEs, follow all problems to resolution (until they no longer exist), or stabilization (they exist, but at a manageable level). Provide referrals as needed/appropriate to other organizations, agencies, and service providers that may be able to help address the problem.

If the reported social impact is associated with an SAE, report the SAE on the Serious Adverse Event CRF. Sites will report to the CMC any social impacts that raise concern about the conduct of the study or raise the possibility of serious or unanticipated risk to study participants. Also report the issue or problem to all IRB responsible for oversight of HPTN 094, if required per IRB guidelines.

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

10.11 Pregnancy

Sites will notify the CMC of any pregnancies reported at the Enrollment Visit or that occur among participants during the study. All pregnancies will be followed until the final outcome is determined. Pregnancy outcomes and obstetric complications should be reported using the appropriate case report form. Sites must report pregnancies that occur among study participants taking ART or PrEP to the Antiretroviral Pregnancy Registry.

10.12 Safety Monitoring, Review, and Oversight

Section 7.6 of the HPTN 094 Protocol outlines the measures to monitor and safeguard participant safety. Safety monitoring of study participants is primarily the responsibility of study staff, under the direction of the IoR. The IoR and designated study staff are responsible for submitting required forms to the HPTN SDMC and reporting any potentially serious or unanticipated risk or problem to the CMC. The CMC will work with the site investigators, LOC CRM, SDMC Biostatistician, SDMC Clinical Coding and Safety Staff, HPTN LC, DAIDS personnel, and other study team members to determine the appropriate response.

The study will be monitored by an HPTN Study Monitoring Committee (SMC) and participant safety data will be monitored by the SDMC Clinical Safety Staff. Descriptions of these groups and their responsibilities can be found on Section 14 and 15 of the HPTN MOP: https://www.hptn.org/resources/manual-of-operations.