

DATE: March 24, 2011

TO: Protocol HPTN 058 Principal Investigators, Study Coordinators and Study Staff

FROM: HPTN 058 Protocol Team:

SUBJECT: Letter of Amendment #2 to Protocol HPTN 058, Version 2.0 dated 16 September 2008 (IND # 73,797), entitled *A Phase III randomized controlled trial to evaluate the efficacy of drug treatment in prevention of HIV infection and death among opiate dependent injectors*

The following information impacts the HPTN 058 study and must be forwarded to your institutional review board (IRB)/ethics committee (EC) as soon as possible for their information and review. This must be approved by your IRB/EC before implementation.

The following information may also impact the sample informed consent. Your IRB/EC will be responsible for determining the process of informing subjects of the contents of this letter of amendment (LOA).

Upon receiving final IRB/EC and any other applicable regulatory entity (RE) approval(s) for this LOA, sites are required to submit an LOA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LOA once the DAIDS PRO verifies that all the required LOA registration documents have been received and are complete. Sites will not be able to implement this LOA until they have received an LOA registration notification from the DAIDS PRO. A copy of the DAIDS PRO LOA registration notification along with this letter and any IRB/EC correspondence should be retained in the site's regulatory files.

The purpose of this LOA is to incorporate use of Version 2.0 of the Manual for Expedited Reporting of Adverse Events to DAIDS (DAIDS EAE Manual). The following language will replace the Expedited Adverse Event Reporting section of the HPTN 058 Protocol Version 2.0 dated 16 September, 2008.

Additions are noted in **bold**. Deletions are noted via ~~strikethrough~~.

I. Protocol Section 6.2 has been revised as follows:

6.2 — Adverse Event Reporting Requirements

~~An adverse event (AE) is defined as 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.~~

A serious adverse event (SAE) is 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, or is a congenital anomaly/birth defect (April 1996 International Conference on Harmonisation (ICH), Good Clinical Practice: Consolidated Guidance, (ICH E6). Important medical events 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 outcomes listed in the definition above may also be considered to be serious (October 1994 ICH guidance (E2A), Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). For the purposes of this study, outpatient or inpatient hospital/medical facility admission for drug addiction treatment or rehabilitation will not be considered a SAE.

The expedited adverse event (EAE) reporting requirements and definitions for this study and the methods for expedited reporting of adverse events (AEs) to the DAIDS Regulatory Compliance Center (RCC) Safety Office are defined in “The Manual for Expedited Reporting of Adverse Events to DAIDS” (DAIDS EAE Manual), dated 6 May 2004. AEs that meet the criteria for expedited reporting to DAIDS must be reported on the DAIDS Expedited Adverse Event Reporting Form (EAE Reporting Form) and sent within 3 business days of site awareness to the DAIDS Safety Office. Both the DAIDS EAE Manual and the EAE Reporting Form are available on the RCC website: <http://rcc.tech-res-intl.com> and will be included in the Study Specific Procedures Manual. Contact and submission information for the DAIDS Safety Office is included in the EAE Manual, on the front page of the EAE Reporting Form (which is designed to serve as the cover page for submissions) and in the SSP Manual.

Specifically, the ‘standard’ level of reporting defined in the DAIDS EAE manual will be followed 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). Conditions and illnesses identified in participants prior to randomization will be considered pre-existing conditions and will not be reported as adverse events, unless the condition worsens after randomization (increases in severity or frequency), in which case it would be reported as an AE.

The study drug in HPTN 058 is the BUP/NX combination (Suboxone), provided for 52 weeks to participants randomized to the substitution arm and, for participants randomized to the detoxification arm, up to 18 days beginning at randomization and/or within 30 days of the six month visit; therefore it is the relationship of all AEs to this product that is to be considered in determining the reporting requirements for each AE (e.g., whether the AE must be reported in an expedited manner to DAIDS).

