

Section 12 Adverse Event Reporting and Safety Monitoring

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Section 12 Adverse Event Reporting and Safety Monitoring

This section presents information related to adverse event (AE) reporting and participant safety monitoring in HPTN 058. Additional information on completion of adverse experience case report forms (CRFs) is included in Section 7 of this SSP, and additional details on the reporting of AEs that meet the criteria for expedited reporting to DAIDS are included in the Manual for Expedited Reporting of Adverse Events to DAIDS, dated January 2010, which is included as Appendix E in this SSP Manual and available at: http://rsc.tech-res.com/Document/safetyandpharmacovigilance/Manual_for_Expedited_Reporting_AEs_to_DAI DS_v2.pdf.

12.1 Definitions and General Reporting Guidance

Table 12-1 below and Appendix E of this SSP manual outline the documentation requirements and time frames for reporting of non-serious and serious AEs for HPTN 058. All AEs will be documented only for the first 52 weeks of follow-up for participants in both study arms (from study enrollment until the participant completes 52 weeks of follow-up or is terminated from study participation for any reason prior to 52 weeks of follow-up). Non-serious AEs will be recorded in the source documents through Week 52. They will only be recorded after week 52 if the study staff are made aware of them (staff are not expected to inquire for routine AEs after Week 52 as there is no physical examination conducted). Only those AEs deemed as serious will be reported to DAIDS via the DAIDS Adverse Event Reporting System (DAERS). After Week 52, only those AEs that meet the definition for Suspected, Unexpected Serious Adverse Events (SUSARs) that staff become aware of on a passive basis will be reported.

12.1.1 Adverse Events (AEs)

Adverse events are defined as any untoward medical occurrence in a clinical research participant administered an investigational product and which may or may not 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 (ICH E6).

For HPTN 058, any medical occurrence that occurs in a participant *after randomization* is considered an adverse event (AE), regardless of the study group to which the participant is assigned. All AEs that occur between randomization and participants' 52 weeks of follow-up must be recorded in the study source documentation, regardless of seriousness, severity or relatedness. This includes AEs reported by the participant and AEs identified through study assessments. The severity of all clinical and laboratory AEs must be graded according to the standard DAIDS Toxicity Table (included in Appendix D). All SAEs and SUSARs are to be recorded on the Adverse Experience DataFax Log.

As stated in the study protocol and above, any medical conditions, problems, signs, symptoms, and findings occurring prior to randomization are to be reported as *pre-existing conditions*. Such conditions should be documented and reported on the Pre-Existing Conditions CRF (see Appendix F). If a pre-existing condition worsens post-randomization (frequency increases and/or severity grade increases), it should be documented as an adverse event.

12.1.2 Serious Adverse Events (SAEs)

The ICH guidance, “Clinical Safety Data Management: Definitions and Standards for Expedited Reporting,” (ICH E2A) defines a **serious adverse event (SAE)** as any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect, or
- 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.

As stated above, SAEs are reported only through Week 52 (the protocol dosing period). SAEs are a subset of all AEs. For each AE identified in HPTN 058, an authorized site investigator must determine whether the AE meets the definition of an SAE. If unsure about whether to report an event as an SAE, contact the CORE Protocol Specialist and SDMC Project Manager who will consult with others as appropriate. Serious adverse events – regardless of relatedness – will be recorded on the Adverse Experience Log DataFax form for all participants through week 52 of participant follow-up.

For purposes of this study, inpatient hospital/medical facility admission for drug addiction treatment or rehabilitation will NOT be considered an SAE.

12.1.3 Suspected Unexpected Serious Adverse Events

An SAE with onset after Week 52 (end of the dosing period) will be reported ONLY if the SAE fulfills the following criteria:

- **Related.** A reasonable possibility that the AE may be related to the study agent(s) and
- **Unexpected.** The nature or severity (intensity) is not consistent with the applicable agent information (Investigator’s Brochure, package insert, or summary of agent characteristics)

12.2 Expedited Reporting To DAIDS

As stated in section 12.1, non-serious AEs will be recorded in the source documents through Week 52. They will only be recorded after week 52 if the study staff are made aware of them (staff are not expected to inquire for routine AEs after Week 52 as there is no physical examination conducted). Only those AEs deemed as serious will be reported to DAIDS via the DAIDS Adverse Event Reporting System (DAERS). After Week 52, only those AEs that meet the definition for SUSARs that staff become aware of on a passive basis will be reported.

