# Section 7. Safety/AE/Social Impact

## 7.1. Overview of Section 7

This section presents information related to adverse event reporting and safety monitoring in HPTN 074. In addition to this section of the HPTN 074 SSP Manual, please refer to the following in relation to participant safety:

- DAIDS Table for Grading Adult and Pediatric Adverse Events (Toxicity Table), dated November 2014 (see HPTN 074 SSP Appendix C)
- Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0 (DAIDS EAE Manual, dated January 2010)
- HPTN 074 Protocol Section 6: Safety Monitoring and Adverse Events Reporting

## 7.2. Definitions and General Reporting Guidance

### 7.2.1. Adverse Event

**For purposes of HPTN 074, an AE is defined as:**

Any untoward medical occurrence in a patient or clinical investigation subject. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease.

For non-serious adverse events, this definition applies to all participants after enrollment and prior to exiting from HPTN 074. Study site staff must document in source documents all AEs reported or observed in HPTN 074 participants, regardless of seriousness or severity. 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)

***Note: A template source document is located below, which may be used for non-serious adverse events in HIV positive participants:***

PTID_____ Date of Visit_____

1) Have you had any changes to your health since your last visit? Yes NO (End of form)
   a. If yes, please describe (if the participant indicates any suicidal thoughts, refer to suicidal ideation SOP).
   b. If pregnant, this is not an adverse event.

2) AE term/diagnosis _____

3) Severity grade (1-5) _____ (4 and 5 are automatic SAE or SUSAR; others may be at Investigator's discretion)
4) Onset date _____
5) Outcome (resolved or ongoing: if Exit visit, note "ongoing" for adverse events that do not meet SUSAR or SAE criteria) _____
6) Outcome date _____
7) Treatment (if any) _____

Note: sites are expected to follow-up on any routine AEs that were unresolved at the last visit up until the time the participant exits the study. Sites are not expected to collect information from other providers (i.e. antibiotics prescribed for non-serious AE).

***If an Investigator notices an unexpected trend in frequency or types of routine adverse events that are outside what is expected in standard practice, the protocol chairs and LOC should be notified.***

### 7.2.2. Serious Adverse Events (SAEs)

Serious Adverse Events (SAEs) are defined by the ICH E2A definition, as described in Version 2 (January 2010) of the DAIDS EAE Manual, section 2.1, Seriousness. An SAE is any untoward medical occurrence that:

1. Results in death,
2. 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.)
3. 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.)
4. Results in persistent or significant disability/incapacity,
5. Is a congenital anomaly/birth defect,
6. 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.

### 7.2.3. Reporting Adverse Events to SDMC (SCHARP)

All SAEs, regardless of grade, must be reported on the AE Log CRF and sent to the SDMC via DataFax. SAE severity will be graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 2.0, November2014 (see HPTN 074 SSP Appendix C).

Sites should submit all safety-related case report forms before the end of the next business day after receiving the information. 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 and refax to the SDMC before the end of the next business day after receiving the new information.

***Note: A new HIV infection is not considered an AE and should not be recorded on the AE Case Report Forms.***

As noted above, source documentation for all AEs should minimally include the following: AE term/diagnosis, severity grade, onset date, outcome, outcome date, and treatment (if any).

Each site's SOP for source documentation should define the extent to which the AE Log Case Report Form will be used as the source document for these data elements.

Site-specific delegation of duties log should designate study staff authorized by the IoR to assess adverse events. Regardless of who initially completes the AE Log, a clinician listed on the site's Investigator Form should review each AE Log form to ensure the accuracy of the data reported and to help maintain consistency of reporting across clinicians.

