

**SUMMARY OF CHANGES
INCLUDED IN THE
FULL PROTOCOL AMENDMENT TO:**

**HPTN 037:A PHASE III RANDOMIZED STUDY TO EVALUATE THE EFFICACY OF
A NETWORK-ORIENTED PEER EDUCATION INTERVENTION FOR THE
PREVENTION OF HIV TRANSMISSION AMONG INJECTION DRUG USERS AND
THEIR NETWORK MEMBERS,
REVISED VERSION 1.0 APRIL 3, 2002**

**THE AMENDED PROTOCOL IS IDENTIFIED AS
FINAL VERSION 2.0 AND DATED
OCTOBER 23, 2003**

SUMMARY OF REVISIONS

This amendment includes changes in study procedures to reduce barriers to the timely screening and enrollment of index and network participants. The minimum network size has been reduced, resulting in a change in total number of networks needed and overall study size. In addition, the optional use of rapid HIV testing has been incorporated. Minor modifications to the sample informed consent forms have been made to reflect the changes. None of the changes affect participant risk, and no additional blood draws or other assessments have been introduced in this amendment. Additional changes have been made throughout as outlined below. All changes are detailed in the following "Implementation" section of this Summary of Revisions.

- 1) Though index participants must be willing to attempt to enroll two network members, only one must be enrolled in order for the network to be eligible (Schema, Sections 2.3, 3.1.1, 3.5, 5.2).
- 2) The overall study size has been revised due to changes in the required network size (Protocol Summary, Sections 3.3, 3.4, 7.3.1, 7.3.2, 7.3.3, Appendix III – V).
- 3) The timeframes in which enrollment/randomization of a network must be completed and the timeframe in which index members are allowed to recruit their network members have been further clarified. Additionally, the timing of the intervention has been revised so participants no longer need to be present at randomization (Schema, Sections 3.4, 3.5, 5.1.2, 5.2).
- 4) Sites may elect to use rapid HIV tests at screening or follow-up visit. The timeframe in which the study staff must report results of non-rapid HIV tests to participants has been clarified (Schema, Sections 3.1.1, 3.4, 4.2, 5.1.1, 5.1.2, 5.3 and Appendix I – V).
- 5) The above-mentioned changes have affected the Screening Procedures section of the sample informed consent for screening index participants (Appendix III).

Since version 1.0 of the protocol was finalized, the following aspects have been revised to describe the intervention more accurately:

- 6) Quality Assurance procedures for the intervention have been fully developed (Section 4.1).
- 7) Descriptions of the Intervention Sessions are revised (Section 4.1).
- 8) Duration and timing of Booster Sessions have been clarified. These will be 1-2 hours long and will occur within no more than 2 months (60 days) of the index participants' 6 and 12-month follow-up target dates. Participants will be able to complete booster sessions only if they have completed their follow-up visits (Sections 2.3, 4.1.2, Appendix IV).

The following changes have been made to include more detail or precision:

- 9) In the inclusion criteria for index participants, “treatment” has been more specifically defined to include only methadone treatment (Section 3.1.1).
- 10) In the exclusion criteria, “biomedical prevention study” has been defined as HIV vaccine research, microbicide research, or any other clinical research to test interventions aimed at preventing or reducing the risk of HIV infection (Section 3.2.1).
- 11) Guidelines for index control group activities have been specified (Section 4.1).
- 12) It is clarified that measurement of contamination and exposure to the Intervention may be assessed by recognition of several components of the Interventions, such as acronyms (Section 4.1).
- 13) To allow for reporting of positive HIV test results as required by local law, the guidelines for counseling sessions and disclosure of test results have been revised (Section 4.2).
- 14) The description of the baseline behavioral risk survey used for network members has been revised to mirror language used to describe the survey given to index participants (Section 5.1.2).
- 15) The guideline used for scheduling follow-up visits for network members has been clarified (Section 5.3).
- 16) The lack of reporting of serious adverse events to the DAIDS SAE office has been conveyed.
- 17) The study secondary endpoint of injection drug use, by drug, is modified to clarify that the number of times an individual practices injection of any drug is the endpoint, not injection of any particular drug (Section 7.2.2).
- 18) The statistical analyses are revised to include HIV-infected network members and to reflect changes in the required network size from 3 to 2 (Sections 7.3.1, 7.3.3, 7.3.4).
- 0 The primary analysis plan has been reworded (Section 7.5.1).
- 20) Plasma specimens for individuals who are screened but not enrolled may be discarded after one year. Participants will be notified of specimen storage in the informed consent (Section 9.3, Appendix III-V).
- 21) Minor additional changes (such as updating the information about the NIDA study referenced in the recruitment setting section, revising the team roster and making grammatical changes) have been incorporated throughout.