12.2.1 Electronic Transmission of Adverse Events that Require Expedited Reporting

All information should be submitted through the DAIDS Adverse Experience Reporting System (DAERS).

If a clinical research site has difficulty accessing the DAERS system at the time an SAE must be reported, the DAIDS Expedited Adverse Event Reporting Form (EAE Form) should be used. This form can be found at the website for the DAIDS Safety Office at <http://rcc.tech-res.com>. All information requested on the EAE Form must be provided and the form faxed or e-mailed as an attachment to the DAIDS Safety Office. Contact information for the DAIDS Safety Office is provided below.

Website:	http://rcc.tech-res.com
Office Phone*:	1-800-537-9979 (U.S. only) or +1-301-897-1709
Office Fax*:	1-800-275-7619 (U.S. only) or +1-301-897-1710
Office Email:	RCC_SafetyOffice@tech-res.com
Office Hours:	Monday through Friday, 8:30 AM to 5:00 PM (U.S. Eastern Time)
Mailing Address:	DAIDS Safety Office 6500 Rock Spring Drive Suite 650 Bethesda, MD 20817

12.2.2 Timeframe for Expedited Adverse Event Reporting to DAIDS

The timeframe for expedited reporting of individual AEs begins when the clinical research site recognizes that **an event fulfills the protocol-defined criteria for expedited reporting to DAIDS**. Clinical research sites must submit AEs to the DAIDS Safety Office immediately, **and no later than 3 reporting days** (Monday through Friday) after the site becomes aware of an event that meets protocol-defined criteria for expedited reporting.

12.2.3 Site Investigator Assessment and Signature

A site physician investigator or sub-investigator listed on the Form FDA 1572 must review and verify the completed EAE form or DAERS report for accuracy and completeness and then sign the report. This physician also makes the site's final assessment of the relationship between the study agent(s) and the SAE.

In the rare event that such physician(s) are not available for signature, sites may submit the AE requiring expedited reporting without the signature to meet reporting time frame requirements. However, the completed EAE report (whether the EAE form or DAERS report) with signature and any necessary corrections or additions must be submitted within the next 3 reporting days (see definition in Appendix D). The IoR or designee is responsible for designating at least one other physician at the site who can perform the assessment and signature so as to provide uninterrupted coverage of monitoring of AEs that will require expedited reporting.

12.3 Adverse Event Relationship Assessment

For each AE identified in HPTN 058, an authorized site investigator must assess the relationship of the AE to study agents. 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 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, and
- Recurrence of the AE after re-challenge or resolution after de-challenge, if applicable.

The terms used to assess the relationship of an event to study agent 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).

Table 12-1 HPTN 058 Adverse Event Reporting and Additional Documentation Requirements*

	ADVERSE EVENT	RELATIONSHIP TO STUDY PRODUCT	Record event and grade in primary source documents	EAE FORM (to DAIDS RSC within 3 reporting days of site awareness)
Serious Adverse Events	Results in Death	Regardless of relationship	YES	YES
	Is life-threatening ¹	Regardless of relationship	YES	YES
	Requires inpatient hospitalization or prolongation of existing hospitalization ²	Regardless of relationship	YES	YES
	Results in persistent or significant disability or incapacity	Regardless of relationship	YES	YES
	Is a congenital anomaly/birth defect ³	Regardless of relationship	YES	YES
	Is an important medical event (may jeopardize the patient or may require intervention to prevent one of the other outcomes above) ⁴	Regardless of relationship	YES	YES
Non-Serious Adverse Events	All non-serious AEs	Regardless of relationship	YES	NO

NOTE: All AEs must be documented in the participant’s source record, regardless of seriousness, severity or relatedness. AEs will only be documented and reported to the SDMC/DAIDS as appropriate for participants in both study arms through Week 52 of follow-up. After week 52, SUSAR reporting is in effect (<http://rsc.tech-res.com/safetyandpharmacovigilance/>).

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 agents(s) and has not increased in severity or frequency as judged by the clinical investigator. In addition inpatient hospital/medical facility admission for drug addiction treatment or rehabilitation will not be considered a serious adverse event. (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. Examples are intensive treatment in the emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; etc.

12.4 Adverse Event Severity (Intensity) Grading

Study staff is required to use the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table) to determine the severity of the AE. All events reported to DAIDS in an expedited fashion must be graded for severity.