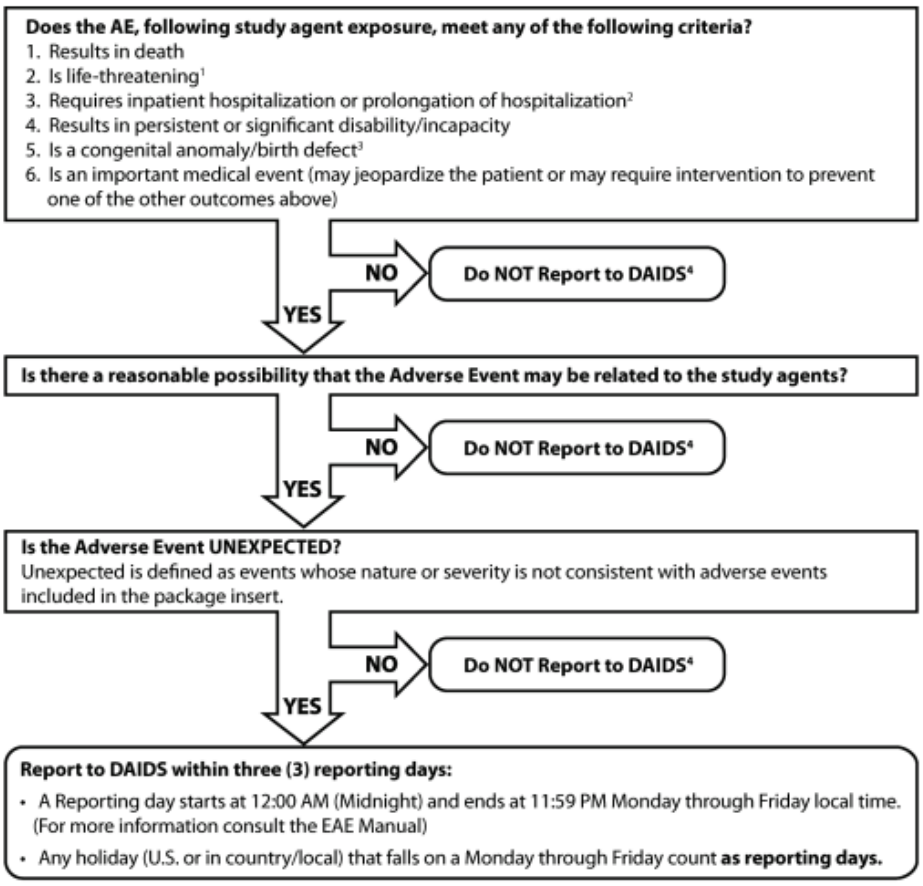
If, at any time, site staff has questions about participant safety or reporting clinical events, they should send an email to the HPTN 074 Clinical Management Committee at 074cmc@hptn.org.

### 7.2.4. Reporting Adverse Events in an Expedited Manner

Only Suspected Unexpected Serious Adverse Reactions (SUSAR) that occur between enrollment and study exit will be reported in an expedited manner to the DAIDS Adverse Event Reporting System (DAERS) (https://daidses.niaid.nih.gov/phoenix/Login.aspx). If the Investigator becomes aware of an SAE that occurred to a participant during the study participation period at any time after the participant has exited, the event should be reported in

the same manner as when the participant was on study.

## APPENDIX B:
## SUSPECTED, UNEXPECTED SERIOUS ADVERSE REACTIONS (SUSAR) REPORTING CATEGORY FLOW CHART




**Contact Information for the DAIDS Safety Office:**
**Website:** http://rcc.tech-res.com • **E-mail:** RCCSafetyOffice@tech-res.com
**Office Phone:** 1-800-537-9979 (U.S. only) or +1-301-897-1709 • **Fax:** 1-800-275-7619 (U.S. only) or +1-301-897-1710
*(Office Phone and Fax are accessible 24 hours per day)*
**Mailing Address:** DAIDS Safety Office 6500 Rock Spring Drive, Suite 650, Bethesda, MD 20817

[1] "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.

[2] Per ICH SAE definition, hospitalization is NOT an adverse event (AE), but is an outcome of the event. **DO NOT REPORT**: 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); protocol-specified admission (e.g., for a procedure required by protocol); 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 be** reportable.)

