

## Section 4 Participant Accrual

---

4.1	Accrual Plans and Targets	4-2
4.2	Recruitment	4-2
4.3	Screening	4-3
4.3.1	Assignment of Participant ID Numbers	4-4
4.3.2	Screening and Enrollment Time Frame	4-4
4.3.3	Screening and Enrollment Log	4-5
4.4	Informed Consent for Study Participation	4-5
4.4.1	Deliver Required Information in an Understandable Manner	4-6
4.4.2	Obtain Consent in a Setting Free of Coercion	4-7
4.4.3	Confirm Participant Comprehension	4-7
4.4.4	Document the Process	4-8
4.4.5	Informed Consent for Future Testing on Blood Specimens	4-9
4.4.6	Storage of Consent Forms	4-9
4.5	Eligibility Determination	4-10
4.5.1	Inclusion Criteria	4-10
4.5.2	Exclusion criteria	4-11
4.5.3	Screening HIV Testing	4-11
4.6	Enrollment/Randomization	4-12
4.7	Screening and Enrollment Tracking	4-14
4.8	Screening and Enrollment Scenarios	4-15
4.8.1	Screening Timeframe/Re-screening	4-15
4.8.2	Laboratory Findings	4-15
4.8.3	Ineligibility at Randomization Visit	4-16
4.8.4	Participant Withdrawal	4-16
Table 4-1	Timing of Screening and Enrollment Assessments for HPTN 058	4-17
Table 4-2	Sample HPTN 058 Screening and Enrollment Log	4-18
Table 4-3	Sample Informed Consent Coversheet for HPTN 058	4-19
Table 4-4	Pre-Screening Sample Form	4-20
Figure 4-1	Sample HPTN 058 Randomization Envelope	4-13
Figure 4-2	Sample Opened HPTN 058 Clinic Randomization Envelope	4-13

## Section 4 Participant Accrual

---

This section provides an overview of requirements and procedures for the screening and enrollment/randomization of participants in HPTN 058.

### 4.1 Accrual Plan and Targets

A total of 1500 injection drug users (IDUs) will be enrolled across all of the sites. It is anticipated the study sites will enroll participants over approximately 30 months. The study will begin with an initial safety and feasibility phase, which will include the first 50 study participants at each site and will last approximately 30 weeks (three months for accrual, one month to follow last participant). Participant accrual will continue uninterrupted during the transition from the safety phase into the full study.

Site staff is responsible for establishing an accrual plan/SOP for this study, and for updating the plan and recruitment strategies if needed to meet the accrual goals. The accrual plan/SOP minimally should contain the following elements:

- Site-specific monthly accrual goals
- Methods for tracking actual accrual versus accrual goals
- Recruitment methods and target locations
- Plans for engaging the community and ensuring support from local authorities
- Pre-screening procedures (a sample checklist is included in Table 4-4)
- Plans for identifying potential participants including ensuring that effective referral systems are in place at recruitment sites
- Methods for identifying the recruitment source of participants who present for screening
- Plans for proactive internal monitoring of recruitment progress and strategy
- Plans for tracking participants who are screened and potentially eligible for the study (e.g., maintenance of screening log)
- Ethical and human subjects considerations
- Staff responsibilities for all of the above (direct and supervisory)
- Staff training requirements
- Quality assurance/quality control procedures related to the above (if not specified elsewhere)
- Copies of recruitment worksheets, scripts, and other operational tools

The protocol team will routinely review screening and accrual performance from each site to determine whether accrual targets should be adjusted across sites to achieve the study objectives most efficiently and to determine when to discontinue accrual at each site. Findings and recommendations from these reviews will be communicated to all study sites, and all sites will adjust their accrual efforts accordingly.

### 4.2 Recruitment

Prospective participants will be recruited according to site accrual plan/SOPs through street outreach, publicity, and respondent-driven sampling (snowball method), where IDUs who participate in screening are encouraged to bring other IDUs to the study site. Street outreach workers will be the primary recruiters, supplying basic information about the study in geographic areas and settings frequented by drug users and encouraging these individuals to seek screening at a local study site. Site staff are encouraged also to work with non-governmental organizations (NGOs), medical care providers, and local media to help recruit appropriate participants.

Ensuring the support of local authorities is critical to ensuring participants are protected from prosecution for illegal drug use when presenting for screening.

Study outreach workers will be trained not to pre-select individuals who fit their description of “drug users,” rather they will provide information to a range of individuals and encourage those individuals to pass information about the study to others in the community. Outreach workers should be research staff from the community and must be knowledgeable about the community’s health care and drug treatment resources as well as the local criminal justice response to drug users. They will be trained by site supervisors in methods of approaching and communicating with potential participants, personal safety, and the importance of maintaining confidentiality. Outreach workers will identify and develop strategies for accessing settings and organizations frequented by drug users. In these geographic areas and settings, outreach workers will disseminate general information about the study verbally and via written materials as approved by the Institutional Review Boards (IRB) or Ethics Committees (EC). They will provide information on available drug treatment resources in the community and encourage prospective participants to participate in screening activities at a local study site.

Sites should also collaborate with local service providers to identify potential participants. Patients at drug treatment centers or other relevant care providers may be given IRB-approved study brochures in these locations and told to contact the study in the future if they are interested. To protect the confidentiality of patients, these other local service providers may not provide names of their patients to the 058 staff directly.

Outreach workers may provide potential study volunteers with basic information about the study and the participation requirements; however, staff should be careful not to divulge the exact entry requirements, such as “injecting opiates at least 12 times in the last 28 days”, as this may encourage others in the community to provide the needed responses to enter the study, even when untrue. All staff should emphasize that not everyone will be eligible for the study during recruiting and screening. No protocol-specific procedures or assessments can be done until after a volunteer has undergone the complete informed consent discussion and signed the screening consent form.

### **4.3 Screening**

The study screening procedures are described in detail in the study protocol (Section 2) and visit checklists (Section 6) in this manual. Instructions for performing clinical and laboratory screening procedures are included in Sections 10 and 11, respectively. Key screening and enrollment topics are described below. Several possible screening and enrollment scenarios are presented for illustrative purposes in Section 4.8.