RATIONALE AND IMPLEMENTATION

Changes in protocol text are underlined and struck through below; additions to the text are underlined and highlighted in the amended protocol.

1) **Network Size:** Schema, Sections 2.3, 3.1.1, 3.5, 5.2:

The original study protocol specified that an index participant must identify and recruit at least two network members to be eligible for the study. Since enrollment began in Philadelphia, many networks have been found to be ineligible because only one network member completed the study screening within the time limit specified in the protocol. Only one network member will now have to complete all study screening procedures in order for the network to be eligible. Index participants will still have to identify and attempt to recruit at least two members in order to ensure that the index actually does have a network of injecting drug users or sex partners with whom he/she interacts. The fundamental assumption that peer mentoring/social influence is an effective mechanism for behavioral change within a community or group of peers remains. The members who enroll in the study are representative of the entire network, and while the required size of a network will be reduced, the requirement that an index does have a network of at least two others has not changed. The number of

network members that an index participant must recruit in order to be eligible for the study has been changed from two to one as follows:

- Schema has been changed to indicate that Index participants with <1 eligible network member will not be eligible for the study.
- Section 2.3, seventh and eighth sentences of the second paragraph will now read:

“Each index participant will then be asked to identify and attempt to recruit at least two members of his/her sex and/or drug HIV risk network over a one month period. One or more of the network members identified must complete all screening procedures and be determined eligible for this network to be randomized and enrolled.”
- Section 3.1.1, sixth bullet will be modified as follows:
 - “Willing and able to recruit to identify and attempt to recruit at least two HIV risk network members who are eligible for study participation according to the criteria in Sections 3.1.2 and 3.2.2.”
- Section 3.1.1, a seventh bullet will be added to read:
 - “Able to recruit at least one HIV risk network member who is eligible for study participation according to the criteria in Sections 3.1.2 and 3.2.2.”
- Section 3.5 and Section 5.2, see Point 3 below.

2) **Study Size:**

The change in the number of required network members affects the total study size by increasing the number of index participants required and decreasing the number of network members. The number of networks has been increased from 660 to 900; the total number of participants has changed from 2640 to 2610.

- The Protocol Summary, page 1, Study Size section will be changed as follows:

~~660~~ 900 networks (300 in Philadelphia, 600 in Thailand) consisting of ~~660~~ 900 index participants and approximately ~~1980~~ 1,350 HIV-uninfected network members (an average of 1.5 per index), ~~network members (an average of three network members per index participant)~~ for a total of approximately ~~2640~~ 2,250 HIV-uninfected participants. Allowing for the enrollment of HIV-infected network members and assuming an HIV prevalence of 20% in Philadelphia and 30% in Thailand, approximately 90 and 270 HIV-infected network members will be enrolled in Philadelphia and Thailand, respectively. The average network size across networks, including both HIV-positive and negative network members, is 1.9 network members per index participant, giving a total sample size of 2,610.

Because it is expected that some networks will have only one network member while others will have more than one, the average number of HIV-uninfected network members needed to achieve 90% power to detect a 40% reduction in rate of infection has been estimated at 1.5. The numbers of HIV-infected network members and the number of networks per site have also been estimated as follows:

- 900 index participants and approximately 1,350 HIV-uninfected network members (an average of 1.5 per index), and 360 HIV-infected network members (an average of 0.4 per index), for a total of approximately 2,610 participants. The number of HIV-infected network members is calculated using seroprevalence estimates of 20% in Philadelphia and 30% in Thailand.
- 450 networks per experimental arm, an increase from 330 in the previous protocol; 150 networks per arm in Philadelphia (750 HIV-uninfected and 90 HIV-infected participants) and 300 networks per arm in Thailand (1500 HIV-uninfected and 270 HIV-infected participants)
- The Philadelphia site will enroll approximately 28 participants (ten index participants and 18 network members) per month, a change from 7 indexes and 21 network members per month in the previous protocol. The site in Thailand will enroll approximately 59 participants (20 index and 39 network members) per month, a change from 15 index and 45 network members per month previously.

All references to study size numbers have been modified in the following sections:

- Protocol Summary: Study Size and Intervention Sections
- 3.3: Recruitment Setting
- 3.4: Recruitment Process
- 7.3.1: Power for seroincidence endpoints, including Table 1
- 7.3.2: Power for Behavioral Endpoints, including Table 2
- 7.3.3: Power for Assessment of Intervention Effect on Behavior, including Table 4
- Appendix III – V

3) **60 Day Window and Timing of Intervention:** Schema, Section 3.4, 3.5, 5.1.2, 5.2:

Protocol version 1.0 states that enrollment/randomization must be completed within 60 days of collecting a blood sample for HIV testing *from the potential index participant*. However, a potential network member can be screened for inclusion in more than one network at a time (even though s/he can ultimately be enrolled in only one). To ensure that HIV tests and other assessments for *all* members of a network are completed within a 60-day window (and thereby minimizing the risk that someone could become HIV infected between screening and enrollment), it is clarified that screening assessments for all members (not only indexes) must be completed within a 60-day window from the index’s screening HIV blood draw to enrollment/ randomization. Should the time between the initial blood draw and enrollment/ randomization of the network exceed 60 days for any individual, screening assessments must be repeated. Note that this does not specifically affect the study eligibility criteria as detailed in section 3.0.