[3] Clinically insignificant physical findings at births including those regarded as normal variants do NOT meet reporting criteria. If a clinically significant anomaly is reported, all findings (including those of no individual significance) should be included in the same report. For example, do NOT report an isolated finding of polydactyly (extra fingers or toes) or Mongolian spot in an infant. But if either finding occurred with a major cardiac defect, report all findings in the SAE Report.

[4] Please ensure that any other protocol-specific reporting requirements are met.

The timeframe for expedited reporting of individual SAEs begins when the clinical research site recognizes that an event meets SUSAR criteria for expedited reporting to DAIDS. The day that the site becomes aware of the event is considered Day 1. Clinical research sites must submit the SUSAR to the DAIDS Safety Office immediately, and no later than 3 reporting days after the site becomes aware of an event that meets criteria for expedited reporting.

"Reporting days" are those that count toward the 3-day timeline provided for reporting of events to DAIDS. The criteria used to determine reporting days are as follows:

- A reporting day starts at 12:00 AM (midnight) and ends at 11:59 PM local time.
- A day is counted as a reporting day regardless of the time of day that awareness occurred. The day a site indicates that site personnel became aware of an event that meets reporting criteria shall count as day 1 (even if it is 23:00) if that day occurs on a reporting day (i.e., Monday through Friday). If that day occurs on a non-reporting day (i.e., Saturday or Sunday), then the next reporting day shall count as day 1.
- Monday through Friday count as reporting days.
- Saturday and Sunday are not considered reporting days.
- Any holiday (U.S. or in-country/local) that occurs on a Monday through Friday counts as a reporting day.

In addition, sites should submit all safety-related case report forms to SCHARP before the end of the next reporting day after receiving the information.

For each HPTN 074 participant, the event reporting period begins with study enrollment (Day 0), and ends when the participant exits the study. All SUSARs should be reported to the DAIDS Regulatory Support Center (RSC) using the internet-based DAIDS Adverse Experience Reporting System (DAERS), per instructions provided in the DAERS Reference Guide for Site Reporters and Study Physicians. The process of SUSAR reporting via DAERS involves a designated "Study Reporter" creating an electronic EAE report and a designated "Study Physician" reviewing the EAE report, signing the EAE report with an electronic signature, and submitting the EAE report to the DAIDS RSC. If an EAE report is not completed and submitted within three reporting days of site awareness of the SUSAR, an explanation must be entered in DAERS before the report can be submitted.

DAERS also may be used to modify or update an EAE (SUSAR) report or to withdraw a SUSAR report that was submitted in error.

DAERS incorporates a report printing function that should be used to print all SUSAR reports —including modifications and updates — for filing in participant study notebooks. Automated email messages confirming submission of SUSAR reports also should be printed and filed with the print-out of the associated SUSAR report.

In the event that DAERS cannot be accessed (e.g., due to poor internet connectivity), paper-based SUSAR reporting should be used, per instructions provided in the Manual for Expedited Reporting of Adverse Events to DAIDS. Completed paper SUSAR Forms may be faxed or digitally scanned and emailed to the DAIDS RSC via email. The EAE Form and form completion instructions are available on the DAIDS RSC web site (http://rsc.tech-res.com). Contact details for submission of EAE Forms to the RSC are provided in the Manual for Expedited Reporting of Adverse Events to DAIDS.

**IMPORTANT:** Sites must submit an AE CRF to SCHARP along with any SUSAR. The following data points must be exactly the same on both the AE Log submitted to SCHARP and the EAE Report submitted to DAERS:

1. Participant ID
2. Onset Date
3. Severity of event
4. Relationship to study product
5. Adverse Event Term (Diagnosis)

It is important to remember that if the site updates any of these data points on one document that same change must be made on the other.