The term “screening” refers to study-specific procedures undertaken to determine whether a potential participant is eligible to take part in HPTN 058 and begins after the volunteer has provided written informed consent for study screening. The study inclusion/exclusion criteria are listed in protocol sections 3.1 and 3.2. The screening and enrollment process is described in protocol sections 5.1 and 5.2. Table 4-1 provides further information on the timing of assessments during screening.

Potential participants will undergo eligibility screening during one or more in-person study visits. Demographic and behavioral eligibility will be determined based on participant responses to standard interview instruments. All participants will receive HIV testing and pre- and post-test counseling as described in Section 10 of this Study Specific Procedures Manual. All assessments

must be conducted within 28 days of the first blood draw for the HIV test. Screening may be discontinued after any one of the individual assessments in Table 4-1 is completed if a participant is found to be ineligible. However, in order to protect the integrity of the entry criteria, staff will be careful not to reveal exact reason for ineligibility, such as need to have a positive urine test for opiates. HIV counseling and testing will be offered to everyone who consents for screening. Those that fail screening for any reason may only be re-screened once for this study.

#### **4.3.1 Assignment of Participant ID Numbers**

SCHARP will provide each study site with a listing of participant ID (PTID) numbers for use in HPTN 058. The listing may be formatted such that it may be used as the log linking PTIDs and participant names at each site.

Further information regarding the structure of PTIDs for HPTN 058 can be found in SSP Section 7. PTIDs will be assigned to all potential participants who provide informed consent for screening. Only one PTID will be assigned to each potential participant, regardless of the number of screening attempts she/he undergoes. Site staff is responsible for establishing SOPs and staff responsibilities for proper storage, handling, and maintenance of the PTID list such that participant confidentiality is maintained.

#### **4.3.2 Screening and Enrollment Time Frame**

Screening and enrollment procedures will be completed over the course of multiple visits. Regardless of the number of visits required, randomization must be completed within 28 days of collecting the first sample for HIV testing from the participant at screening. If all required procedures are not completed within 28 days, the participant must repeat the entire screening process, including the screening informed consent process (including the consent form and comprehension quiz), but not including PTID assignment, which is not repeated. The term “screening attempt” is used to describe each time a participant screens for the study.

A participant who does not meet entry criteria the first time, such as does not meet DSM-IV definition of opiate dependence or has a negative drug screen, may re-screen one more time after waiting at least 30 days from the date she/he had blood drawn for HIV testing.

The following tests are allowed to be re-tested within the 28 day window period between the initial blood draw and enrollment should the first draw prove ineligible:

- Hematology (CBC and platelet count)
- Blood chemistry (creatinine)
- Liver function tests (ALT, bilirubin)

Once an individual is found to be ineligible for any reason, the screening process may be discontinued. The reason for ineligibility must be documented on the screening log and in the individual participant’s source documents; however, the site staff will not reveal to the participant the exact reason for ineligibility except in the case of HIV positive status or other medical condition requiring referral and care, such as elevated ALT or pregnancy.

### 4.3.3 Screening and Enrollment Log

The DAIDS SOP for Essential Documents (Appendix B) requires study sites to document study screening and enrollment activities on screening and enrollment logs to document identification of subjects who enter pre-trial screening and the chronological enrollment of subjects. Screening and enrollment logs may be maintained separately or combined into one log. See Table 4-2 for a sample screening and enrollment log that may be adapted for local use.

The logs must include the following information for all screened participants at a minimum: participant initials, PTID number, date of screening visits, and, if enrolled, the date of randomization. Participant initials need not be recorded on screening and enrollment logs if doing so presents a potential threat to participant confidentiality. In such cases, a separate document must be available to document the link between a participant's name and PTID. If a screened participant is not enrolled/randomized, the reason must also be noted in the log. For the purposes of HPTN 058, a screened participant is defined as a participant who has signed a screening informed consent form.

## 4.4 Informed Consent for Study Participation

Written informed consent must be obtained from all study participants prior to the performance of any protocol-specified screening or enrollment procedures and assessments. This study will employ five different informed consent forms including screening and enrollment consents for participants enrolled during the safety and feasibility phase, screening and enrollment consents for the full study, and an optional informed consent for future testing on blood specimens.

Informed consent is a process by which an individual voluntarily expresses his/her willingness to participate in research, after having been informed of all aspects of the research that are relevant to the decision. Informed consent is rooted in the ethical principle of respect for persons. It is not merely a form or a signature, but a process, with four key considerations — information exchange, comprehension, voluntariness, and documentation — each of which is described below. See Section 4.8 of the ICH GCP guideline (Appendix A) and the informed consent section of the DAIDS SOP for Source Documentation (Appendix C) for detailed guidance on the informed consent process and documentation requirements.

US regulations specify the elements of informed consent that must be conveyed to research participants through the consent process. It is the responsibility of the Investigator of Record and his/her staff to deliver complete and accurate information to potential participants. Based on the technical and regulatory reviews that are completed as part of the HPTN protocol development and study activation processes, adequate assurance exists that once the site receives final approval for study initiation through an Activation Notice from the CORE, the IRB-approved site-specific informed consent form specifies all information required by the regulations.

As a condition for study activation, each study site must establish an SOP for obtaining informed consent from potential study participants. This SOP should reflect all of the information provided in this section and minimally should contain the following elements:

- Procedures for ascertaining participant identity and age
- Procedures for ascertaining participant literacy
- Procedures for providing all information required for informed consent
- Procedures for ascertaining participant comprehension of the required information

- Procedures to ensure that informed consent is obtained in a setting free of coercion and undue influence
- Procedures for documenting the informed consent process
- Considerations and requirements for illiterate participants, including specification of who may serve as a witness to the informed consent process
- Storage locations for blank informed consent forms
- Storage locations for completed informed consent forms
- Procedures (e.g., color-coding) to ensure that the study informed consent forms —screening and enrollment for the safety phase and the full study and specimen storage — are easily distinguished and used appropriately
- Procedures for implementing a change in the version of the informed consent form
- Staff responsibilities for all of the above (direct and supervisory)
- Staff training requirements
- QC/QA procedures related to the above (if not specified elsewhere)
- Attached copies and instructions for use of all forms, worksheets, flipcharts, checklists, etc. to be used during the informed consent process

Responsibility for informed consent does not end with preparation of an adequate informed consent form. It also is the responsibility of the Investigator and designated study staff to complete the procedures listed below.