Protocol version 1.0 indicated that the time allowed for recruitment of network members by the index participant is 30 days following the index participant’s post-test counseling visit. The purpose was to allow sufficient time to recruit and complete HIV testing and post-test counseling for the network members within 60 days of the index’s blood draw. To allow more leeway in the recruiting timeframe, it is clarified that recruitment must be completed within 60 days of the index’s pre-test counseling visit. The following changes will be made:

- Schema, Overview of Study Design and Randomization Schema:

The timeframe for recruitment of network members by index participants has been modified to state within 60 days of pre-test visit.

Reference to the Index Participant Randomization Visit and Randomization Baseline Surveys has been deleted.

- Section 3.4, fifth paragraph, last sentence has been modified as follows:

“For 30 days following Within 60 days of each prospective index participant’s post pre-test counseling session, their prospective network members will be able to go to the local study site to participate in study screening, as described above.”

- The first and second paragraphs in Section 3.5 have been modified as follows:

“Prospective index participants in networks consisting of one or more eligible network members (either HIV-negative or positive) will be asked to return to the study clinic approximately 30 days after their initial post contacted within 60 days of their HIV pre-test counseling visit to learn of their eligibility status. All individuals to be randomized must have initiated screening procedures fewer than 60 days prior to the planned date of randomization. Individuals who exceed this 60-day limit may be re-screened, and all screening procedures must then be completed before their network is qualified for randomization. Index participants ~~in networks that contain at least two eligible and consenting network members~~ will be randomized along with their network member(s) to either the experimental or control arm. ~~At this point participants will be officially enrolled in the study.~~ Study staff will ~~then~~ contact index participants and network members to confirm their enrollment status.

~~If fewer than two~~ no prospective network members identified by an index have presented for screening, been found to be eligible, and provided study consent within the ~~30~~60 days following the index participant’s post-pre-test counseling visit, the index participant ~~and any network members that may have presented for screening~~ will be considered ineligible for the study as a member of that network. Note: If identified as a network member as a network member of another prospective index participant, then he/she would be eligible to participate as a network member for that index.) Individuals identified by a prospective index member who is ultimately not eligible, may be recruited by study staff as an index member after three months of being determined ineligible to allow for the dissipation of any measurement effects.”

- The following has been added after the second paragraph in Section 3.5:

“Note: Individuals who initially screen (and provide consent) as an index member may subsequently be screened as a network member for another network, but must first complete the network member informed consent process and member screening assessment. As above, if the time between the participants initial HIV blood draw and enrollment/randomization of the network exceeds 60 days, screening procedures as specified in the SSP manual must be repeated.

Note: Individuals who initially screen as a network member may subsequently be screened as a network member for another network, but must first complete the member screening assessment for each network they are screening for. As above, if the time between the participants’ initial HIV blood draw and enrollment/ randomization of the network for which they qualify exceeds 60 days, screening procedures as specified in the SSP manual must be repeated.

Note: Individuals who initially screen as a network member may not screen as an index member for 3 months after their initial blood draw for HIV testing to allow for the dissipation of any measurement effects. After this three-month period, the individual may undergo the screening procedures as an index member after completing the index screening informed consent process.”

- Section 5.1.2, first paragraph will now read:

“Since randomization and enrollment of a network must occur within 60 days of the first screened participant’s pre-test visit, ~~an~~ individuals who ~~were~~ was provided with an identification card by ~~the~~ an index participant and identified as a member of ~~their~~ his/her HIV risk network must come into ~~will be able to drop in~~ at the local study site ~~to participate in~~ and complete all study screening procedures before the end of this 60 day period in order for the network to be eligible ~~for 30 days following the index participant’s post test counseling session.~~”

- Section 5.2 will be changed as follows:

An eligible network consists of an index and one or more network members who have presented for screening, been found to be eligible, and provided study consent. Screening and eligibility procedures for all index and network members must be completed within 60 days of the randomization date. ~~Index participants will be asked to return to the clinic for final enrollment and randomization approximately one month after the HIV test result visit. If two or more prospective network members identified by an index have presented for screening in the interim, been found to be eligible, and provided study consent, then the index will be considered eligible for the study and the investigators will close the network to additional members.~~ Eligible index participants will be randomized along with their network members to either the experimental or control arm. Those index members randomized to the experimental arm will be provided instructions about when their first peer-education training session is to take place; this will be within approximately one week of randomization ~~will be given an appointment to return for their first peer education training session.~~ Network members will be contacted to inform them of their eligibility/enrollment status.”