All adverse events occurring in participants through week 52 will be graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, dated December 2004, which will be included in the SSP Manual and is available at the following website: <http://rcc.tech-res-intl.com>. All serious adverse events (SAEs), regardless of severity or relatedness, and all AEs that otherwise meet the criteria for expedited reporting to DAIDS (EAEs) occurring to participants in either study arm through week 52 will be reported on a standard AE DataFax case report form for entry into the study database. AEs that are not serious or do not otherwise meet the criteria for

~~expedited reporting to DAIDS will be recorded in the study source documentation but will not be included in the study database. As noted above, for the purposes of this study, outpatient or inpatient hospital/medical facility admission for drug addiction treatment or rehabilitation will not be considered a serious adverse event.~~

~~There will be no active reporting of adverse events after the period specified above (52 weeks of follow up); however, unexpected, serious adverse drug reactions must be reported if the study site staff become aware of the events on a passive basis, i.e., from publicly available information.~~

~~Information on all AEs included in the study database will be included in annual reports to the US FDA, and other applicable government and regulatory authorities. The investigators will report information on AEs and SAEs to the responsible Institutional Review Boards/Ethics Committees in the US and the host countries in accordance with applicable regulations and individual IRB/EC requirements.~~

6.2 Adverse Event (AE) and Expedited Adverse Event (EAE) Reporting

6.2.1 Adverse Event Reporting to DAIDS

Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at <http://rsc.tech-res.com/safetyandpharmacovigilance/>.

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov. Site queries may also be sent from within the DAERS application itself.

Where DAERS has not been implemented, sites will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: <http://rsc.tech-res.com/safetyandpharmacovigilance/>. For questions about EAE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com).

AEs that are not serious or do not otherwise meet the criteria for expedited reporting to DAIDS will be recorded in the study source documentation but will not be included in the study database. For the purposes of this study, outpatient or inpatient hospital/medical facility admission for drug addiction treatment or rehabilitation will not be considered a serious adverse event.

6.2.2 Reporting Requirements for this Study

- The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.**

- The study agents for which expedited reporting are required are BUP/NX (Suboxone®), provided for the first 52 weeks to participants.

6.2.3 Grading Severity of Events

The most current Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table) is used and is available on the RSC website at <http://rsc.tech-res.com/safetyandpharmacovigilance/>.

6.2.4 Expedited AE Reporting Period

- The expedited AE reporting period for this study is from the time that the first dose taken of Suboxone® up until Week 52. For the purposes of this study, outpatient or inpatient hospital/medical facility admission for drug addiction treatment or rehabilitation will not be considered a serious adverse event.
- After Week 52, all deaths will continue to be reported. After Week 52, the protocol defined AE reporting period is concluded and only SUSARs as defined in Version 2.0 of the EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

Note: Information on all AEs included in the study database will be included in annual reports to the US FDA, and other applicable government and regulatory authorities. The investigators will report information on AEs and SAEs to the responsible Institutional Review Boards/Ethics Committees in the US and the host countries in accordance with applicable regulations and individual IRB/EC requirements.

II. The original Appendix VI has been has been revised as follows:

~~APPENDIX VI: HPTN 058 Adverse Event Reporting and Documentation Requirements*~~

	Adverse Event	Relationship to Study Product	Record event and grade in primary source documents	AE Log (DataFax to SDMC)	EAE Form (to DAIDS RCC within 3 business days of site awareness)
Serious Adverse Events	Results in Death	Regardless of relationship	YES	YES	YES
	Results in persistent or significant disability or incapacity	Regardless of relationship	YES	YES	YES
	Is a congenital anomaly or birth defect or fetal loss	Regardless of relationship	YES	YES	YES
	Requires or prolongs hospitalization	Probably not related Possibly related	YES	YES	YES (if meets one of the relationship

		Probably related Definitely related			criteria)
	Requires intervention to prevent significant incapacity/permanent disability or death	Probably not related Possibly related Probably related Definitely related	YES	YES	YES (if meets one of the relationship criteria)
	Is life-threatening (including all Grade 4 AEs)	Probably not related Possibly related Probably related Definitely related	YES	YES	YES (if meets one of the relationship criteria)
	All other SAEs	Not related to study product	YES	YES	NO (unless directly related to study participation)
Non-Serious Adverse Events	All non-serious AEs	Regardless of relationship	YES	NO	NO

* 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.

APPENDIX VI: HPTN 058 ADVERSE EVENT REPORTING AND DOCUMENTATION REQUIREMENTS

	ADVERSE EVENT	RELATIONSHIP TO STUDY PRODUCT	Record event and grade in primary source documents	EAE FORM (to DAIDS RSC within 3 business days of site awareness)
Serious Adverse Events	Results in Death	Regardless of relationship	YES	YES
	Is life-threatening¹	Regardless of relationship	YES	YES
	Requires inpatient hospitalization or prolongation of existing hospitalization²	Regardless of relationship	YES	YES
	Results in persistent or significant disability or incapacity	Regardless of relationship	YES	YES
	Is a congenital anomaly/birth defect³	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.

The above information will be incorporated into the next version of the protocol at a later time if it is amended.