#### **4.4.1 Deliver Required Information in an Understandable Manner**

As a starting point at the screening visit, assess participant literacy. If the participant is literate, give him/her a copy of the informed consent form to read. Also provide the participant with other IRB/EC-approved informational materials developed to complement the informed consent form, if any (the responsible IRBs/ECs must approve such materials prior to use). Because many of the research concepts and terms may be unfamiliar even to literate people, the consent form must be reviewed very carefully with each potential volunteer. It is suggested that each paragraph be reviewed by the study staff member conducting the consent discussion and that the key points of each be emphasized, pausing after each paragraph to allow for questions and to probe for understanding. If the participant is not literate, read the materials verbatim – pausing after each paragraph to emphasize key points and to allow for questions. A checklist highlighting key points may serve as a useful guide for reviewing the consent with the potential participant. For example, you may note the main points described in each paragraph of the informed consent form, and ask if the participant has questions or concerns about each point. Listen carefully to the questions and/or concerns expressed by the participant, and discuss these thoroughly. Take as much time as needed to address each question and concern.

*Note: If the participant is not literate, a literate witness must be present during the entire informed consent discussion. As part of the documentation step described in Section 4.4.4, the witness will be asked to sign and date the informed consent form to attest that the information in the consent form was accurately explained to and apparently understood by the participant, and that informed consent was freely given by the participant. Each site must specify its procedures for obtaining informed consent from illiterate persons in its SOP for obtaining informed consent. The SOP should define who may serve as the witness to the informed consent process. It is recommended that each site seek IRB/EC review and approval of these procedures.*

#### **4.4.2 Obtain Consent in a Setting Free of Coercion**

During the informed consent discussion, take care to not overstate the possible benefits of the study, nor to understate the risks. Also emphasize to the participant that the availability of medical care and other services routinely obtained from the recruitment site and/or research institution will not be affected by his/her decision whether or not to take part in the study. Encourage the participant to take as much time as needed and to talk about potential participation with others, if she/he chooses, before making a decision.

*Note: If the participant is not literate, and therefore a witness is present during the entire informed consent discussion, care should be taken to minimize the perception of coercion due to the presence of the witness. For example, the purpose of having the witness present should be clearly explained to the participant, with emphasis on the fact that the witness is there as a protection for the participant, not as an agent of the study.*

#### **4.4.3 Confirm Participant Comprehension**

The participant must not be asked to agree to take part in the study or to sign or make his/her mark on the informed consent form until she/he fully understands the study. Study staff is responsible for implementing procedures to ensure that each participant understands the screening process and the study prior to signing/marketing the screening and enrollment informed consent forms and undertaking any screening or study procedures. Study staff should emphasize with potential volunteers aspects of the study that may be most challenging for them – for example, the concept of randomization, that the study does not provide care for HIV, the fact that the study staff may need to contact them at home, etc. It is critical that volunteers fully understand what participation in the study entails before agreeing to participate.

Sites will assess participant comprehension by administering oral comprehension quizzes, in which participants must demonstrate sufficient comprehension of the study prior to signing/marketing an informed consent form. Quizzes will be used for both screening and enrollment and are included in SSP Appendix F. Quizzes will be administered orally by site staff after the participant has read the consent form or having had it read to them but prior to signing/marketing the consent form.

At both screening and enrollment, participants will be given three attempts to correctly answer 75% of the comprehension quiz questions. Participants who cannot answer 75% of the questions correctly cannot participate in screening activities or enroll in the study. However, participants who do not pass either the screening or enrollment comprehension quiz may re-screen for the study 30 days after the initial blood draw for HIV testing.

To administer the consent comprehension quizzes, study staff will read all questions as listed and record participants' answers under the first attempt column. At the end of the quiz, staff will first review all questions in the quiz and discuss the correct answers. As needed, staff will re-review the contents of the informed consent form to help the participant better comprehend questions they answered incorrectly. Participants who answered at least 75% of the questions correctly can proceed to sign/mark the consent forms. Participants who do not answer correctly at least 75% of the questions will be given two more attempts to answer the questions correctly (three total). Staff will re-ask only the questions answered incorrectly during the previous attempt and record the participants' new answers in the next attempt column. Study staff will review each re-asked question following the process described above. The participant cannot participate in screening or enroll in the study after the third attempt unless she/he has answered at least 75% of the

questions correctly during the three attempts. Sites must use the forms provided in this SSP Appendix F and for enrollment the checklist will be a DataFax form, and should be faxed to SCHARP. This will help the study team assist sites in tracking potential problems in the Informed Consent process.

At enrollment only, participants who pass the informed consent comprehension quiz will be administered the informed consent evaluation survey. The informed consent evaluation survey must be administered by different staff from those who administered the informed consent comprehension quiz with the participant. The survey can be administered immediately after the comprehension quiz or later in the study visit, but must be completed the same day the comprehension quiz was administered. It should be emphasized prior to administering the evaluation survey that the purpose of the survey is to give researcher information about how to do a good job in obtaining informed consent for research and not make participants feel uncomfortable. Participants should be informed that their answers to the survey have no impact on their participation in the study. The survey is **OPTIONAL** for all participants.

If the participant has concerns about possible adverse impacts if she/he were to take part in the study, or indicates that s/he may have difficulty adhering to the study requirements, do not ask him/her to sign the informed consent form or continue screening for the study. If the potential volunteer has serious concerns about family members or others learning that she/he is in the study (e.g., because she/he would be coming frequently to the study clinic) and she/he is not willing or able to discuss this with them in advance, s/he should not be asked to sign the consent and participate (enroll) in the study.