The DAIDS AE Grading Table is located on the DAIDS Safety Office website at http://rsc.tech-res.com/Document/safetyandpharmacovigilance/Table_for_Grading_Severity_of_Adult_Pediatric_Adverse_Events.pdf. The severity of the parameters listed in the table ranges from grade 1 (mild) to grade 4 (potentially life-threatening). Death is defined as grade 5 severity.

The term severity is described as the intensity grade or level for a specific event, i.e., mild, moderate, severe, or life-threatening. Importantly, severity is *not* the same as seriousness, which is based on participant/event *outcome or action* criteria usually associated with events that pose a threat to a subject's life or functioning (ICH E2A).

There are five severity grades that can be assigned to AEs, which are defined as follows:

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

NOTE: For the grading of clinical AEs not specified in the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events or in the study protocol, a guide for estimating severity is included on page 3 of the DAIDS grading table.

If the severity of an AE could fall under either one of two grades (e.g., the severity could be a grade 2 or a grade 3), the higher of the two grades should be assigned.

12.5 Adverse Event Terminology

Both the Adverse Experience Log CRF and the DAIDS EAE Form require site staff to assign a term or description to each AE. Whenever possible, a diagnosis should be reported, rather than a cluster of signs and/or symptoms. 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 reported as an individual AE. When relevant, an anatomical location should be included in the term or description. The use of abbreviations other than standard laboratory test results is to be avoided.

12.6 Adverse Events Associated with BUP/NX

BUP/NX (Suboxone) received US FDA approval following extensive study into its safety and efficacy. The following table is adapted from the BUP/NX package insert of September 2006 and illustrates the types of AEs that were reported in a comparative trial. This table may be of assistance to HPTN 058 clinicians assessing potential AEs.

Table 12-2 Adverse events ($\geq 5\%$) by body system and treatment group in 4-week study

Adverse Event	N (%)	N (%)	N (%)
	BUP/NX: 16 mg/day N=107	BUP: 16 mg/day N=103	Placebo N=107
Asthenia	7 (6.5%)	5 (4.9%)	7 (6.5%)
Chills	8 (7.5%)	8 (7.8%)	8 (7.5%)
Constipation	13 (12.1%)	8 (7.8%)	3 (2.8%)
Diarrhea	4 (3.7%)	5 (4.9%)	16 (15.0%)
Headache	39 (36.4%)	30 (29.1%)	24 (22.4%)
Infection	6 (5.6%)	12 (11.7%)	7 (6.5%)
Insomnia	15 (14.0%)	22 (21.4%)	17 (15.9%)
Nausea	16 (15.0%)	14 (13.6%)	12 (11.2%)
Pain	24 (22.4%)	19 (18.4%)	20 (18.7%)
Pain: Abdomen	12 (11.2%)	12 (11.7%)	7 (6.5%)
Pain: Back	4 (3.7%)	8 (7.8%)	12 (11.2%)
Rhinitis	5 (4.7%)	10 (9.7%)	14 (13.1%)
Sweating	15 (14.0%)	13 (12.6%)	11 (10.3%)
Vasodilation	10 (9.3%)	4 (3.9%)	7 (6.5%)
Vomiting	8 (7.5%)	8 (7.8%)	5 (4.7%)
Withdrawal Syndrome	27 (25.2%)	19 (18.4%)	40 (37.4%)

12.7 Lab Abnormalities

The Investigator or designee should carefully review all laboratory abnormalities relevant to the participant's health available since the last visit to identify any adverse events or health problems. Documentation of this review is required by initialing and dating each page of lab results.

The severity of all lab abnormalities will be graded and recorded in the source documentation. Results of protocol-specified local laboratory results will also be reported on the Local Laboratory Results CRF for entry into the study database. Lab abnormalities that are serious according to the definition of SAE provided in Section 12.1.2 of this manual but are not attributable to/symptomatic of a clinical diagnosis will be reported on the Adverse Experience Log CRF and, if required based on the reporting criteria, also on the DAIDS EAE form. In the case of a lab abnormality that is associated with a clinical diagnosis, the clinical diagnosis is to be reported as the AE. If a lab abnormality is reported as an AE (in the absence of a clinical diagnosis), the type of assay performed and the direction of the abnormality should be reported (e.g., decreased platelets, elevated ALT).