4) **Rapid Testing:** Schema, Sections 3.1.1, 3.4, 4.2, 5.1.1, 5.1.2, 5.3 and Appendix I - V:

When Version 1.0 of the protocol was developed, the FDA had not approved the use of rapid HIV testing. Consequently, the study procedures for screening visits and follow-up visits were designed to allow 1 week between drawing the blood sample to getting the results back from the laboratory. Use of the now-approved rapid testing will allow sites to determine eligibility more quickly, report test results within one visit, and provide more flexibility in scheduling visits.

For the rapid HIV tests, sites will select an approved kit and follow one of the algorithms that are attached to the amended protocol.

The protocol has been modified so that sites *not* using rapid testing may give results in a more flexible timeframe. The one-week timeframe specified in the original protocol was not to be applied as a strict window period. The time needed to perform ELISA and Western Blot tests varies from site to site and scheduling conflicts may occur. Post-test appointments are to be scheduled and test results made available as soon as possible, but provision of counseling and results outside of one week is acceptable.

- Schema will be changed from “Return for Results ~1 week” to “Results Available” for returning for post-test results.
- Section 3.1.1, fifth bullet will now read:
“HIV ~~ELISA~~ negative on specimen obtained within 60 days prior to randomization”

- Section 3.4, fourth sentence from the end of fourth paragraph will be changed as follows:

“Participants will be scheduled for a visit to return for their HIV test result and post-test counseling either the same day (for rapid testing) or in approximately one week (for standard testing) in one week.”
- Section 3.4, sixth paragraph, fourth sentence will be revised as follows:

“All individuals who participated in pre-test counseling and testing ~~will be scheduled to return in one week for HIV test results and post-test counseling and~~ must return for their HIV test results and post-test counseling for eligibility.”
- Section 4.2: second paragraph, second to last sentence will be changed as follows:

“The second counseling session will be conducted in conjunction with the confidential disclosure to participants of their HIV test results, ~~usually one week following the pre-test counseling session and phlebotomy.~~”
- Section 5.1.1: Paragraph that begins “Prospective index participants will be asked to return in approximately one week . . .” will now read:

“For non-rapid HIV tests, Prospective index participants will be asked to return in approximately one week for their second counseling session and their HIV test results and to undergo further eligibility screening. If the site is using rapid HIV testing, the potential participant will be asked to wait for the results. Regardless of which test the sites use for screening, the procedures for post-test counseling are the same. Those who test . . .”
- Section 5.1.2: Second paragraph will be modified as follows:

“Screening of network members is expected to take place over one (for rapid tests) or two more visits. During the pre-test first-visit, prospective network members will undergo the following...
 During the post-test visit (which may occur the same day if using the rapid tests), network members will receive their HIV test results, post-test counseling, and appropriate referrals. . . .”
- Section: 5.3: Follow-up Visits: In the first paragraph, the sentence that begins “Post-test counseling visits will occur 7 to 14 days . . .” will be modified as follows:

“Post-test counseling visits will occur either the same day (for rapid tests) or in approximately 7 to 14 days (for non-rapid tests) after HIV testing.”
- Section 5.3: Follow-up Post-test Visits: This section will be modified as follows:

“Section 5.3.1 Follow-up Post-test Visits: Regardless of HIV-test results, participants who undergo HIV-testing ~~at follow-up visits~~ will complete a follow-up, post-test visit approximately 7 to 14 days after testing if using non-rapid testing or the same day if using rapid testing. ~~and~~ During this visit ~~which~~ (at a minimum) their HIV test results will be disclosed and HIV post-test counseling and appropriate referrals will be provided.”
- Appendix I: Algorithms for rapid HIV testing have been added.

- Appendix II: Footnote † will be modified as follows:

“Regardless of HIV test results, participants will complete a post-test counseling visit either the same day (for rapid tests) or approximately 7-14 days (for non-rapid tests) after HIV testing”

- Appendix III: Screening Procedures section will be revised as shown in Point 5.

- Appendix IV, Study Procedures, Follow-up visits, second and fifth sentences will now read:

“Each follow-up visit will last about one to two hours... You will be told when your can return for your test results will be available.”

- Appendix V, Study Procedures, Screening and Enrollment section, first and seventh sentences will be revised as follows:

“If you agree to participate in the study, your first visit will last about 1 to 2 hours and may proceed today, if you are willing... You will be told when your can return for your HIV test result will be available.”

- Appendix V, Follow-up Visits section, second and fifth sentences will now read:

“Each follow-up visit will last about one to two hours... You will be told when your can return for your test results will be available.”