#### **4.4.4. Document the Process**

US regulations require that informed consent be documented by "the use of a written informed consent form approved by the IRB/EC and signed and dated by the subject or the subject's legally authorized representative at the time of consent."

It is essential that the date documented on the screening consent form either precedes or coincides with the first study screening date. In addition, the participant chart should include documentation that informed consent was obtained prior to the initiation of any study procedures. Finally, regulations require that participants be given a signed copy of all informed consent forms. If a participant chooses not to receive a copy, document this in the participant chart.

Signatures on the consent forms must be the legal name and not include fabricated or falsified names. Sites are not required to verify a person's legal name; however, if the site becomes aware that a person has not used his/her legal name, then the instructions provided for this situation in the DAIDS SOP for Source Documentation must be followed.

Use of initials for first name is discouraged but it is not prohibited as long as it is acceptable per the policy of the local institution. The consent must be dated by the person signing the form; it is not acceptable for study staff to complete the date for another signer. All entries must be in ink.

*Note: If the participant is not literate, the witness who was present during the informed consent discussion must sign and date the informed consent form to attest that the information in the consent form and any other written information was accurately explained to and apparently understood by the participant, and that informed consent was freely given by the participant. If the participant cannot write his/her name or the date, this should be documented in the research record, in a chart note and/or on a face sheet or other documentation tool. In addition, the*

*participant printed name, signature, and signature date blocks on the informed consent form should be completed as follows:*

- *The “participant’s printed name” block should be left blank and the name should be recorded below the line by the person conducting the consent discussion, and initialed and dated. The participant chart should include documentation that the participant could not sign for him/herself.*
- *The participant should make his/her mark in the “participant’s signature” block.*
- *The “participant signature date” block should be left blank and date should be recorded below the line by the person conducting the consent discussion, and initialed and dated.*

The DAIDS SOP for Source Documentation (Appendix C) provides detailed requirements and suggestions for documenting the informed consent process. All requirements listed in the DAIDS SOP must be met. In order to also meet some of the suggestions listed in the DAIDS SOP, site staff may consider the use of an informed consent “coversheet” similar to the example included in Table 4-3 at the end of this section.

The above describes aspects of obtaining informed consent from study participants during screening. Nevertheless, key elements of informed consent also should be reviewed at all study follow-up visits. At these visits, study staff should review key elements of informed consent with the participant, focusing on the remainder of their study participation. For example, at the Week 26 visit, the discussion might focus on the fact that the treatment portion of the study is half over, and explain again what the procedures will be over the coming months.

#### **4.4.5 Informed Consent for Future Testing on Blood Specimens**

Storage of specimens remaining after trial completion is optional for each site. If a site chooses to store leftover blood specimens after all of the protocol-specified assessments and quality control procedures are completed, separate written informed consent must be obtained from each participant. This consent may be obtained any time before or after a participant is enrolled in the study (i.e., it need not be done at screening). Participants may choose not to have their specimens stored for possible future research testing and still enroll/remain in the study. To facilitate completion of case report forms (CRFs) at the end of the study and management of specimens, sites should keep a record that can be used to ascertain and verify who signed the consent for storage of leftover specimens. Future use of blood samples approved for post-study testing/use of stored specimens must be approved by the relevant IRBs/ECs.

#### **4.4.6 Storage of Consent Forms**

All consent forms completed during the screening process must be retained even if the volunteer was not enrolled in the study. Sites are encouraged to maintain consent forms in a file separate from a subject’s research record and to separate those for enrolled participants from those screened but not enrolled, provided that the site does this consistently for all subjects. Sites should maintain any subsequent versions of the consent in the same manner.

### **4.5 Eligibility Determination**

Documentation to address each of the protocol’s inclusion and exclusion criteria must be present in the individual’s research record. It is the responsibility of the site Investigator of Record and other designated staff to ensure that only participants who meet the study eligibility criteria are enrolled/randomized in the study. As a condition for study activation, study sites must establish

an SOP that describes how study staff will fulfill this responsibility. This SOP minimally should contain the following elements:

- Eligibility determination procedures, including:
  - During-visit eligibility assessment procedures
  - Post-visit eligibility assessment and confirmation procedures
  - Final confirmation and sign-off procedures prior to enrollment/randomization
- Documentation of each inclusion/exclusion criteria
- Ethical and human subjects considerations
- Staff responsibilities for all of the above (direct and supervisory)
- Staff training requirements
- QC/QA procedures related to the above (if not specified elsewhere)

Should site staff identify that an ineligible participant has inadvertently been enrolled in the study, the Investigator of Record or designee should contact the HPTN 058 Protocol Safety Review Team (PSRT) for guidance on subsequent action to be taken. PSRT contact details are provided in Section 12 of this manual.

#### **4.5.1 Inclusion Criteria**

Participants must meet all of the following criteria to be eligible for the study:

- At least 18 years old
- Able and willing to provide written informed consent for study participation and able to provide correct answers to 75% of the questions in the informed consent comprehension quiz during enrollment on no more than three attempts
- HIV-uninfected as evidenced by two different rapid tests on specimens obtained within 28 days of enrollment
- Meets Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for opiate dependence, as determined by study clinician
- Positive urine test for opiates
- Injected opiates at least twelve times in the last 28 days, according to self-report
- If female, evidence of inability to become pregnant or self-reported willingness to use an effective method of contraception for the first twelve months of the study
- Able to provide contact information and stated willingness to be contacted by study staff as needed
- Stated plans to be available for study visits for at least two years

