

HIV Prevention Trials Network

Clarification Memorandum # 1 to HPTN 058: A Phase III randomized controlled trial to evaluate the efficacy of drug treatment in prevention of HIV infection and death among opiate dependent injectors
Final Version 2.0, 16 September 2008
IND # 73,797

Date of Clarification Memorandum: 17 March 2011

Section 1: Summary of Clarifications and Rationale

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 this Clarification Memorandum is not required by the sponsor; however, investigators may submit the clarification memo to the IRBs/ECs overseeing the study at their site for their information.

Clarification is needed regarding the maximum allowable daily dosing for a participant. The original intent was to allow for physicians to set each participant's dose individually based on need. Section 4.3.3 could be mis-interpreted for a maximum daily dose of 16 mg.

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

Section 2: Implementation

The modifications detailed below will be incorporated into the next full protocol amendment. Text to be deleted is noted below by ~~striketrough~~; text to be added is noted below in **bold**.

This section should specify exactly where the protocol document will be modified to reflect the clarification when it is next amended.

4.3.3 Treatment Dose and Administration

Substitution Treatment Arm

Dosing will begin with a titration over a period of two to three days under supervision in the study clinic using the COWS as described above. On the first day of treatment, patients will initially receive a 4 mg dose of BUP/NX (expressed as the amount of buprenorphine) to be taken sublingually. Most participants will begin with a total first day's dosage of 8 mg. On

Day 2, up to 16 mg may be given. Up to 32 mg may be given on Day 3 and thereafter until three-times-weekly dosing begins. The induction strategy is primarily dependent on three factors: 1) time since last opiate use; 2) type of opiate (e.g., long or short-acting) used; and 3) degree of physical dependence. Therefore, each dosing schedule will be tailored to the individual participant.

Individuals randomized to the substitution treatment arm will come to the study site daily for direct observation of dosing until they have stabilized (for up to three weeks). Participants may be given a double dose or a take-home dose for days that the site is not staffed for dosing. After induction and stabilization, participants will be asked to come to the site for dosing three-times-weekly. **For example,** ~~the target dosage schedule for individuals whose daily dose was 16 to 24 mg/day or more is expected to be 32/32/48 mg administered on a three-times-weekly schedule (e.g., M/W/F); this is also the maximum three-times-weekly dosage. On rare occasions, for individuals who require more than 24 mg/day (i.e., 26, 28, 30, or 32 mg/day), it is unlikely that.~~ **In some individuals,** the 32/32/48 mg **three-times-weekly** dosage schedule **may not** be adequate. For **such** individuals, as well as for others who received 24 mg or less per day but for whom the 32/32/48 mg three times weekly schedule is not adequate, dosing may be continued on a daily basis through Week 52 of the study, with take-home doses administered for those days on which in-clinic dosing is not possible (e.g., 32 mg on M/Tu/W/Th/F/Sat with a take-home 32 mg dose on Sun) **dosing may be observed in the clinic 4-times to 7-times per week during the maintenance phase as required for optimal treatment response. The maximum dose that may be administered at one time (i.e., to cover > 1 day) is 48 mg.** Participants receiving daily doses may also be given alternative day take home doses, which would conform to the visit schedule of those participants on three-times weekly dosing, at the discretion of the local investigators.