5) **Appendix III:** Sample Informed Consent for Screening Index Participants:

Changes in network size, the 60 day screening window, the timing of the intervention, and the use of rapid testing have resulted in the following changes to the Screening Procedures section of the Sample Informed Consent for Screening Index Participants:

“Overview

The screening process will take about 2 months. During this time you will be asked to come to the study clinic two ~~three~~ or more times. At the first visit, you will be asked some questions about yourself, including questions about your sexual and drug use practices. You will be offered HIV counseling and testing. ~~About one week later~~ When your HIV test results are ready, you will return to this study clinic to learn be given your HIV test results and receive counseling at this clinic. To be eligible to participate in the research study, you must identify and attempt to recruit at least two other people with whom you have sex or take drugs who might be willing to participate in the study. You will be asked to provide a description of these people and their initials to the study staff. The study staff will not contact these individuals directly. You will be given a card to give to each person to bring back to the study clinic for screening. At least one of these individuals must come to the clinic for screening within ~~three weeks~~ 60 days of the visit at which you have your blood drawn for your ~~are told your~~ HIV test result. Some people may not be able to join the study because of information found during the screening.

Screening Visit # 1:

The first screening visit will last about 1 hour and may proceed today if you are willing. To find out if you are eligible for the study, the study staff will ask you some personal questions about your sexual practices and drug use. You may feel embarrassed by these questions. You may choose not to

answer any of these questions. ~~You will also be asked to provide the initials and a short description of at least two people with whom you have sex or do drugs and whom you would be willing ask to also participate in the study.~~ A study staff member will draw a sample of about 8 ml of blood (about 2 teaspoons or local equivalent) from you to be tested for HIV. Your blood sample will be stored at a local laboratory and discarded at or before the end of the study. Your name will not be linked to the sample. The study staff will also ask you to provide information on where you can be contacted.

Screening Visit #2:

The second screening visit will take place ~~when your HIV test results are available about one week after the first visit~~ and will last about one hour. At this visit, you will be given your HIV test result. The study staff will talk with you about the meaning of your HIV test result and how you feel about it. You must receive your HIV test result to be eligible for the research study.

If you are infected with HIV, study staff will counsel you about what this means and how to avoid passing the virus to other people. You will be given information about where you can go for additional counseling and help, and you will be referred for medical care and treatment. You will also be told about any other research studies for which you may be eligible.

If you are NOT infected with HIV and you meet all of the other eligibility criteria, the study staff will fully explain the purpose and the risks and benefits of the research study to you. They will explain what will be expected of you if you decide to participate. If you are willing to participate in the research study, you will be asked to sign another consent form. You will also be asked to provide the initials and a short description of at least two people with whom you have sex or do drugs and whom you would be willing to ask to also participate in the study. You will be asked to proceed with recruiting at least two other people to participate in the study. These will be the people whose initials and description you gave the study staff at the first screening visit. The study staff will give you an identification card to give to each person to bring into the study clinic for screening. The study staff will not contact these people directly. During the next ~~three weeks~~ month or two, these individuals may come to the clinic at any time for study screening.

~~You will be given an appointment to return to the study clinic three weeks later. During the next 4-8 weeks, the staff may contact you to let you know if any of the persons you have identified have come to the clinic and to see if you are still interested in participating.~~

For you to be eligible, at least one of the individuals you identified must be also be eligible for the research study and willing to participate. If you are eligible for the study, you will be given an appointment for your next study visit.”

6) **Quality Assurance for Intervention:** Section 4.1, eighth paragraph will be changed as follows:

Group facilitators will follow a detailed intervention manual covering specific topics and activities conducted at each of the peer education sessions. A basic description of each of the sessions is provided below. The site supervisor will perform quality assurance reviews ~~will be completed~~ on 10% of the education sessions via direct observation or audiotape. The sessions will be evaluated based on the session length, completion of the intervention components, and impressions of the quality of the delivery by the study site supervisor.

7) **Intervention Description:** Section 4.1, following paragraph eight:

Version 1.0 of the protocol included an illustrative description of the planned intervention sessions. Section 4.1 has been updated to reflect the final content of the sessions. Descriptions of the intervention sessions will be changed as follows:

Session 1: Introduction: Participants will identify concerns facing their community, gain an understanding of the role of helping others in their community, start to identify ways in which people have peer mentored them or they have been peer mentors, and identify barriers and solutions to completing the intervention.

Session 2: Sex and Drug Use Risks and Prevention Strategies: Participants will gain an understanding of drug-related risk practices; learn how to effectively clean and disinfect injection equipment; learn prevention strategies to teach to others in outreach, and identify risky situations and strategies to avoid them. Participants will learn and practice how to talk to peers about drug-related risk reduction behaviors.