*Note: Available contraception in China and Thailand may vary, but acceptable options include but are not limited to: hormonal methods (birth control pills or patch, Depo-Provera, etc), barrier methods (diaphragm or condom), intrauterine devices, and complete abstinence from sexual intercourse. Women who report that they are abstinent will be counseled about contraceptive options and asked if they are willing to use an effective method of birth control in the event that they become sexually active. Male condoms will be offered to both male and female participants along with referrals to family planning providers. Self-reported sterilization is acceptable, but appropriate probes should be used to confirm that participants have correctly understood the meaning of sterilization and are reporting accurately. Women who have recently given birth cannot be breastfeeding at the time of enrollment and must agree not to resume breastfeeding after enrollment because of the risks involved with exposing the infant to the study*

*drug. If you find that a woman is/was breastfeeding while taking Suboxone, contact the PSRT immediately.*

#### **4.5.2 Exclusion criteria**

Participants who meet any of the following criteria will not be eligible for the study:

- Current or recent (within the last 12 weeks) clinician-guided treatment for opioid dependence with methadone, LAAM, buprenorphine, naltrexone, or nalmefene, according to self-report
- Current enrollment in another HIV prevention or drug use intervention study
- Known clinically-diagnosed hypersensitivity to buprenorphine or naloxone, according to self-report
- Meets DSM-IV criteria for dependence on alcohol or benzodiazepines; requiring immediate medical attention for dependence on other substances (except tobacco) as judged by the study clinician
- Currently injecting substances other than opiates more than twice in the last 28 days, according to self report
- Psychological disturbance or cognitive impairment interfering with the participant's ability to comply with the study visit schedule and procedures, as judged by the local study clinician
- Pregnant or lactating
- Acute or chronic renal failure as judged by study clinician
- ALT greater than three times the upper limit of normal value
- Hemoglobin less than 8g/dL for men, less than 7g/dL for women
- Platelet count less than 50,000/mm<sup>3</sup>
- Total bilirubin greater than 2.5 times the upper limit of normal
- Any other medical or psychiatric condition that, in the opinion of the investigator, would make participation in the study unsafe, or otherwise interfere with the study objectives or interpretation
- Does not pass the screening or enrollment checklist after three attempts.

*Note: Enrolling the right participants is essential for ensuring a high level of retention later in the study. Study staff should be judicious in participant enrollment rather than enrolling anyone who meets eligibility criteria. Potential participants who seem ambivalent about study participation or who will have difficulty attending frequent study visits should most likely not be enrolled.*

#### **4.5.3 Screening HIV Testing**

HIV counseling and testing will be offered to all persons who consent for screening, even if they are found to be ineligible for study participation. HIV infection status at screening will be assessed using two rapid HIV tests with confirmation of positives using a Western Blot (WB) or IFA (see Protocol Appendix II-A and Section 11 of this manual). Participants found to be HIV positive at screening will have their sample tested for recent HIV infection utilizing BED (or similar) assay at the end of the study.

FDA approved rapid HIV test kits will be used if available in country. If FDA approved kits are not available or easily imported, sites must provide information regarding available kits prior to study activation and in the event that the kit changes during the study. Non-FDA approved rapid test kits must be validated by the local laboratory and approved by the Network Laboratory before they can be used. FDA approved Western blot kits must be used to confirm HIV status.

If both of the rapid tests are negative, the participant will be considered HIV-uninfected; no further HIV testing is required and screening can continue. If either of the initial rapid tests are positive, these individuals are not eligible for enrollment. Confirmatory testing and support services are offered. If confirmatory testing with the WB is negative, the participant may be re-screened according to protocol requirements. All local health care and drug treatment services available to drug users will be actively discussed. When the participant wishes, the site staff will facilitate access to the referral services (such as calling to make an appointment while the participant is at the study site) and may follow-up with the participant to see if the service was obtained.

Again participants with negative or indeterminate WBs may return to the site after 30 days for re-screening if they are still interested in study participation. At that time, the entire screening process will be repeated including rapid tests and WB, and the participant may be eligible if the HIV tests are negative.

Further instructions for performing HIV tests during screening are provided in SSP Section 11. At all sites, all tests must be documented on local laboratory log sheets or other laboratory source documents.

#### **4.6 Enrollment/Randomization**

**The effective point of enrollment is randomization.** At all study sites, enrolled participants will be randomly assigned in equal numbers to one of the two study arms: 1) substitution BUP/NX treatment plus drug- and risk-reduction counseling for one year; or 2) short-term detoxification treatment with BUP/NX with a second detoxification possible at Week 26 plus one year of drug- and risk-reduction counseling. The SDMC will generate and maintain the study randomization scheme and associated materials including the HPTN 058 Randomization Envelopes (Figures 4-1 and 4-2).

HPTN 058 Randomization Envelopes will be shipped from the SDMC to each study site. They will be assigned in sequential order to participants who have been confirmed as eligible and willing to take part in the study. Randomization and initiation of study drug must commence on the same day. Envelopes must be assigned in sequential order, and only one envelope may be assigned to each participant. Once an envelope is assigned to a participant, it may not be re-assigned to any other participant.

