

Clarification Memo # 3 to:

HPTN 058: A Phase III randomized controlled trial to evaluate the efficacy of drug treatment in prevention of HIV infection among opiate dependent injectors, Final Version 1.0, Dated 7 October 2005

Date: 6 July 2007

Summary of Revisions and Rationale

1. The timing of acceptability assessments during the safety phase of the study has been adjusted to include assessment at week 4 only to allow participants more time to reflect on their experience with study participation.
2. Five of the exclusion criteria have been re-worded to clarify meaning, to be more specific and/or to improve operationalization. Specifically, to prevent individuals from leaving another treatment program just to enroll in the study, the exclusion criterion related to treatment for opioid dependence has been elaborated to indicate that participants cannot currently be receiving treatment or have received treatment within the last twelve weeks. Also, the criterion related to dependence on alcohol and benzodiazepines has been strengthened because of safety concerns related to use of Suboxone in participants who are dependent on these substances.
3. The protocol has been clarified to allow potential participants to be re-screened for the study only once after 30 days from the initial screening blood draw.
4. The dosing regimen has been clarified to allow site clinicians flexibility when determining daily dosing schedules.
5. To allow for greater flexibility, it has been clarified that the order of screening procedures should be followed as written in the protocol but can be modified if needed.
6. To eliminate an internal inconsistency, the protocol has been corrected to reflect that social harms will be actively monitored only at follow-up visits every six months, as well as weekly for the first four weeks for participants in the safety phase.

Implementation

The procedures clarified in this memorandum have been approved by the NIAID Medical Officer and are to be implemented immediately upon issuance. IRB approval of Clarification Memorandum #3 to HPTN 058 Protocol Version 1.0 is not required by the sponsor; however, sites may submit the clarification memo to the responsible IRBs/ECs for their information.

No change in the informed consent forms is necessitated by or included in this Clarification Memo.

The modifications included in this Clarification Memo will be incorporated into the next full protocol amendment. Deletions to the text are indicated by strikethrough, and additions are indicated in bold.

1. Acceptability Assessments

- *Section 2.3.2, Assessments during the Safety and Feasibility Phase, last bullet:*
 - Acceptability assessment at weeks ~~2 and~~ 4
- *Section 2.3.2, Assessments during the Safety and Feasibility Phase, next to last paragraph:* Each participant will complete an intervention acceptability assessment at the completion of the ~~second week of the study, and again at completion of the~~ fourth week. Study staff not involved in delivery...

- *Section 5.3, Assessments during Safety Phase, last bullet:*
 - Acceptability assessment at weeks ~~2 and~~ 4
- *Appendix I-B: Schedule of Procedures and Evaluations—Safety Phase:* Under “Intervention Acceptability Assessment” remove X in Week 2 column.

2. Exclusion Criteria

Section 3.2 Exclusion Criteria:

- Current **or recent (within the last 12 weeks)** treatment **for opioid dependence** with methadone, ~~morphine~~, LAAM, **buprenorphine**, naltrexone, or nalmefene, according to self-report
- Current enrollment in another HIV prevention or drug use intervention study
- Known ~~hypersensitivity~~ **allergy** to buprenorphine or naloxone, according to self-report
- ~~Requiring immediate medical attention~~ **Meets DSM-IV criteria** for dependence on alcohol, ~~or benzodiazepines~~ **or; requiring immediate medical attention for dependence on** other substances (except tobacco), as judged by study clinician.
- Currently injecting substances other than opiates more than twice ~~per month in the~~ **last 28 days**, according to self-report

3. Re-screening:

Section 3.4, Screening and Enrollment Process: The following sentence has been added to the end of the first paragraph: **Participants who do not enroll within 28 days or who are otherwise found to be ineligible may re-screen for the study once. Re-screening may be conducted after 30 days from the initial screening blood draw.**

4. BUP/NX Dosing

Section 4.3.3, Treatment Dose and Administration, third paragraph, first sentence: Beginning on Day 4, participants will have their ~~daily~~ dosage of BUP/NX decreased by **approximately 2 mg/day at the clinician’s discretion** until a dosage of 0 mg is reached.

5. Order of Screening Procedures

Section 5.1, Screening Visit, first paragraph: Screening procedures will typically take place over two or more visits. All potential participants must provide independent written informed consent for screening before completing any other procedures. **Thereafter, the order of the procedures specified below is suggested but not required.** The following procedures will initially occur as part of screening:

6. Social Harms Assessments

- *Section 5.4.2, Drug and Risk Reduction Counseling Visits, third paragraph, first sentence:* Locator information ~~and social harms~~ will also be assessed at four-week intervals.
- *Section 5.4.3, Booster Sessions:* Refer to Section 4.2.2 for a description of sessions. At each of these sessions, participants will be asked to update their locator information and provide urine for opiate and pregnancy testing (for women in the substitution treatment arm only). ~~Participants will also be asked about social harms they may have experienced...~~
- *Appendix I-A, Schedule of Procedures and Evaluations—Full Study, Social Harms Assessment:* Remove X³ in both “Intervention Visits” columns.