Session 3: Sexual Decision Making and HIV Risk, Prevention and Outreach: Participants will identify HIV/STI narratives; discuss and role play effective communication about risk reduction and discuss influences on sexual decision-making. Participants will learn how to use condoms effectively, practice discussing condom use with partners, and practice doing outreach with network members.

Session 4: Tools for Effective Outreach: Participants will practice and learn effective components and strategies for conducting outreach and education with peers. Participants will start to develop a personal toolbox of strategies for conducting effective peer education and outreach, and will discuss and rehearse methods for conducting outreach safely.

Session 5: Outreach: Participants will review HIV/STI risks from sex and drug use; identify barriers to the conduct of effective peer education and outreach, and will strategize about ways to overcome these barriers.

Session 6: Outreach Experience and Graduation: Participants will be accompanied by facilitators to do peer outreach. They will set goals for their own outreach at the end of this session and will graduate from the program.

“Session 1: Introduction: Participants will be introduced to study goals and will establish group rules in order to build group cohesion. They will discuss ways HIV is transmitted and the role of a peer mentor in disseminating harm reduction messages.

Session 2: Peer Mentoring and Injection-related HIV Risk Behaviors: This session will teach the basic concepts of harm reduction with safer injection behaviors, and how mentors can deliver these concepts within their social networks. Participants will view a video and practice with role-plays.

Session 3: Safer Sex Practices and Communication Skills: This session will motivate participants to adopt less risky sexual behavior. Participants will view a video and practice condom skills.

Session 4: Personal Resistance to Change: Participants will identify their own personal barriers to adopting safer behavior and learn negotiation skills in reducing sexual and injection risk. The session includes training in Active Listening skills.

Session 5: Interpersonal Barriers to Peer Mentoring: During this session, participants will identify and re-frame their barriers to peer mentoring and will practice effective ways to approach others as a peer mentor.

Session 6: Review, Mentor Plans, and Graduation: Participants will set goals for their roles as mentors and will review lessons about harm reduction. There will be a graduation ceremony and refreshments.

8) **Booster Sessions:** Sections 2.3, 4.1.2, Appendix IV:

The timing of the booster sessions following 6- and 12-month follow-up visits has been changed to allow for greater flexibility in scheduling. The duration of the booster sessions has also been changed to allow more time to accommodate large groups and/or extensive discussions.

- Section 2.3, fourth sentence of the third paragraph will be revised as follows:

“There also will be a one to two hour booster training session held for the index participants after their six and 12-month follow-up assessments.”

- Section 4.1.2 will now read:

“Within no more than 1-2 months (60 days) following their 6-month and 12-month follow-up ~~assessments-target dates~~, index participants who were randomized to the treatment arm will meet in small groups with a maximum of 12 participants for a one to two hour booster session. Participants must complete the follow-up visit prior to attending the booster session. An Index may not attend a booster session once the 60-day window closes. These booster sessions will...”

- Appendix IV, Study Procedures, fourth sentence of the Education and training sessions section will be revised as follows:

“Each of these two training sessions will last about one to two hours.”

9) **Methadone:** Section 3.1.1, fourth bullet:

An inclusion criterion for index participants in revised protocol version 1.0 states that individuals must have been “out of treatment for at least 3 months and have relapsed.” The purpose of the criterion is to exclude individuals who may be at a lower risk of acquiring HIV. The definition of treatment for operationalization of the protocol has been more clearly defined as “methadone maintenance treatment” only (not methadone received as part of detoxification). Research over the past 15 years has documented the impact of participation in methadone treatment in reducing the frequency of injection and drug related risk behaviors. There is also substantial evidence that participants in methadone maintenance treatment have lower prevalence and incidence of HIV infection. Other forms of drug treatment have not produced comparable results with respect to HIV risk and incidence and emerging data suggest that drug detoxification alone is a marker for an increased likelihood of incident infections. The treatment inclusion criterion for index members has been clarified as follows:

“Been out of methadone maintenance treatment for at least 3 months and have relapsed.”

10) **Biomedical Definition:** Section 3.2.1, first bullet:

In version 1.0 of the protocol, the first bullet in Section 3.2.1 indicates that “Prior or concurrent enrollment in the last 6 months in another HIV behavioral or biomedical prevention study” is an exclusion criterion. However, biomedical prevention study was not specifically defined.

“Biomedical prevention study” is now defined as HIV vaccine research, HIV microbicide research, or any other clinical research to test an intervention aimed at preventing or reducing the risk of HIV infection as follows:

“Prior or concurrent enrollment in the last 6 months in another HIV behavioral or biomedical prevention study (HIV vaccine research, HIV microbicide research, or any other behavioral or clinical research to test an intervention aimed at preventing or reducing the risk of HIV infection).”