Figure 4-1 Sample HPTN 058 Randomization Envelope

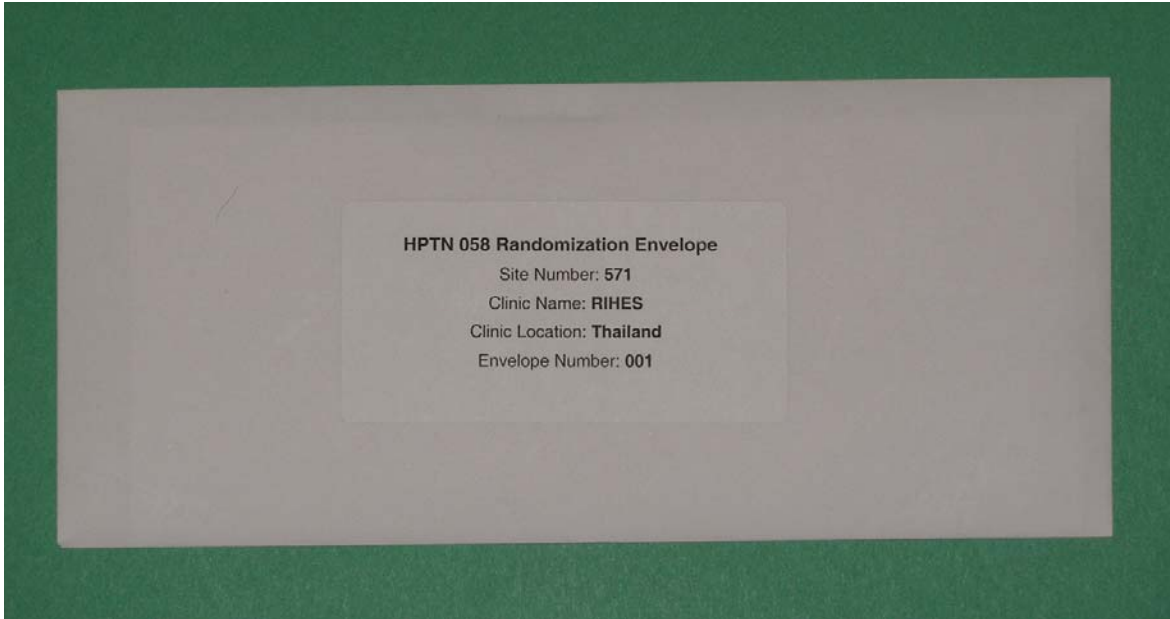
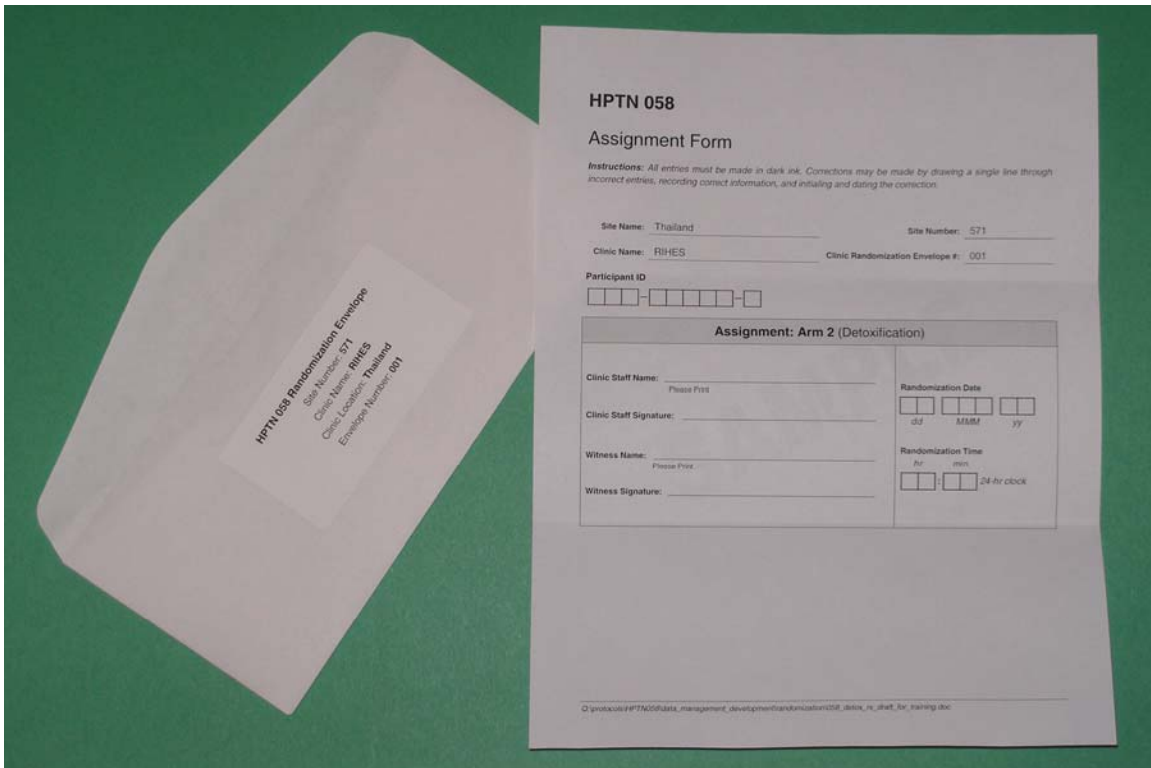


Figure 4-2 Sample Opened HPTN 058 Clinic Randomization Envelope



Random assignment will take place after the participant has been confirmed eligible, including the COWS assessment, and willing to take part in the study. Participants must be present at the study site for enrollment/randomization. Participants will provide consent for study enrollment on or before the visit at which they are randomized. If a participant states that she/he has recently used opiates or if staff is not available to begin study drug dosing on the day the enrollment consent is signed, study staff should wait to randomize the participant. Female participants will be asked to provide urine for another pregnancy test to confirm that the participant is not pregnant at the time of first dosing if the date of randomization is different from the date of the signing of the enrollment consent. Locator information will be reviewed.

When the participant is ready for the first induction dose, the randomization procedures listed below will then be performed:

1. A staff member and a witness must be present to open the randomization envelope.
2. Obtain the next sequential HPTN 058 Randomization Assignment Envelope and inspect it to verify that the correct envelope has been obtained and that there is no evidence that the envelope has previously been opened or otherwise tampered with.
3. Open the envelope, remove the assignment form, and confirm the envelope number printed on the assignment form matches the number printed on the outside of the envelope. If the envelope does not contain an assignment or if any information pre-printed on the letter appears to be incorrect, contact the SDMC Project Manager immediately. Do not proceed with this randomization or the randomization for any other participant until instructed to do so by the SDMC.
4. Complete the assignment form by entering the PTID, randomization date, and time. Enter staff and witness name and both sign the form.
5. Document the assignment in the site HPTN 058 Randomization Enrollment Log by recording the PTID, date of birth, date assigned, time assigned and authorized clinic staff initials in the row corresponding to the assigned envelope number.
6. Inform the participant of the treatment arm assignment and follow appropriate procedures for the visit.
7. Complete the Enrollment/Randomization Form (CRF ENR-1).