The primary lab abnormalities that might be associated with the use of BUP/NX will be related to the liver or biliary tract since the drugs are metabolized through the liver and because opioids in general have been shown to increase intracholedochal pressure. As noted in the package insert, the liver abnormalities are often explained by the presence of pre-existing conditions, such as

hepatic damage due to chronic drug use, infection with hepatitis B and/or C virus, or concomitant use of alcohol and other hepatotoxic drugs. BUP/NX should be discontinued in any acute case of hepatitis involving jaundice or an elevation of the ALT > 10 times the upper limit of normal. Since there will be baseline laboratory measurements of all HPTN 058 participants and close follow-up monitoring, clinicians should have better context for interpreting laboratory abnormalities encountered in HPTN 058 in conjunction with the Toxicity Table included in Appendix D.

12.8 Follow-up Information on Adverse Events

Site clinicians are responsible for closely monitoring and following all AEs until resolved OR stabilized and for documenting this in the participant's source records. In addition to performing protocol-specified assessments at each follow-up visit, the study clinician must review all previously reported ongoing AEs (that are either not resolved or not stabilized) to evaluate the current status. This applies to all events regardless of seriousness.

To assist study sites in following unresolved SAEs, the HPTN SDMC will generate listings of such SAEs throughout the period of study implementation (see also Section 13 of this manual). In some cases the final outcome of an SAE will not be available when the Adverse Experience Log CRF is first completed and faxed to the SDMC. In such cases, a new AE Log CRF is NOT required when submitting follow-up information for a previously reported SAE (unless the SAE increases in severity grade). The existing CRF should be updated and re-faxed to the SDMC.

If an SAE increases in severity or frequency (worsens) after it has been reported on an Adverse Experience Log CRF, it must be reported as a new SAE at the increased severity or frequency on a new AE Log CRF. In this case, the outcome of the first SAE will be documented as "severity/frequency increased." The outcome date of the first SAE and the onset date of the new (worsened) AE will both be the date upon which the severity or frequency increased.

Staff members are not required to report the outcome of EAEs to the DAIDS Safety Office, unless outcome information is specifically requested by DAIDS. However, if an EAE increases in severity to a higher grade than previously reported, it must be reported to the DAIDS Safety Office as a new EAE on a new EAE Form.

EAE follow-up information also must be reported to the DAIDS Safety Office under the following circumstances:

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

In these circumstances, the required follow-up information should be reported on a new EAE Form as a Follow-Up Report.

12.9 Reporting Recurrent Adverse Events

For an event previously reported to the DAIDS Safety Office, if the AE fully resolved but then recurs with an outcome meeting expedited reporting criteria, the AE must be reported as a new initial report to the DAIDS Safety Office.

12.10 Social Harms

In addition to medical AEs, participants in HPTN 058 may experience social harms — 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. They also could experience stigma or discrimination from family members and members of their community. In the event that any social harm occurs, study staff should fully document the issues or problems and make every effort to facilitate their resolution as described in this section.

At Weeks 1, 2, 3, and 4 for the Safety Phase and Weeks 26, 52, 78, 104, 130, and 156 for the Full Study, the Social Impact Assessment (SIA-1) form 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.

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 12.1.3 above. 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).
- As with medical AEs, follow all problems to resolution or stabilization.
- Provide referrals as needed/appropriate to other organizations, agencies, and service providers that may be able to help address the problem. Update referral lists at least every six months (see protocol Appendix IV).
- Consult the HPTN 058 Protocol Safety Review Team (PSRT) for further guidance as needed.

As with medical AEs, data collected on social harms will be monitored by the HPTN 058 PSRT and the NIAID Data and Safety Monitoring Board (DSMB), as described below.

12.11 HPTN 058 Safety Review and Oversight

Participant safety is of critical importance in HPTN 058. A three-tiered safety review process will be employed during the conduct of the trial.

The first tier includes close monitoring of all trial participants by on-site study staff under the direction of the site Investigator of Record, expedited NIH Medical Officer review of EAE Reports submitted to the DAIDS Safety Office from the sites, and the ongoing review of clinical and laboratory safety data by clinical staff of the HPTN SDMC.

The second tier includes frequent Protocol Safety Review Team (PSRT) review of safety data reports prepared for HPTN 058 by the SDMC. The PSRT will meet routinely via conference call to discuss the accumulating study safety data and any potential safety concerns. Please refer to the description of the roles and responsibilities of the PSRT at the end of this section.