11) **Control Group:** Section 4.1, following fourth paragraph:

Version 1.0 of the protocol does not specify guidelines for index control group activities. Note that all study participants – both indexes and network members – regardless of study group, are provided enhanced HIV counseling at each study visit as described in the protocol. No change in these activities is required. A new paragraph describing control group activities is added as follows:

“The only control group activities will be to contact the index members to inform them of their group assignment and to set up next scheduled appointments. However, sites may elect to hold focus groups with some of the control group indexes provided they have IRB approval.”

12) **Exposure of Participants To HIV Prevention-Related Messages:** Section 4.1, seventh paragraph, third sentence:

Protocol Version 1.0 states: “Participants will also be tested on their level of recognition of logos affiliated with the experimental arm intervention.” Since version 1.0 was approved, the experimental intervention has undergone revision. There are other components of the intervention that will be tested for recognition during the follow-up data collection. The sentence will be changed to:

“Participants will also be tested on their level of recognition of various components ~~logos~~ affiliated with the experimental arm intervention.”

13) **Reporting Requirements:** Section 4.2, third paragraph:

To allow for reporting of positive HIV test results as required by local law, the guidelines for counseling sessions and disclosure of test results have been revised.

– The second bullet is changed as follows:

- “It is solely the right and choice of the participant to disclose his/her HIV status to others, except as mandated by local reporting requirements.”

– The fourth bullet is changed as follows:

- “Neither counselors nor any other member of the study staff will provide information about a participant without a written and signed request from the participant, except as required by local reporting laws. If a participant makes ~~Even with~~ such a request, the desired information will only be directly released to him/her ~~the participant.~~”

14) **Behavior Survey:** Section 5.1.2, second paragraph, bullet three:

The same behavioral baseline HIV risk survey is given to both index and network participants during screening. The description of the survey for network members is revised as follows to mirror language used for index participants in section 5.1.1:

- “Baseline HIV behavioral-risk behavior survey (prior to counseling)”

15) **Follow-up Visits:** Section 5.3, last sentence:

The guideline used for scheduling follow-up visits for network members has been clarified as follows:

“For the purposes of scheduling follow-up visits, a single “Day 0” enrollment/randomization will be assigned to all network members according to the randomization date of their respective index.”

16) **Serious Adverse Event Reporting:** Section 6.0, first sentence:

As specified in the protocol, no serious adverse events (SAEs) are expected because of the behavioral nature of this study. Therefore, no SAEs will be reported. A sentence has been added as follows:

“Because of the purely behavioral nature of the intervention, no "biological" adverse experiences directly attributable to the intervention are anticipated. As such, no adverse events will be reported to the DAIDS SAE Office.”

17) **Secondary Endpoint:** Section 7.2.2, first bullet:

Protocol Version 1.0 lists, “Frequency of injection drug use, by drug” as a secondary endpoint. The primary purpose of this endpoint is to assess the number of times that a needle entered the person's body, an aggregate frequency of injection behavior. Asking the number of times *by drug* would have been an unnecessary burden to the participant and would not have added value to the desired endpoint. The secondary endpoint of injection drug use is modified as follows:

- “Frequency of injection drug use, ~~by drug~~”

18) **Statistical Considerations:** Sections 7.3.1, 7.3.3, and 7.3.4:

The statistical analyses are revised to reflect changes in the required network size from 3 to 2 and the number of networks needed for analyses. In addition, the statistical considerations in protocol version 1.0 did not account for the enrollment of both HIV-infected and uninfected network members, though this was always allowed. Estimates of the number of HIV-infected study participants have been added.

– Section 7.3.1, paragraphs under Table 1 have been modified as follows:

“The sample size has been chosen to achieve 90% power to detect a 40% reduction in rate of infection, from 6% per year to 3.6% per year. This requires ~~343~~⁴⁴⁵ networks per arm, ~~assuming networks of four IDUs~~ followed for an average of 27 months (minimum of 18 month, maximum of 30 months), with a ~~mean~~-seroincidence evaluation of ~~four~~ an average of 2.5 HIV-uninfected people per network (HIV-uninfected peer leader and ~~three~~ one or more network members, HIV-uninfected at enrollment) and loss to follow-up of 10% per year, using two-sided alpha of 0.05

and intraclass correlation of 0.2. To achieve the same power to detect a 33% reduction, from 6% to 4%, requires ~~515~~669 networks per arm.