The act of opening a Randomization Envelope is considered the effective point of randomization and enrollment in the study. Once a Clinic Randomization Envelope is opened, the participant is considered enrolled in the study. The randomization envelope itself, as well as its contents, should be kept as part of the participant's case source documentation.

#### **4.7 Screening and Enrollment Tracking**

In accordance with HPTN policies, study staff will report the number of IDUs screened, the number eligible for enrollment, and the number of participants actually enrolled in the study to the CORE Protocol Specialist on a weekly basis (each Friday). The PS will routinely distribute a consolidated report presenting accrual information from all sites to the Protocol Team as needed to monitor the accrual process. In addition, the SDMC will routinely report the number of participants enrolled based on data received and entered into the DataFax study database.

As the study accrual period comes to an end at each site, care must be taken to manage the recruitment, screening, and enrollment process in order not to exceed the protocol-specified sample size of 1500 across all sites. Particularly in the last 3 months of accrual, enrollment must be monitored closely, and potential participants must be informed that although they may screen and be eligible for the study, they may not be enrolled if the target sample size is reached before

they are able to complete the enrollment process. This may be difficult to explain to potential participants — especially those who are very interested in taking part in the study — therefore all sites are advised to work with their local community advisory board (CAB) members to develop strategies to address this issue either prior to or soon after study start-up.

## **4.8 Screening and Enrollment Scenarios**

### **4.8.1 Screening Timeframe/Re-screening**

- **A participant completes his first screening visit on August 1 and meets all eligibility requirements. He is scheduled for randomization on August 10<sup>th</sup>, but he does not return to the clinic until September 1. Is he still eligible for randomization?**

No. Potential participants must be randomized within 28 days of their initial blood draw for HIV testing. Inform the participant that he may re-screen for the study after 30 days from the date of the initial screening blood draw.

If he returns to the clinic for re-screening, begin the entire screening process again from the beginning (including the screening informed consent process) but assign the same PTID as he had at first screening.

- **A participant has a positive HIV rapid test at the first screening visit. What do you do?**

Provide post-test counseling and inform the volunteer that another test will be done. Process blood for a WB or IFA and other lab work. Sites may choose to perform the medical history and physical exam as part of the local standard of care for these presumably ineligible participants.

**The participant returns in a week for the results of the Western Blot. The results are indeterminate. What do you do?**

The participant is not eligible for enrollment at this time. After providing counseling, refer him to other appropriate services and further testing. The participant will be eligible for re-screening in 30 days from the date of the initial screening blood draw if he is still interested in study participation.

### **4.8.2 Laboratory Findings**

- **A participant is being screened to participate in the study and you discover he has Hepatitis B. What do you do?**

When the participant returns for his randomization visit, provide results and continue the enrollment process. If the participant is otherwise eligible for the study, he may be enrolled at this visit. Potential participants diagnosed with hepatitis during the screening process may still be eligible for study participation if their liver function tests are not outside the ranges defined in the exclusion criteria and the investigator does not believe participation in the study would be unsafe for the participant.

- **A male participant's lab results are as follows:**

**Hemoglobin = 8.5 g/dL**

**Platelet count= 250,000/mm<sup>3</sup>**

**Creatinine = 0.9 mg/dL**

**ALT = 25 U/L**

**Total bilirubin = 1.5 mg/dL**

**Is this candidate eligible for HPTN 058?**

Yes, the participant's values for platelets, creatinine, ALT, and total bilirubin all fall within the normal ranges and, thus, meet the protocol criteria. His hemoglobin level is below average (grade 3) but within protocol specified criteria for men; he is anemic and the site should refer or provide treatment per standard of care. Retesting is allowed and encouraged. This lab result would be reported on the pre-existing conditions form.

#### **4.8.3 Ineligibility at Randomization Visit**

- **A female participant completes all assessments required in the screening visit and appears to be eligible. On the day she is scheduled to be randomized, she completes the enrollment consent, but her urine pregnancy test is positive. What do you do?**

Discontinue all study procedures. The participant must have a negative pregnancy test performed on the day of induction. Since the test is positive, the participant is ineligible to participate and should not be randomized. Document the reason for ineligibility in the screening log. Inform her that she can re-screen one more time after 30 days if she is no longer pregnant. Provide appropriate referrals for medical care and alternative drug treatment options as appropriate. Counselors should be prepared to provide counseling about pregnancy and drug use and assist with referrals if the participant desires.

- **A participant completes all assessments required in the screening visit and appears to be eligible. On the day he is scheduled to be randomized, he says he has not used drugs in 24 hours but his initial COWS score is only three. What do you do?**

Regardless of stated last use of drugs, induction is based on visible and objective signs of withdrawal. If the COWS score is less than 8, repeat the assessment in one hour. Continue repeating at one-hour intervals until score is 8 or greater. If the participant does not want to stay at the clinic, schedule him for a second visit for randomization and induction. Remind him that he should not use any opiates before coming to the clinic so that he will be in mild withdrawal for induction. **Do NOT randomize until COWS score is 8 or higher.**

#### **4.8.4 Participant Withdrawal**

- **A male participant meets all eligibility criteria for the study. When randomized to the detoxification arm, he decides he does not want to continue in the study. What do you do?**

Encourage the participant to continue study participation, pointing out the importance of both arms to the research and benefits of the detoxification arm such as a chance at reducing his drug use, on-going counseling, and HIV testing. If he still refuses, complete a Termination form (TM-1). Participants may not re-screen once they have been randomized.