The third tier of the safety review process is the periodic review by the NIAID DSMB. Through this three tiered system, both individual and aggregate safety data are reviewed and evaluated on an ongoing basis by qualified personnel through a consistent and methodical process.

Prior to each DSMB review and independently, the HPTN Study Monitoring Committee will also periodically review trial data with a focus on performance indicators such as accrual, retention and intervention adherence compared with targets. While site staff are not typically directly involved with these reviews, it is important to be aware that these groups may make decisions or recommendations to the sponsor (DAIDS) or the HPTN leadership that affect the study and the sites in a significant way. These decisions are based on careful review of the study data and consideration of participant safety and study viability.

12.12 Toxicity and Dosing Management Procedures

Participant safety is of utmost concern. Management of adverse events should be according to the best clinical practice available and the judgment of the site Investigator or designated clinician and reported as described in SSP Table 12.1. Study clinicians should be fully aware of the issues surrounding management of study drug dosing (holding, restarting or permanently discontinuing study drug) relative to the occurrence of toxicities or because of events that necessitate dosing modifications. Site staff should seek the advice and counsel of the PSRT on these matters.

The following events may occur with the use of BUP/NX and will require contact with the PSRT regarding the dosing of participants:

- Evidence of an allergic reaction to BUP/NX (such as rash, hives or pruritus) will lead to the discontinuation of BUP/NX.
- Suspicion or proof of pregnancy: BUP/NX is a Pregnancy Category C drug and as such will be discontinued in any pregnant HPTN 058 participant (see SSP section 5.6.2).
- Initiating treatment with a CYP3A4 inhibitor such as an azole antifungal drug (e.g., ketokonazole) or macrolide antibiotics (e.g., erythromycin) may require a dose reduction of BUP/NX.
- Initiating treatment with a CYP3A4 inducers (such as phenobarbital, carbamazepine, phenytoin or rifampicin) may require a dose increase of BUP/NX.
- Respiratory or CNS depression: both respiratory and CNS depression may indicate the concomitant use of benzodiazepines or other depressants, including alcohol. The primary goal of the site staff will be to stabilize the patient during an acute event. If the participant requires concomitant treatment with a depressant, dose reduction of the BUP/NX and/or the depressant should be considered.

One of the key roles of the PSRT is to consider and rapidly respond to queries from on-site study staff regarding study drug dosing resumption or discontinuation following occurrence of toxicities as outlined in the protocol. Queries and communications with the PSRT should be sent via email to 058PSRT@hptn.org. A standard format for site queries will be used to elicit sufficient detail to allow the PSRT to make an informed determination. See the PSRT Query Form attached to the end of this section.

12.13 Safety Distributions from DAIDS

As noted in Section 1 of this manual, study sites will receive product- and safety-related information throughout the period of study implementation. This information will be distributed by DAIDS, through its Regulatory Compliance Center and/or the HPTN Coordinating and Operations Center, and may include:

- Updated Investigator's Brochures and Package Inserts
- IND Safety Reports
- DSMB review summaries
- Other safety memoranda and updates

Each distribution will include a cover memo providing instructions on how the document is to be handled. In all cases, a copy of the distribution must be filed in the study site Essential Document files for HPTN 058. Study staff responsible for clinical oversight of study participants should be made aware of any newly available safety information. In many cases, the distribution will need to be submitted to all study site IRBs/ECs. Safety distributions do not require IRB/EC approval; however acknowledgement of receipt is desirable. Submission letters/memos for IRB/EC submissions should specify the name and date of all documents submitted.

HPTN 058 Protocol Safety Review Team Plan

Introduction

A three-tiered safety review process will be employed during the conduct of HPTN 058. The first tier includes close monitoring of all trial participants by on-site study staff, rapid NIH Medical Officer review of adverse event reports submitted to the DAIDS Regulatory Compliance Center (RCC) from the sites in an expedited manner (EAEs), and the ongoing review of safety data by clinical staff of the HPTN Statistical and Data Management Center (SDMC). The second tier includes frequent routine review of safety data by a Protocol Safety Review Team (PSRT). The role of the PSRT is the primary subject of this document and is outlined below. The third tier of the safety review process is the periodic review by the NIAID Data and Safety Monitoring Board (DSMB). Through this three-tiered system, both individual and aggregate safety data are reviewed and evaluated on an ongoing basis by qualified personnel through a consistent and methodical process.