Enrolling ~~343~~445 networks per arm implies a ~~total~~ study enrollment of approximately ~~2736~~2,250 HIV-uninfected participants: approximately ~~110~~120~~150~~ networks per arm in Philadelphia (~~900~~total~~750~~ HIV-uninfected participants) and ~~220~~230~~300~~ networks per arm in Thailand (~~1800~~total~~1500~~ HIV-uninfected participants). The protocol allows for the enrollment of HIV-infected network members, and assuming a prevalence of 20% and 30% amongst injectors in Philadelphia and Thailand respectively, we are projecting enrollment of 90 HIV-infected network members in Philadelphia and 270 in Thailand. The total participant enrollment, including both HIV-infected and HIV-uninfected participants, is thus projected to be 2610: 1770 in Thailand and 840 in Philadelphia, with an average of 1.9 network members per index participant. Network members who are infected with HIV will be excluded from the analysis of the primary endpoint.

For the endpoint at the Thailand site alone, assuming a higher seroincidence of 8% per year, 90% power to detect a 40% reduction in seroincidence is achieved with ~~255~~332 networks per arm ~~80% power is achieved with 191 networks.~~

~~No prior estimates are available for a κ . For the design above, 40% reduction from a baseline of 6% seroincidence with average network size of 4, κ of 0.2 corresponds to a 10% increase in probability of concordance, from 52.25% under independence to 62.25% assuming correlation within networks. κ of 0.3 corresponds to a 14% increase, and 0.1 to a 5% increase.”~~

- Section 7.3.3, Table 4 has been revised. The last sentence in second paragraph and next to last sentence in third paragraph will now read:

For these calculations, the sample size is taken as fixed by the requirement for adequate power for the primary endpoint, at ~~445~~343 networks of average size ~~2.9~~4-per arm, and it is assumed 2/3 of the networks are in Thailand.

If the true prevalence in Philadelphia were ~~62~~60% or 26%, there would be 80% power to detect this. . . .”

- Section 7.3.4, second paragraph will now read only:

~~“A proportion of the network members of an HIV-uninfected index will be HIV-infected, so it may be difficult to attain an average of 4 endpoints per network. However, the unit of randomization is the network, not the individual, so obtaining fewer assessments within each network has relatively little effect on power. For example, if the mean assessment were reduced to 3 per network (640 fewer people), only 120 additional networks (240 people) would need to be enrolled to retain 90% power. In addition, the increased risk of seroconversion to the HIV-uninfected members of the network from having a HIV-infected person in their risk network may offset the loss of information. The seroincidence rate and the average number of network members will be monitored closely during the study to assure that adequate power is attained. The seroincidence rate and the average number of network members will be monitored closely during the study to assure that adequate power is attained.”~~

19) **Primary Analysis:** Section 7.5.1:

Consistent with the primary study objective, the primary analysis plan will be revised as follows:

- HIV seroincidence

“Comparison of HIV seroincidence rates in the two arms will be based on the decrease in risk of infection between the two arms estimated via proportional hazards regression, stratified by site. Statistical estimation and inference will be based on the marginal models approach to extending the Cox model to the analysis of correlated survival data, described for example in Therneau. This has much in common with the Generalized Estimating Equation (GEE) approach of Zeger, et al.³⁶ comparison of the mean of the aggregate network seroincidence rates in each arm (i.e., average of seroincidence rates within each network). Statistical inference will use a Generalized Estimating Equation (GEE) approach, as the observations from each network are correlated. A Poisson distribution has been assumed for an individual’s risk of infection over the observed time on study. This leads to GEE estimation with an overdispersed Poisson family.”

- HIV seroincidence in Thailand

The comparison analysis of seroincidence rates between per arms will be repeated for the Thailand site alone.”

20) **Specimen Storage:** Section 9.3, Appendices III – V:

It is clarified that specimen storage requirements apply only to specimens for *enrolled* participants. Plasma specimens for *non-enrolled* may be discarded one year following collection. Participants will be notified of specimen storage in the informed consent.

- Section 9.3, Storage for plasma specimens has been modified as follows:

“Study site staff will store all plasma specimens for enrolled participants collected in this study at least through the end of the study. All plasma specimens for enrolled participants will be subject to possible quality assurance testing—for HIV antibody—as described in Section 9.2. Specimens from non-enrolled participants may be discarded one year following the collection date.”

- Appendix III, Screening Procedures section will be revised as shown in Point 5.
- Appendix IV & V, Follow-up visits section, a new paragraph will be added after the second paragraph to say:

“Your blood samples will be stored at a local laboratory and will be discarded at or before the end of the study. Your name will not be linked to any of your blood samples.”

21) **Protocol Team Roster:** The team roster has been modified as follows:

Spelling of Namthip Srirak, RN, PhD has been corrected

Spelling of Tasañai Vongchak, RN, MPH has been corrected

Kevin Ryan’s email address has been corrected

Telephone number for Tom Perdue has been corrected, (206) 6767-6216

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- 22) **Grammar and Spelling:** Several grammatical and spelling corrections have been made throughout the document. The information about the NIDA study referenced in the recruitment setting section, 3.3, has been updated.