## 7.3. Adverse Event: Terminology

Study staff must assign a term or description to all AEs identified in HPTN 074. Whenever possible, a diagnosis should be assigned. When it is not possible to identify a single diagnosis to describe a cluster of signs and/or symptoms, each individual sign and symptom must be identified and documented as an individual AE. Additional information and tips may be found in the HPTN 074 Study Specific Training Materials. Non-Serious Adverse Events must be recorded in the source documents as per local procedures, modifying the source document table in section 7.2 as necessary, but will not be recorded in the study database.

Further tips and guidelines for assigning AE terms are as follows:

1. Use a diagnosis whenever possible.
2. Use specific medical terms whenever possible (e.g. “ulcers” instead of “sores”)
3. Use correct spelling for all terms; and,
4. 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 cancer diagnosis, include the cancer diagnosis in the AE term or description. For example: “joint pain related to rheumatoid arthritis.”

## 7.4. Adverse Event: Relationship

The site investigator is responsible for assessing the relationship between the AE and the

study agents (ART or MAT therapy). Site investigators must determine whether there is a reasonable possibility that the study agent(s) caused or contributed to a SAE. The relationship assessment, based on clinical judgment, often relies on the following:

- A temporal relationship between the event and administration of the study agent(s)
- A plausible biological mechanism for the agent(s) to cause the AE
- Another possible etiology for the AE
- Previous reports of similar AEs associated with the study agent or other agents in the same class
- Recurrence of the AE after re-challenge or resolution after de-challenge, if possible.

The terms used to assess the relationship of an event to study agent(s) are:

- Related - there is a reasonable possibility that the AE may be related to the study agent(s).
- Not Related - There is not a reasonable possibility that the AE is related to the study agent(s).

When an SAE is assessed as "not related" to study agent(s), an alternative etiology, diagnosis, or explanation for the SAE should be provided. If new information becomes available, the relationship assessment of any AE should be reviewed again and updated as required.

## 7.5. Adverse Event: Severity

Severity is not the same as seriousness. Severity is determined by the intensity of the event and is graded using the DAIDS Toxicity Table. Seriousness is based on the outcome or action associated with an event. The severity of all AEs identified in HPTN 074 must be graded on a five-point scale using the DAIDS Toxicity Table:

Grade 1 = Mild
Grade 2 = Moderate
Grade 3 = Severe
Grade 4 = Potentially life-threatening
Grade 5 = Death

The severity of all AEs identified in HPTN 074 will be graded using the DAIDS Table for Grading Adult and Pediatric Adverse Events (Toxicity Table), dated November2014 (see HPTN 074 SSP Appendix C). The DAIDS Toxicity Table can also be accessed on the DAIDS RSC web site (http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx).

Further clarifications, guidelines, and tips for grading the severity of AEs in HPTN 074 are as follows:

1. If the severity of an AE either falls into more than one grade or between grades on the Toxicity Table, assign the higher of the two grades to the AE.
2. If a single AE term is used as a unifying diagnosis to report a cluster of signs and symptoms, and the diagnosis is not specifically listed in the Toxicity Table, assign the AE the highest severity grade among each of the associated signs and symptoms.

Record the diagnosis as the AE term and record each associated sign and symptom in the AE Log Comments section.

3. Seasonal allergies should be graded according to the "Estimating Severity Grade" row of the Toxicity Table (not the "acute systemic allergic reaction" row). This section is the first one listed in the Toxicity Table on page 3.
4. If a participant reports an adverse event that is not identified in the DAIDS AE grading table, use the category "Estimating Severity Grade" located on Page 3. This category should only be used for reporting clinical events. Do not use this category for reporting laboratory results.

## 7.6. Reporting Serious Adverse Event Follow-Up and Outcome

Routine or non-serious adverse events do not need to be followed beyond the planned participation termination date. However, site clinicians must follow all SAEs including SUSARs 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. If an adverse event meets SUSAR criteria it must be reported to DAIDS in an expedited manner using the DAERS electronic reporting system.