**Table 4-1: Timing of Screening and Enrollment Assessments for HPTN 058**

	Assessed prior to blood draw	Assessed after blood draw	Assessed the day of Randomization
<b>Screening Assessments</b>			
Screening informed consent	X		
Screening Informed Consent Comprehension Quiz	X		
Collection of demographic information	X		
Interviewer administered eligibility questionnaires, including DSM-IV diagnosis	X		
Urine collection for drug testing	X		
Urine collection for pregnancy testing	X		X
Collection of locator information	X		X
Risk assessment (must be prior to Pre-test HIV counseling)	X		
Pre-test HIV counseling	X		
Blood draw for laboratory test including: <sup>1</sup> <ul style="list-style-type: none"> <li>• Rapid HIV tests<sup>2</sup></li> <li>• Hematology (CBC and platelet count)</li> <li>• Hepatitis B surface antigen and hepatitis C antibody testing</li> <li>• Creatinine</li> <li>• Liver function (ALT and total bilirubin)</li> </ul>		X	
Post-test HIV counseling		X	
Physical exam		X	
Targeted medical history		X	
Clinician review lab results		X	
Enrollment informed consent			X <sup>3</sup>
Enrollment Informed Consent Comprehension Quiz			X
Informed Consent for Enrollment Evaluation Survey (optional)			X <sup>4</sup>
Hepatitis B vaccine (if indicated, optional)			X <sup>5</sup>
COWS assessment			X
Randomization and Suboxone Induction			X <sup>6</sup>

<sup>1</sup> When laboratory results are received by the site (within approximately one week after the blood draw), staff will determine if individuals meet entry criteria. If a potential participant has abnormal test results, the clinician may conduct further testing before determining eligibility and should provide participants with appropriate referrals. Laboratory test results will be provided to all participants regardless of eligibility.

<sup>2</sup> Sites will follow the HIV testing algorithm described in section 4.5.3. Individuals with positive initial rapid tests will be asked to return to the clinic in about a week to receive results of the WB or IFA and other lab tests.

<sup>3</sup> Participants may sign enrollment consent prior to the day of randomization.

<sup>4</sup> If the participant agrees to participate in the evaluation survey then it must be completed on the same day as the enrollment quiz.

<sup>5</sup> Participants who are randomized and who are not infected and show no antibodies with hepatitis B will be offered the hepatitis B vaccine over the course of the following year though it is not a requirement for study participation.

<sup>6</sup> Participants must be randomized and begin induction *on the same day*. If a participant states that she/he will not be available, has recently used opiates, does not exhibit signs of withdrawal, or if staff is not available to conduct induction on the day the enrollment consent is signed, study staff must wait to randomize the participant.

**Table 4-2 Sample HPTN 058 Screening and Enrollment Log (May be adapted as needed for local use)**

Site Location and Number:							
	Participant ID	Participant Initials or name	Date Screened*	Eligible?	Randomization Date	If not enrolled, specify reason (include all applicable codes).	Staff Initials
1				Y N			
2				Y N			
3				Y N			
4				Y N			
5				Y N			
6				Y N			
7				Y N			
8				Y N			
9				Y N			
10				Y N			
11				Y N			
12				Y N			

\* Note: Volunteers should not be considered screened unless they have completed the informed consent process.

**Ineligibility Code Key**

A. Refused participation	M. Current enrollment in another HIV prevention or drug use intervention study
B. Unable to provide written informed consent	N. Hypersensitivity to buprenorphine or naloxone
C. Less than 18 years old	O. Requires medical attention for dependence on alcohol, benzo or other drugs
D. Pregnant or breastfeeding	P. Currently injecting substance other than opiates more than 2 times/month
E. HIV infected or discordant results	Q. Psychological disturbance or cognitive impairment
F. Does not meet DSM-IV diagnosis	R. Acute or chronic renal failure
G. Urine test negative for opiates	S. ALT greater than 3 X upper normal value
H. Did not inject at least 12 times in 28 days	T. Hemoglobin < 8g/dL for men, 7g/dL for women
I. Not willing to use contraceptive	U. Platelet count < 50,000 /mm <sup>3</sup>
J. Unable to provide locator information	V. Total bilirubin > 2.5 X upper limit of normal
K. Plans to leave area	W. Other medical or psychiatric condition as judged by clinician
L. Current treatment w/methadone, morphine, LAAM, naltrexone, nalmefene	X. Did not pass informed consent comprehension quiz

**Table 4-3 Sample Informed Consent Coversheet for HPTN 058**

<b>Participant Name:</b>	
<b>Study Phase</b>	<input type="checkbox"/> Safety and Feasibility Phase <input type="checkbox"/> Full Study
<b>Type of consent discussion:</b>	<input type="checkbox"/> Study Screening <input type="checkbox"/> Study Enrollment <input type="checkbox"/> Specimen Storage (if used at site)
<b>Date of informed consent discussion:</b>	
<b>Time of informed consent discussion:</b>	
<b>Name of study staff person completing informed consent discussion (and this coversheet):</b>	
<b>Is the potential volunteer literate?</b>	<input type="checkbox"/> Yes <input type="checkbox"/> No ⇒ If no, a witness should be present during the entire informed consent discussion. Refer to informed consent SOP for specific instructions.
<b>Was a copy of the informed consent form given to the participant?</b>	<input type="checkbox"/> Yes <input type="checkbox"/> No, refused to accept

**Notes/Comments (not documented elsewhere):**

**Table 4-4: Pre-Screening Sample Form**

Outreach Worker Name:

Date:

Location:

	<b>Continue Screening</b>	<b>Stop Screening</b>
1. How old are you?	<b>18+</b>	<b>Less than 18</b>
2. Do you inject opiates (including heroin, opium, and methadone)?	If yes, go to 2a.	<b>No</b>
2a. How many times do you inject opiates in a month?	<b>three times per week</b>	<b>Less than three times per week</b>
3. Do you inject substances other than opiates?	<b>No</b>	If yes, go to 3a.
3a. How many times do you inject other substances in a month?	<b>Less than 2</b>	<b>2+</b>
4. Have you ever been tested for HIV?	No	If yes, go to 4a.
4a. If yes, what was the result?	<b>Negative</b>	<b>Positive</b> (provide referral info to local care as appropriate)
	If all answers checked in this column, individual may be eligible. Refer for screening.	If any answers checked in this column, individual is not eligible. Thank him/her for his/her time.