Roles and Responsibilities of the PSRT

Per the HPTN 058 protocol, the roles and responsibilities of the HPTN 058 Protocol Safety Review Team (PSRT) are to:

1. Conduct regular reviews of standardized study safety data reports (protocol Section 6.1). Once the SDMC begins receiving study follow-up safety data, the PSRT will convene via conference calls approximately every two weeks. The frequency of calls may be adjusted throughout the period of study implementation as agreed upon by the PSRT (for example, calls may be less frequent after the Safety or Dosing Phase of the study is completed).
2. Respond to Investigator queries regarding withholding, adjusting, or resuming study drug (protocol Section 4.4.1). The protocol specifies a limited number of situations in which study participants may have study drug dosage adjusted or withheld with appropriate dose tapering pending further evaluation. Decisions regarding resumption of study drug will be made in consultation with the PSRT as required. These situations are:
 - (a) Intoxication with any drug at the time of the dispensing visit
 - (b) In need of temporary use of medication that may interfere with BUP/NX
 - (c) Serious adverse event not related to withdrawal that is potentially related to the study drug
 - (d) Continued dosing or dosing at the current level is temporarily contraindicated for any reason (e.g. elevated ALT)
3. Respond to Investigator queries regarding permanent discontinuation of study drug (protocol section 4.4.2). Decisions regarding permanent discontinuation of study drug should be made in consultation with the PSRT. Study drug will be permanently discontinued with appropriate dose tapering in participants who meet one or more of the following criteria:
 - a) Pregnant
 - b) Continued dosing is contraindicated for safety reasons (for example, participant has reported frequent benzodiazepine injection)
 - c) Enrollment in another study that will interfere with full participation in or interpretation of HPTN 058
 - d) Evidence of hypersensitivity to BUP/NX

4. Respond to Investigator queries regarding general AE management and reporting.
5. Respond to Investigator queries regarding study eligibility determination.
6. Respond to Investigator requests for participant withdrawal from the study (protocol Section 3.6).
7. Respond to queries from the SDMC Study Team when information is needed to guide clinical data management and safety reporting. The PSRT Chair or Alternate Chair is the point person for SDMC staff queries and will consult with other PSRT members as needed.

The PSRT Chair or Alternate Chair has ultimate responsibility for providing an answer to the site within three business days following receipt of a query. All members of the PSRT are encouraged to review the information provided by the site and to offer their opinions, and ad hoc calls will be held within that time-frame, as needed. However, final responsibility for communicating a decision rests with the PSRT Chair or Alternate Chair on behalf of the PSRT. A standard format for site queries will be used to elicit sufficient detail to allow the PSRT to make an informed determination (form attached).

Site clinicians may be asked to participate in the routine or ad hoc calls to provide additional information and respond to PSRT members' questions.

Routine questions regarding protocol interpretation and implementation, and clinical management of co-morbidities will be answered as needed by CORE (FHI) Clinical Research Managers, SDMC (SCHARP) Protocol Operations Coordinators, or protocol clinicians.

As noted above, the NIAID DSMB will conduct periodic reviews of study data (at least annually). In the interim, should any safety concerns be identified by the PSRT, these will be referred to the DSMB, the HPTN Study Monitoring Committee, the US FDA, and the study drug manufacturer as appropriate.

PSRT Composition

The following individuals will serve as members of the HPTN 058 PSRT:

- Greg Lucas, JHU representative, PSRT Chair
- Apinun Aramrattana, Site Investigator of Record, Alternate Chair
- Wei Liu, Site Investigator of Record
- Liping Fu, Site Investigator of Record
- Dave Metzger, Protocol Chair
- David Burns, DAIDS Medical Officer
- Brooks Jackson, Protocol Co-Chair
- David Celentano, Protocol Co-Chair
- Yiming Shao, Protocol Co-Chair
- Deborah Donnell, Protocol Statistician
- Jack Blaine, NIDA Medical Officer and Protocol Consultant
- Yevgeny Grigoriev, SDMC Clinical Affairs Safety Associate (CASA)

Ideally all of the above-listed PSRT members will take part in routine PSRT conference calls; however a quorum of at least four members is required. The quorum must consist of:

- Either the PSRT Chair or Alternate Chair
- The DAIDS or NIDA Medical Officer (or designee)
- SDMC CASA

If a quorum is not present, the call may be deferred until the next scheduled call time unless a quorum member requests a more immediate call.