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 an AE Log Case Report Form. In many cases, the final outcome of an AE will not be available when the AE Log is first completed and faxed to DataFax (for those AEs that are reportable in the databases). In such cases, the form should be updated when the final outcome becomes known, or when other status changes occur, and re-faxed to DataFax. Do not hold the CRF at the site in anticipation of additional information.

In some cases, a Site Investigator may determine that an SAE has "stabilized" i.e., it has not increased in intensity for a period of time. It is important to remember that an instance in which an SAE stabilizes can only be reported when submitting an update to an SAE (SUSAR in this case) that is submitted to DAERS. When reporting an SAE on an Adverse Event CRF to be sent to SCHARP, sites must only use one of the following options:

- Continuing
- Resolved
- Increased in severity or frequency
- Continuing at end of study

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 an AE Log CRF, it must be reported as a new SAE, at the increased severity or frequency, on a new AE Log. 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 "continuing". 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 "Increased in Severity/Frequency" 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 'continuing' until it returns to baseline or resolves completely.***

**DAERS:**
If an SAE (i.e., a SUSAR) previously reported in an expedited manner increases in severity to a higher grade than previously reported, the existing EAE form must be updated using DAERS (a new form is not completed). However, as noted above, an increase in severity must be reported as a new SAE to the SDMC (as described in the previous paragraph).

Study staff are required to report the outcome of EAEs to the DAIDS RSC routinely until the case is resolved or becomes stable. Exceptions to this rule involve the following cases:

- Requests from DAIDS for additional information
- A change in the relationship between the SAE and study product by the study physician
- Additional significant information that becomes available for a previously reported SAE (this is particularly important for new information addressing cause of death if the initial assignment was "pending")

Any change in the assessment of the severity grade of the SAE will also require an update to the existing EAE report in DAERS.

## 7.7. Reporting Adverse Events at a Final Study Visit

Sites should review with participants any remaining AEs, SAEs/SUSARs marked "continuing" in an attempt to determine whether they have resolved since the last visit. Routine Adverse Events do not need to be followed past the final study visit. However, SAE and SUSAR 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 AE Log must be completed and faxed prior to or at the same time the termination form is sent to SCHARP. New AE Log pages should be completed as follows:

- The **"Status/Outcome" field** is marked as "ongoing" 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 the AE 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 "Continuing at end of study" and the SAE Log should be re-faxed to DataFax.

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

## 7.8. Reporting Recurrent Adverse Events

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

If an SAE 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.

## 7.9. Social Harms

In addition to medical AEs, participants in HPTN 074 may experience social harms — non-medical adverse consequences — as a result of their participation in the study or screening for the study. For example, participants could experience difficulties in their personal relationships with partners, family members, and friends. They also could experience stigma or discrimination from family members and members of their community. In the event that any social harm occur, 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 harm must be recorded on the Social Impact Log (SIL-1) and faxed to SCHARP DataFax.

At every visit, the Social Impact Log will be used to probe for interpersonal, legal, housing and healthcare problems or life improvements that have occurred *as a result of study participation*. In addition to responding to this standardized assessment at the specified visits above, participants also may spontaneously report study-related issues and problems to study staff at any study visit.

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.

As with medical AEs, follow all negative social impacts to resolution (until they no longer exist) or stabilization (they exist but at a manageable level) or until study exit. 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 harm is associated with an AE, report the AE on an AE Log. If the social harm is associated with a SUSAR that meets criteria for expedited reporting to the DAIDS RSC, report it on an EAE form. Also report the issue or problem to all IRBs/ECs responsible for oversight of HPTN 074, if required per IRB/EC guidelines.

As is the case for medical AEs, data collected on social harms will be monitored by the HPTN 074 SMC.

The following are suggested strategies for responding to social harms that may be adapted and tailored to best meet participant needs at each site:

- When first responding to an issue or problem, actively listen to the participant's description of the problem and ask questions to elicit as much detail as possible about the problem, including the participant's perception of the severity of the problem. Record all pertinent details on the Social Impact Log CRF (SIL-1). If the issue or problem meets criteria for expedited reporting to the DAIDS Safety Office, report it as described in SSP Section 7.6. Also report the issue or problem to all responsible IRBs/ECs, if required per IRB/EC guidelines.
- Ask the participant to articulate his/her thoughts on what can/should be done to address the problem, including what she/he would like study staff to do in response to the problem (if anything).
- Discuss with the participant any additional or alternative strategies to address the problem and collaborate with him/her to develop a plan to try to address the problem.
- Take all possible action to try to address the problem, per the plan agreed upon with the participant. Document all action taken, and outcomes thereof, on the Social Impact Log (SIL-1).
- Provide referrals as needed/appropriate to other organizations, agencies, and service providers that may be able to help address the problem.

## 7.10 Suicide Ideation

Social Impact Assessment (SIA-1) CRF questions 2e or 2f or Systems Navigator CRF (SNE-2) question #8 may indicate that the participant has thoughts of self-harm or suicide. Participants or their supporters may also indicate such thoughts or feelings at any time. In such cases, the study staff member should follow the assessment for suicide risk described below.

If a participant is determined to be a Moderate or High suicide risk after assessing for suicide risk (below), or otherwise reports active suicidal ideation or a suicide attempt:

- The study staff member should personally escort the participant to an emergency room or other appropriate facility

- The clinician evaluates the participant and confirms or modifies the diagnosis (see below worksheets/questions)
- If a referral to more specialized services is necessary, arrangements for such a referral should be made accordingly
- The study staff member will inform the Investigator of Record after ensuring that the participant is at the appropriate facility

### 7.10.1 Assessment for Suicide Risk

**I. Response to Social Impact Assessment (SIA-1) CRF questions 2e or 2f or Systems Navigator CRF (SNE-2) indicates potential thoughts on suicide/ self-harm (OR other statements made by participants or their support persons)**

Some participants may reveal suicidal thinking during their participation in the study. It is essential to immediately assess all such patients to determine whether they are a very low, low, moderate, high, or acute suicide risk and to act accordingly.

If site staff suspect that a participant is thinking of hurting him or herself, start off by asking "In the last two weeks, how often have you had thoughts you would be better off dead or of hurting yourself in some way." The four possible choices to ask the participant are "not at all; "several days;" "more than half the days;" and "almost every day" (see below part II).

Any positive response to this question (other than "not at all") suggests the presence of either ***passive suicidal thoughts*** (i.e. "…thoughts you would be better off dead…") or ***active suicidal thoughts*** ("thoughts…of hurting yourself in some way"). There is no way to tell the difference between active and passive suicidal thinking without further questioning. Participants may also reveal suicidal thoughts at other points during a planned or unplanned (interim) study visit.

For all such patients, probe via the following questions *(site may create a source document form based on this information):*

**II. Differentiation of passive from active suicidal thoughts**

***"In the last two weeks, have you had any thoughts of hurting yourself in some way?"***

1 – not at all 2 - several days 3 - more than half the days 4 - nearly every day

**{If patient responds "not at all" to this question, the patient denies active suicidal thoughts. He or she is considered "very low or no risk" and the suicide risk assessment may be concluded at this point.**

**III. Care management assessment of patients who demonstrate some evidence of *active* suicidal thinking.**

Some patients will admit to having had some thoughts of hurting themselves in the last two weeks, with one of the following responses: "several days," "more than half the days," or "almost every day" to the preceding question. All these patients must be asked the following 5 questions.

1. *"Since your last study visit, have you made any plans or considered a method that you might use to harm yourself"* (circle one)

YES NO

2. *"Since your last study visit, have you attempted to harm yourself?"* (circle one)

YES NO

3. *"There's a big difference between having a thought and acting on a thought. Do you think you might actually make an attempt to hurt yourself in the near future?"* (circle one)

YES NO

4. *"Since your last study visit, have you told anyone that you were going to commit suicide, or threatened that you might do it?"* (circle one)

YES NO

5. *"Do you think there is any risk that you might hurt yourself before your next study visit?* (circle one)

YES NO

**Note regarding a positive ("yes") response to Question 5:**
**"Active suicide thoughts: acute risk"**

If participant's response is "yes" to question 5, the participant will be considered a high suicide risk. If the participant presents an obvious acute risk, stay with the participant or do your best to ensure that he or she goes immediately to an emergency room or other appropriate facility. Inform the Investigator of Record or designee immediately. **This is a Serious Adverse Event. Follow the guidelines in the protocol and SSP Manual for SAEs.**

**Note regarding any positive ("yes") response to Questions 1-4:**
**"Active suicidal thoughts: Moderate to High Risk"**

If the participant has any positive answer ("yes") to questions 1-4, this information must be communicated to appropriate staff (IoR or designee) immediately. **This is a Serious Adverse Event. Follow the guidelines in the protocol and SSP Manual for SAEs.**

**Note regarding all negative ("no") responses to Questions 1-4:**
**"Active suicidal thoughts: Low Risk"**

If the participant answers "no" to questions 1-5, the participant will be considered a low suicide risk and this information should also be communicated to the Investigator of Record or designee.

**In all cases of "active suicidal ideation," clinical decisions regarding continuation in the study must be made by a study physician (Investigator).**

### 7.10.2 Source Documentation: Suicide Risk Assessment Form

**I. Complete this form with all participants who reveal suicidal thinking during their participation in the study.**

Refer to the SOP for Adverse Events and information on the Assessment for Suicide Risk for guidance in completing this form.

Date (DD/MMM/YYYY) _____ / _____ /

Participant Study ID _____

**II. Differentiation of passive from active suicidal thoughts**

***"In the last two weeks, have you had any thoughts of hurting yourself in some way?"***

1 – not at all 2 - several days 3 - more than half the days 4 - nearly every day

**If "NOT AT ALL": Very low risk (passive suicidal thoughts only). Skip to Section IV.**

**OTHERWISE: Active suicidal thoughts. Continue with Section III.**

**III. Assessment of patients who demonstrate some evidence of *active* suicidal thinking (any "Yes" answer on questions 1-5 will mean that you should report an SAE).**

1. *"In the past month, have you made any plans or considered a method that you might use to harm yourself"* (circle one)

YES NO

(If yes, ask, "*Please be specific about these plans or methods you have considered."*)

2. *"Have you ever attempted to harm*

*yourself?"* (circle one)

YES NO

(If yes, ask, "*When was this? What happened*?")

3. "*There's a big difference between having a thought and acting on a thought. Do you think you might actually make an attempt to hurt yourself in the near future?"* (circle one)

YES NO

(If yes, ask, "*Can you be specific about how you might do this*?")

4. *"In the past month have you told anyone that you were going to commit suicide, or threatened that you might do it?"* (circle one)

YES NO

(If yes, ask, *"Who have you told and what have you said to them?*")

5. *"Do you think there is any risk that you might hurt yourself before your next study visit?* (circle one)

YES NO

(If yes, ask, *"What do you think you might do?"*)

**If "YES" to Question 5: Acute (High) Suicide Risk (complete SCHARP AE form as this is an SAE); report to Investigator of Record (IoR)**

**Otherwise, if "YES" to any of Questions 1-4: Moderate to High Suicide Risk (complete SCHARP AE form as this is an SAE); report to IoR**

**If "NO" to ALL of Questions 1-5: Low Suicide Risk**

**IV. Summary of risk assessment. Check one.**

__ Passive (very low) __ Moderate to high __ Acute

**If Moderate/High or Acute Risk→ Escort patient to clinician or referral clinic immediately (this is a Serious Adverse Event).**

**If Passive or Low→ Continue with questionnaire. Include referral letter in chart and send patient to schedule appointment for appropriate care and/or counseling after finishing interview.**

Form completed by:

Name Signature

Date:

## 7.11 Safety Monitoring, Review, and Oversight

Please refer to Section 6 of the HPTN 074 protocol and Sections 14 and 15 of the HPTN Manual of Operations for a complete description of the participant safety monitoring procedures in place for HPTN 074, as well as the DAIDS Toxicity Table. Also refer to Section 11 of this manual for a description of the reports prepared by the HPTN SDMC in support of HPTN 074 safety monitoring procedures.

Participant safety is of paramount importance in HPTN 074. Primary safety monitoring and

safeguarding of individual study participants is the responsibility of study staff, under the direction of the IoR. The IoR and designated study staff also are responsible for submitting case report forms to the HPTN SDMC and EAE reports to the DAIDS RSC, such that relevant safety data are available in a timely manner for other study-specific safety monitoring procedures, as follows:

- Clinical Affairs staff at the HPTN SDMC will review SAE reports received at the SDMC and apply clinical data quality control notes (queries) to data requiring confirmation, clarification, or further follow-up by site staff. These clinical queries will be sent to site staff for additional information or resolution on an ongoing basis throughout the period of study implementation.
- The DAIDS RSC, DAIDS RAB Safety Specialist, and DAIDS PSB Medical Officers will review all EAE Forms received for HPTN 074 and follow up on these reports with site staff and the HPTN 074 Protocol Team.
- The HPTN 074 Clinical Management Committee (CMC) has been set up as a sub-group of the Protocol Team to answer any questions that may arise in the management of study participants. For any questions please contact *074cmc@hptn.org*
- The HPTN Study Monitoring Committee (SMC) also will periodically review HPTN 074 safety data with a focus on SAEs and Social Harms.

### 7.12 Clinical Management of Pregnancy

Participants who identify as pregnant, either index participants or network injection partners, will remain in the study. For HIV-infected pregnant women, ART will be managed according to national guidelines for prevention of mother-to-child transmission of HIV and treatment of the mother's HIV infection. No data on pregnancy or pregnancy outcomes will be submitted to the study database.

### 7.13 Deaths

As noted in Section 7.2.2 above, all deaths are considered SAEs, and could be a SUSAR if unexpected and related to antiretrovirals or substitution treatment. For all deaths, as much information should be collected as possible on the background and cause(s). Use the Verbal Autopsy guide below for source documentation. Please alert 074cmc@hptn.org that:

- Death has occurred
- Cause (if known)
- Comment whether related to ART or OST
- PTID

In addition, submit the necessary forms for SAE (DataFax form to SCHARP) and SUSAR (DAIDS ES) IF APPLICABLE/RELATED to SU and/or OST and unexpected according to the respective guidelines. Do not submit participant names or any identifying information to the 074cmc@hptn.org email alias list.

### 7.13.1 Verbal Autopsy Form (site documentation not to be sent to CMC or SCHARP)

# HPTN 074 Verbal Autopsy

**Information on the Deceased**
**Name**

| |
|---|
| |

**PTID**

| |
|---|
| |

**Date of Death**

| |
|---|
| |

**Where did the death occur?**
☐ Hospital
☐ Other health facility
☐ Home
☐ On route to hospital or facility
☐ Work
☐ Shooting Gallery or Injection House
☐ Other

**Did a health care worker tell you the cause of death?**
☐ Yes
☐ No

**If yes, what was the cause of death?** (Complete box below)

| |
|---|
| |

**If not, what do you think was the cause of death?**
☐ HIV related
☐ HIV medicine related
☐ Methadone (or buprenorphine) treatment related

☐ Drug overdose
☐ Accident

☐ Violence
☐ Other (complete box below)

**Death registration number/certificate** (if available)

**Name of contact** (person communicated with regarding the death)

**What is the contact's relationship to the deceased?**

☐ Parent
☐ Child
☐ Other family member
☐ Friend
☐ Health worker
☐ Public official
☐ Another relationship

**Name/ Signature of staff interviewer**

**Date of interview**

**Optional open narrative**