The HPTN CORE (FHI) Protocol Specialist and SDMC (SCHARP) Project Manager assigned to the protocol will also participate in and facilitate PSRT calls and reviews.

When appropriate, observers to the PSRT calls may include:

- CORE Associate Directors (ADs)
- SDMC Statistical Research Associates
- DAIDS PAB Protocol Pharmacist
- HPTN Central Lab Representatives

Routine Data Summary Reports: Content, Format and Frequency

The SDMC will generate and distribute standard safety data reports to the PSRT via e-mail 4-5 days prior to each PSRT conference call. Tabulations will be generated for all study participants combined (i.e., across all treatment groups). The following events will be included in the standard data reports regardless of relationship to study product:

- Significant clinical and laboratory events
- Adverse events reported to SDMC
- All other adverse events that meet criteria for expedited reporting to DAIDS as defined in the study protocol and the DAIDS EAE Manual
- Pregnancies and pregnancy outcomes

Reports will include summary information regarding the number and frequency of events that meet the criteria above organized by body system (using MedDRA terminology), severity, and relatedness. Individual participant profile reports will be supplied on an ad hoc basis in response to specific queries resulting from PSRT review. Each distribution will consist of one set of reports listing cumulative data and one set listing only new events reported since the last distribution.

During PSRT conference calls, the DAIDS Medical Officer will summarize any additional EAE Forms received at the DAIDS Safety Office after the cut-off date for the SDMC data summary.

PSRT Communications

An email alias (058PSRT@HPTN.org) will be used to facilitate communication with the PSRT. All safety data summary reports from the SDMC, all PSRT queries from study sites, and all query responses from the PSRT will be distributed via this alias.

HPTN 058 Protocol Safety Review Team Query Form

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Instructions: Email completed form to 058PSRT@hptn.org. IMPORTANT: Complete all required fields so the PSRT has all information needed to respond to your query. Include sufficient detail to ensure an appropriate and timely response.

Site: _____ **Query Date (dd-MMM-yy):** _____
Completed by: _____ **Email address:** _____

PTID: _____ **Participant Age (in years):** _____
Study Arm: Substitution Detoxification

Reason for query: Study drug use consultation:
 Should study drug be temporarily discontinued?
 Should study drug be permanently discontinued?
 Should study drug dose be adjusted?
 Should study drug use be resumed?
 Request for consultation on AE management
 Request to withdraw participant from the study
 Other, specify: _____

Current status of BUP/NX use:

Induction On temporary hold, as of (dd-MMM-yy): _____
 Detoxification Permanently discontinued, as of (dd-MMM-yy): _____
 Maintenance Therapy Other: _____
 Not currently receiving BUP/NX

Is this query a request for the PSRT to consult on an adverse event (AE)?

Yes → continue completing this page
 No → skip to Narrative Summary on page 2

Primary AE (diagnosis or symptom) of concern:

AE onset date (dd-MMM-yy): _____ **AE severity grade at onset:** _____

Relatedness to BUP/NX:

Definitely related
 Probably related
 Possibly related
 Probably not related
 Definitely not related

Study Drug Dosing Information:

Date of first dose (dd-MMM-yy): _____
Date of last dose (dd-MMM-yy): _____

Has AE been reported on a SCHARP AE Log? **Has AE been reported as an EAE?**

Yes Yes
 No No

Has this AE been assessed more than once?

Yes → date of most recent assessment (dd-MMM-yy): _____
 No → skip to Comments on page 2

Status of AE at most recent assessment:

Continuing, stabilized (severity grade unchanged)
 Continuing, improving → severity grade decreased to _____
 Continuing, worsening → severity grade increased to _____
 Resolved

HPTN 058 Protocol Safety Review Team Query Form
Page 2 of 2

Narrative Summary: Provide additional details relevant to this query, such as relevant past history including use of other substances, sequence of signs and symptoms, lab results, intervention and/or treatment and current status of participant. Clarify exactly what action the site is proposing:

End of Form for Site Staff. Email completed form to 058PSRT@hptn.org. If an email response is not received from the PSRT within 3 business days, re-contact the PSRT and/or the HPTN CORE (srose@fhi.org or bdye@fhi.org) for assistance.

PSRT use only — provide response to query here

PSRT Responding Member:

PSRT Response Date (dd-MMM-yy):

Query Outcome:

- Approved
- Not approved
- Not applicable

PSRT Comments: