

CLARIFICATION #2 to:

HPTN 037

A Phase III Randomized Study to evaluate the efficacy of a network-oriented peer education intervention for the prevention of HIV transmissions among injection drug users and their network members, Revised Version 1.0, dated April 3, 2002

May 14, 2003

SUMMARY OF REVISIONS

Note: None of the items addressed in this clarification affect the informed consent forms or risks to study subjects in any way.

1. 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)
2. Guidelines for index control group activities have been specified. (Section 4.1)
3. The timeframe in which the study staff must report results of HIV tests to the individual has been clarified. (Sections 5.1.1 and 5.3)
4. The timing of the first intervention session has been clarified.
5. Plasma specimens for *non-enrolled* may be discarded after one year. (Section 9.3)

RATIONALE AND IMPLEMENTATION

1) In version 1.0 of the protocol, Page 12, Section 3.2.1, the first bullet 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. The definition will be added to the protocol with the next amendment in a footnote linked to the exclusion criterion.

Implementation: In the next amendment to the protocol, the definition provided above will be added in parentheses at the end of the bullet specifying this exclusion criterion as underlined below: “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 interventions aimed at preventing or reducing the risk of HIV infection).”

2) Version 1.0 of the protocol does not specify guidelines for index control group activities. A control group guide has been added to the SSP and is now referenced in the protocol to ensure consistency across sites and over time. The control group guide clarifies the nature of activities/information to which indexes who are not randomized to the intervention group may be exposed. 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.

Implementation: In the next amendment to the protocol, a statement briefly describing the control group activities and referring to the control group guide in the SSP will be added to Section 5.5.

3a) In version 1.0 of the protocol, page 20, Section 5.1.1, the first full paragraph states: “Prospective index participants will be asked to return in one week for their second counseling session and their HIV test results and to undergo further eligibility screening.”

3b) In version 1.0 of the protocol, page 22, Section 5.3 states: “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, . . .”

The timeframes specified above are not to be applied as strict window periods. The time needed to perform ELISA and Western Blot tests varies from site to site and scheduling conflicts are expected. Post-test appointments are to be scheduled and test results made available as soon as possible, but provision of counseling and results outside of the timeframe referred to above is acceptable.

Implementation: In the next amendment to the protocol, Section 5.1.1 will be changed to state that: “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.” Section 5.3 need not be changed. (Note that use of rapid HIV testing may be introduced in the next amendment and, if so, the exact wording will need to accommodate that strategy as well.)

4) In protocol, Version 1.0, Page 21, Section 5.2 states: “Those randomized to the experimental arm will be given an appointment to return for their first peer-education training session.” It is clarified that the first intervention session may be completed on the same day as randomization; therefore no separate appointment will be necessary. This flexibility will reduce the possibility that randomized subjects will be lost to follow-up before completing the first intervention session and will reduce the number of times a participant must return to the site.

Implementation: In the next amendment to the protocol, Section 5.2 will be changed to state that: “Those randomized to the experimental arm will be provided instructions about when their first peer-education training session is to take place; this may be the same day as randomization.”

5) In protocol, Version 1.0, Page 37, Section 9.3, states: “Study site staff will store all plasma specimens collected in this study at least through the end of the study. All plasma specimens

will be subject to possible quality assurance testing-- for HIV antibody-- as described in Section 9.2.” It is clarified that this requirement applies only to specimens for *enrolled* participants. Plasma specimens for *non-enrolled* may be discarded one year following collection.

Implementation: In the next amendment to the protocol, section 9.3, will be changed to state that: “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.”

CLARIFICATION #1 to:

HPTN 037

A Phase III Randomized Study to evaluate the efficacy of a network-oriented peer education intervention for the prevention of HIV transmissions among injection drug users and their network members, Revised Version 1.0, dated April 3, 2002

December 12, 2002

SUMMARY OF REVISIONS

Note: None of the items addressed in this clarification affect the informed consents or risks to study subjects in any way.

1. The timeframe in which enrollment/randomization of a network must be completed has been further clarified (Sections 3.5, 5.1, 5.1.2).
2. The timeframe in which the index members are allowed to recruit their network members into the study has been clarified. (Overview of study design and randomization schema Sections 3.4, 3.5, 5.1.2)
3. In the inclusion criteria for index participants, “treatment” has been more specifically defined.
4. Corrections have been made to the protocol team roster list.

RATIONALE

1) 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 minimize 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 screening HIV blood draw to enrollment/randomization). Should the time between the initial screening HIV blood draw and enrollment/randomization of the network exceed 60 days for any individual, screening assessments as specified in the SSP manual must be repeated. Note that this does not specifically affect the study eligibility criteria as detailed in section 3.0.

2) Protocol version 1.0 indicates that the time allowed for recruitment of network members by the index participant is 30 days after or 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 for the fact that screening procedures for a network member initially screened for another network may

occur before the index has completed the post test counseling visit and to allow more leeway in the recruiting timeframe (while adhering to the overall 60 day window addressed above), it is clarified that recruitment must be completed “within approximately” 30 days of the index’s post test counseling visit. Note that this does not specifically affect the study eligibility criteria as detailed in section 3.0.

3) 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 (1, 2). 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.

1. Metzger D, Navaline H, Woody G. Drug abuse treatment as HIV prevention. Public Health Reports, 1998;118 (suppl.), 97-106

2. Sorensen J, and Copeland A. Drug abuse treatment as an HIV prevention strategy: a review. Drug and Alcohol Dependence. 2000;59, 17-31.

IMPLEMENTATION

THE FOLLOWING MODIFICATIONS ARE MADE TO PROTOCOL 037 (REVISED VERSION 1.0) TO IMPLEMENT THE REVISIONS DESCRIBED ABOVE. THESE MODIFICATIONS WILL BE INCORPORATED INTO THE BODY OF THE PROTOCOL IN THE NEXT VERSION.

Overview of Study Design and Randomization Schema:

- The timeframe for recruitment of network members by index participants has been modified to state within approximately 30 days after test result.

Section 3.1.1:

- The treatment inclusion criterion for index members has been clarified as follows;
“Have not received methadone maintenance treatment for at least 3 months and have relapsed.”

Section 3.4 (5th paragraph):

- The last sentence in paragraph 5 of section 3.4 has been modified as follows

“For approximately 30 days following each prospective index participant’s post-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.”

Section 3.5 (2nd paragraph):

- The second paragraph in Section 3.5 has been modified as follows:

If fewer than two prospective network members identified by an index have presented for screening, been found to be eligible, and provided study consent within approximately 30 days following the participant’s post-test counseling visit, the index participant and any network member that have presented for screening will be considered ineligible for the study as a member of that network. If identified as a network member of another prospective index participant then he/she would be eligible to participate as a network member for that index; however, if it has been more than 60 days from the planned randomization day that the screening procedures have been completed, then all screening procedures for that individual must be repeated. 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 dissipation of any measurement effects.

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 exceed 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 exceed 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. 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 (1st paragraph):

- The firsts paragraph in Section 5.1.2 has been modified as follows:

Individuals who were provided with identification cards by the index participants and identified as members of their HIV risk network will be able to drop-in at the local study site to participate in study screening for approximately 30 days following the index participant’s post-test counseling session.

Protocol Team Roster List:

- Spelling of Namtip Srirak, RN, PhD has been corrected
- Spelling of Tasanai Vongchak, RN, MPH has been corrected
- Telephone number for Tom Perdue has been corrected, (206) 667-6216

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

A Study of the HIV Prevention Trials Network

Sponsored by:

US National Institute of Allergy and Infectious Diseases and
U.S. National Institute of Child Health and Human Development
U.S. National Institute on Drug Abuse
U.S. National Institute of Mental Health
U.S. National Institutes of Health

Protocol Chair:

Carl Latkin, PhD

Johns Hopkins University
Johns Hopkins Bloomberg School of Public Health
Baltimore, MD USA

Protocol Co-chairs:

David D. Celentano, DSc

Johns Hopkins University
Johns Hopkins Bloomberg School of Public Health
Baltimore, MD USA

David Metzger, PhD

University of Pennsylvania
Center for Studies of Addiction
Philadelphia, PA USA

**Revised Version 1.0
April 3, 2002**

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**

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND ACRONYMS	iii
PROTOCOL TEAM ROSTER.....	iv
PROTOCOL SUMMARY	1
OVERVIEW OF STUDY DESIGN AND RANDOMIZATION SCHEMA	4
1.0 INTRODUCTION.....	6
1.1 Background.....	7
1.2 Study Rationale.....	10
2.0 STUDY OBJECTIVES AND DESIGN	10
2.1 Primary Objective	10
2.2 Secondary Objectives.....	10
2.3 Study Design	11
3.0 STUDY POPULATION.....	12
3.1 Inclusion Criteria	13
3.2 Exclusion Criteria	13
3.3 Recruitment Setting.....	14
3.4 Recruitment Process.....	15
3.5 Enrollment of Networks and Randomization.....	16
3.6 Participant Retention.....	17
3.7 Participant Withdrawal.....	17
4.0 BEHAVIORAL INTERVENTIONS.....	18
4.1 Experimental Peer Education Intervention	18
4.2 Enhanced Risk Reduction Counseling and HIV Testing Intervention.....	20
5.0 STUDY PROCEDURES	21
5.1 Screening (-60 to -1 Days).....	22
5.2 Study Enrollment/Randomization of Index and Network Members (Day 0)	23
5.3 Follow-up Visits.....	23
5.3 Follow-up Post-test Visits.....	24
5.4 Locator contacts.....	24
5.5 Interim Visits.....	24
5.6 Study Endpoint Assessment for Participants who Withdraw.....	24
6.0 SOCIAL HARMS	25
6.1 Monitoring of Social Harms	25
7.0 STATISTICAL CONSIDERATIONS.....	26
7.1 General Design.....	26
7.2 Study Endpoints	26
7.3 Sample Size and Accrual.....	27
7.4 Random Assignment.....	33
7.5 Analysis Plan.....	33

7.6	Interim Monitoring Process.....	34
8.0	HUMAN SUBJECTS CONSIDERATIONS.....	34
8.1	Ethical Review	34
8.2	Informed Consent	35
8.3	Risks.....	35
8.4	Benefits	36
8.5	Confidentiality.....	37
8.6	Communicable Disease Reporting Requirements.....	38
8.7	Study discontinuation.....	38
8.8	Community Preparedness.....	38
9.0	LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT.....	39
9.1	Local Laboratory Specimens	39
9.2	Laboratory Quality Assurance	39
9.3	Specimen Storage	39
9.4	Biohazard Containment	39
10.0	ADMINISTRATIVE PROCEDURES.....	40
10.1	Study Activation	40
10.2	Study Coordination.....	40
10.3	Study Monitoring.....	40
10.4	Protocol Compliance	41
10.5	Investigator's Records	41
10.6	Use of Information and Publications	41
11.0	REFERENCES.....	42
	APPENDICES.....	45
I	HIV Antibody Seroconversion Testing Algorithm II Schedule of Visits and Procedures.....	45
II	Study Visit Procedures Table	46
III	Sample Informed Consent for Screening of Index Participants	48
IV	Sample Informed Consent for Enrollment of Index Participants.....	53
V	Sample Informed Consent for Screening and Enrollment of Network Members.....	58

LIST OF ABBREVIATIONS AND ACRONYMS

AIDS	acquired immunodeficiency syndrome
ALIVE	AIDS Link to Intravenous Drug Users
CAB	Community Advisory Board
CDC	U.S. Centers for Disease Control and Prevention
CI	confidentiality interval
CL	(HPTN) Central Laboratory
CMU	Chiang Mai University
CORE	(HPTN) Coordinating and Operations Center
DAIDS	U.S. National Institute of Allergy and Infectious Diseases, Division of AIDS
DSMB	Data and Safety Monitoring Board
EC	Ethical Committee
FHCRC	Fred Hutchinson Cancer Research Center
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
FHCR	Fred Hutchinson Cancer Research Center
GEE	generalized estimating equations
HIV	human immunodeficiency virus
HPTN	HIV Prevention Trials Network
HPTU	HIV Prevention Trials Unit
IATA	International Air Transport Association
IDU	injection drug user
IFA	immunofluorescence assay
IRB	Institutional Review Board
LDMS	Laboratory Data Management System
LL	local laboratory
mL	milliliter
NDTC	Northern Drug Dependency Treatment Center
NGO	non-governmental organization
NIAID	(U.S.) National Institute of Allergy and Infectious Diseases
NIDA	(U.S.) National Institute on Drug Abuse
NIH	(U.S.) National Institutes of Health
OR	odds ratio
PRC	(HPTN) Protocol Review Committee
PSRC	(DAIDS) Prevention Science Review Committee
QA	quality assurance
RIEHS	Research Institute for Health Sciences
SAFE	Stop AIDS for Everyone Study
SDMC	(HPTN) Statistical and Data Management Center
SCHARP	Statistical Center for HIV/AIDS Research & Prevention
SHIELD	Self Help and Eliminating Life Threatening Disease Study
SSP	study-specific procedures
STI	sexually transmitted infection
UNAIDS	United Nations Programme on HIV/AIDS
US	United States
VSPH	vaccine preparedness cohort study
WB	Western blot

WHO

World Health Organization

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

PROTOCOL TEAM ROSTER

Protocol Chair

Carl Latkin, PhD
Associate Professor
Johns Hopkins Bloomberg School of Public Health
Department of Health Policy and Management
624 N. Broadway Street
Baltimore, MD 21205 USA
Phone: 410-955-3972
Fax: 410-955-7241
clatkin@jhsph.edu

Protocol Co-Chairs

David D. Celentano, Sc.D.
Professor, Infectious Disease Program
Johns Hopkins Bloomberg School of Public Health
Department of Epidemiology
615 North Wolfe Street, Suite E-6008
Baltimore, MD 21205 USA
Phone: 410- 955-1356
Fax : 410-955-1383
dcelenta@jhsph.edu

David Metzger, PhD
Associate Professor
University of Pennsylvania
Center for Studies of Addiction
3900 Chestnut Street
Philadelphia, PA 19104 USA
Phone: 215 746-7346
Fax: 215-746-7377
metzger@mail.trc.upenn.edu

Thailand Site Investigators

Thira Sirisanthana, MD
Professor, Department of Medicine
Faculty of Medicine
Director, Research Institute for Health Sciences
Chiang Mai University
Chiang Mai Thailand
Phone: 66 53 221 966
Fax: 66 53 221 849
ssirisan@mail.med.cmu.ac.th

Jaroon Jittiwutikarn, MD
The Northern Drug Treatment Center
Department of Medical Services
Ministry of Public Health
Ampur Mae Tang
Chiang Mai Thailand
Phone: 66 53 221 966
Fax: 66 53 221 849
jaroon@loxinfo.co.th

Apinun Aramrattna, MD, PhD
Assistant Professor
Department of Family Medicine
Faculty of Medicine
Chiang Mai University
Chang Mai Thailand
Phone: 66 53 221 966
Fax: 66 53 221 849
apinun@mail.med.cmu.ac.th

Namthip Srirak, RN, PhD
Senior Researcher
Research Institute for Health Sciences
Chiang Mai University
Chiang Mai Thailand
Phone: 66 53 221 966
Fax: 66 53 221 849
rhonsrrk@chiangmai.ac.th

Tasani Vonchuk, RN, MSc
Researcher
Research Institute for Health Sciences
Chiang Mai University
Chiang Mai, Thailand
Phone: 66 53 221 966
Fax: 66 53 221 849
tvongcha@chiangmai.ac.th

Thailand Site Representatives
Johns Hopkins University

Susan Sherman, MPH, PhD
Johns Hopkins Bloomberg School of Public Health
615 North Wolfe Street, Suite E-6008
Baltimore, MD 21205 USA
Phone: 410-614-3518
Fax: 410-955-1388
ssherman@jhsph.edu

Surinda Kawichai, PhD, MSc
Johns Hopkins Bloomberg School of Public Health
615 N. Wolfe St., Room E7132
Baltimore, MD 21205
(In Thailand)
Research Institute for Health Sciences
P.O. Box 80 CMU
Chiang Mai, 50202 Thailand
Phone: 66 53 221 966
Fax: 66 53 221 849
surinda@loxinfo.co.th

Philadelphia Site Representatives

Annet Davis-Vogel, RN, MSW
Manager Research Projects
UPENN Prevention Research Division
3535 Market Street 4th fl Suite 4088
Philadelphia, PA 19104
Phone: (215)746-7357
Fax: (215)746-7377
vogel_a@mail.trc.upenn.edu

Valerie Simpson
Community Representative

University of Pennsylvania
3843 N. 9th Street
Philadelphia, PA 19140 USA
Phone: 215-227-7028

Protocol Statistician

Deborah Donnell, PhD
SCHARP-FHCRC
1730 Minor Ave N. MP-1195
PO Box 19024
Seattle, WA 98109-1024 USA
Phone: 206-667-5661
Fax: 206-667-6888
deborah@scharp.org

DAIDS Program Officer

Kevin Ryan, PhD
Prevention Science Branch
Division of AIDS/NIAID/NIH
6700-B Rockledge Dr.
Bethesda, MD USA
Phone: 301-435-4896
Fax: 301-402-3684
kr90@nih.gov

NIDA Representative

Jacques Normand, PhD
National Institute on Drug Abuse
6001 Executive Blvd, MSC 5197
Bethesda, Maryland 20892-9561 USA
Phone: 301-443-1801
Fax : 301-443-4100
jn86a@nih.gov

Protocol Operations Coordinator

Tom Perdue
SCHARP-FHCRC
1730 Minor Ave N. MP-1195
P.O. Box 19024
Seattle, WA 98109-1024
Phone: (206) 677-6216
Fax: (206) 667-6888
tperdue@scharp.org

Central Laboratory Representative

Hua Shan, MD PhD
Johns Hopkins University
600 N. Wolfe St.
Carnegie 469A
Baltimore, MD 21287
Phone: (410) 614 4246
Fax: (410)-955-5961
hshan@jhmi.edu

Protocol Specialist

Kathy George
Family Health International
1118 Milan Street
New Orleans, LA 70115
Phone: 504-897-3001
Fax: (N.C.) 919-544-0207
kgeorge@fhi.org

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

PROTOCOL SUMMARY

- Purpose:** To determine the efficacy of a network-oriented peer educator intervention for the prevention of HIV infection through reduction of HIV risk behaviors among injection drug users and members of their HIV risk network
- Design:** Phase III, multi-site, two-arm, randomized controlled study
- Study Population:** HIV-uninfected injection drug users (**index participants**) and individuals identified by each index participant as members of his/her sex and/or drug using networks (**network members**) in Philadelphia, Pennsylvania, USA and Chiang Mai and Chiang Rai, Thailand.
- Study Size:** 660 networks consisting of 660 index participants and approximately 1,980 network members (an average of three network members per index participant), for a total of approximately 2,640 participants
- Intervention:** Index participants will be randomized in a 1:1 ratio with their network members to one of two study arms as shown below

Study Arm	Behavioral Intervention	
	Index Participants	Network Members
Experimental Arm n~330 networks (330 index participants and approximately 990 network members)	Enhanced HIV counseling and testing plus Six 2-hour network oriented peer-educator sessions during weeks 1 to 4 and Booster session at months 6 and 12	Enhanced HIV counseling and testing
Control Arm n~330 networks (330 index participants and approximately 990 network members)	Enhanced HIV counseling and testing	Enhanced HIV counseling and testing

- Study Duration:** Approximately 48 months total. Enrollment will require approximately 30 months. Participants will be followed for a minimum of 18 months and a maximum of 30 months.
- Primary Objective:** To determine whether the peer-educator intervention reduces the rate of HIV infection among injection drug users and members of their HIV risk network

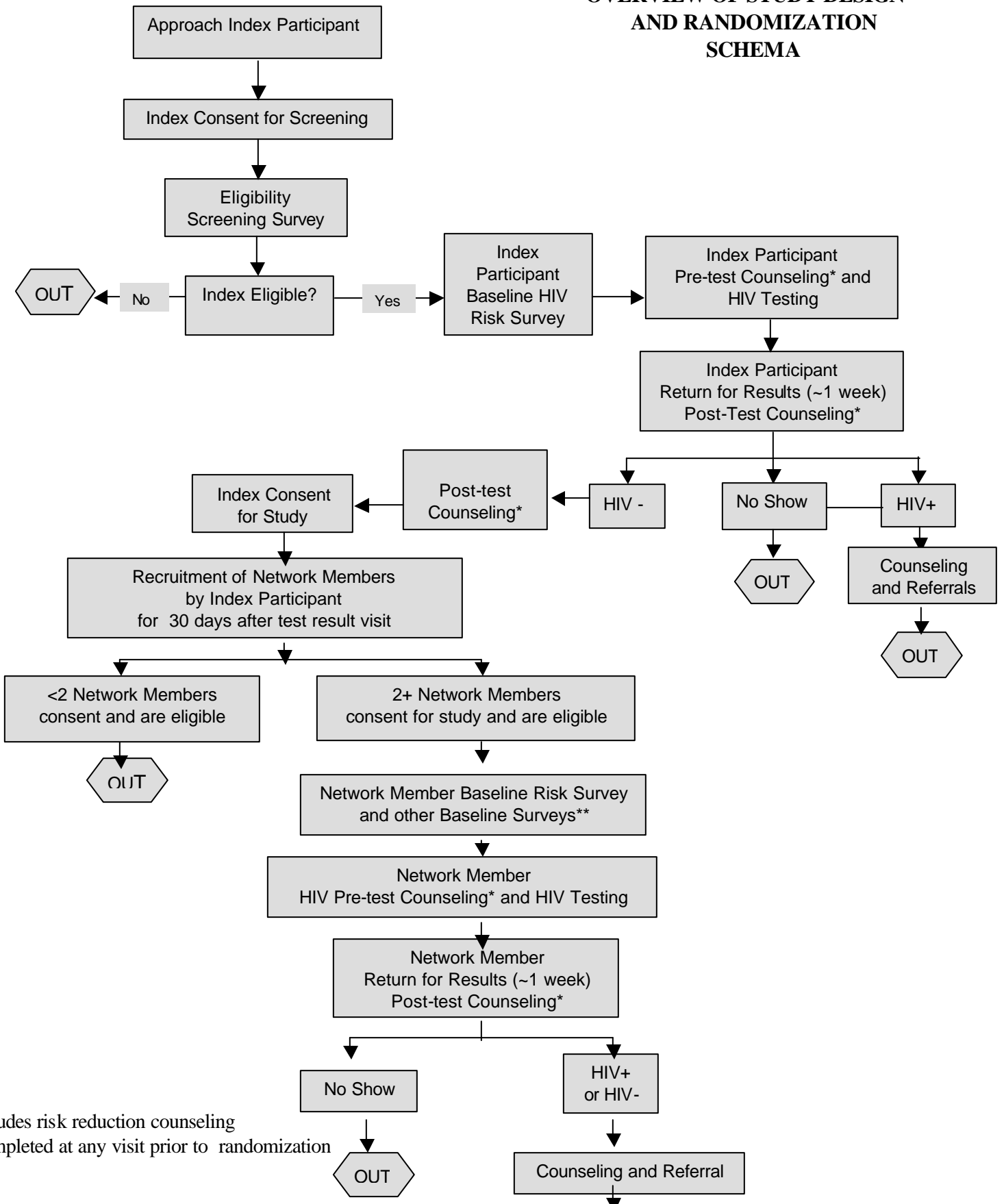
Secondary Objectives:

1. To determine whether the intervention reduces reported injection and sexual HIV risk behaviors in index participants and/or network members
2. To determine whether the intervention changes substance use network norms for injection and sexual HIV risk practices
3. To determine whether the intervention effects on injection and sexual HIV risk behaviors differ between index and network participants, or by HIV status in each study arm
4. To determine whether the intervention effect on behaviors identified as important mediators of the intervention is similar at both sites

Study Sites:

Approximately 2/3 of the participants will be enrolled in Chiang Mai and Chiang Rai, Thailand with the remaining participants enrolled in Philadelphia, Pennsylvania, USA

**OVERVIEW OF STUDY DESIGN
AND RANDOMIZATION
SCHEMA**



includes risk reduction counseling

*completed at any visit prior to randomization

1.0 INTRODUCTION

Drug abuse and HIV/AIDS are global public health problems. Concurrent epidemics of injection drug use and HIV have been reported in 114 countries. In 1998, 134 countries reported injection drug use, whereas in 1992, only 80 countries reported injection drug use, with only 52 reporting HIV infection among injection drug users (IDUs).¹ Injection drug use currently is the major mode of transmission of HIV in Eastern Europe and the Newly Independent States, Central Asia, East Asia, parts of South and Southeast Asia, North Africa, the Middle East, Southern Europe, and parts of North and South America. Twenty-six countries report injection drug use as the primary mode of HIV transmission.¹

HIV epidemics among IDUs often are characterized by rapid and even explosive spread. Reports indicate that in many countries HIV prevalence has increased from under five percent to more than 40 percent in less than one year.¹ Explosive spread of HIV among IDUs has occurred in a number of countries, including Thailand (Bangkok, Chiang Mai), India (Manipur), Vietnam (Ho Chi Minh City, Hai Phong, Quang Ninh), Brazil, United States (New York City), China (Yannan Province), the Newly Independent States (Ukraine, Belarus, Moldova), and Russia (Moscow). Serial use and sharing of drug injection equipment, such as needles, syringes, cookers, cotton and water, create risks for acquiring and transmitting HIV as well as viral hepatitis. Further, preparing drugs for injection and collectively using shared drug solutions pose additional risks for HIV transmission.¹

IDUs and other drug users, and commercial sex workers (e.g. injectors and non-injection drug users) can also transmit the virus through high-risk sexual behaviors. In addition to injection drug use, unprotected sex with HIV-infected persons; non-parenteral (non-injection) use of drugs such as crack cocaine, often accompanied by trading sex for drugs, and sex under the influence of drugs are major modes of transmission of HIV, viral hepatitis and other sexually transmitted infections (STIs) among adults. Drug users can play a critical role in the spread of HIV into the broader population through heterosexual and/or homosexual transmission and through mother-to-child transmission. The overlapping drug and sexual risks also are reported for especially vulnerable youth around the world, such as children living in the streets, a lifestyle that places them at extreme risk for HIV and other STIs.²

More than 20 years of research in implementing interventions for IDUs indicate that HIV transmission among IDUs can be prevented, slowed, and stopped. Research has generated guidelines and principles for designing and implementing feasible, sustainable, and effective interventions. Intervening early, with multiple strategies, before HIV prevalence among IDUs reaches five percent, can prevent epidemic spread and its consequences. WHO, UNAIDS, CDC, NIDA, and regional harm reduction coalitions have contributed greatly to developing “best-practice” guidelines and prevention principles for responding to the epidemic of HIV in IDUs and other drug users.^{1,3,4,5,6,7} Even after prevalence has increased substantially, prevention interventions can prevent the further spread of HIV in drug-using populations and transmission into other populations. Despite increasing evidence-based findings on the effectiveness of interventions, HIV epidemics among injection and non-injection drug users continue to occur.

Effective HIV prevention with IDUs and other drug users requires reaching the at-risk populations and providing access to the means for behavior change to enable these populations to reduce their injection and non-injection drug use as well as risky sexual practices. A public policy environment that promotes a public health approach to understanding and responding to the concurrent epidemics of injection drug abuse and HIV/AIDS among IDUs is fundamentally important to implementing a comprehensive HIV

prevention strategy. Preventing new HIV infections in drug-using populations depends on reaching the target population (coverage) and rapidly making core interventions available, by planning and scaling-up of services for the target population. Specifically, there is an urgent need for approaches to HIV prevention that may affect behavioral norms and impact larger segments of at risk populations⁸

The UNAIDS, CDC and NIDA recommend a comprehensive approach to preventing HIV and other blood-borne infections among IDUs. One such approach is to train outreach workers to access hard reach, out-of-treatment IDUs and non-injecting drug users and present them with risk-reduction information and supplies in settings that are familiar to them (e.g., streets, parks, other neighborhood settings). Outreach workers provide HIV/AIDS education information and the means for behavior change, such as bleach kits for disinfecting injection equipment, condoms for safer sex, and referrals for testing and counseling for HIV, hepatitis B virus, hepatitis C virus and other STIs, and to drug addiction treatment, medical and social services, and syringe access programs.⁹ The NIDA Community-Based Outreach Model defines outreach workers as those who are indigenous to the local community, familiar with the drug use subculture, and trusted as a source of information. Outreach workers are uniquely able to serve as role models, educators, and advocates, who can provide drug users with up-to-date and accurate risk reduction information in settings that are familiar to them and at times of greatest risk.¹⁰

1.1 Background

The intervention tested in this study draws upon theoretical and empirical evidence suggesting that peer educator programs can have significant effects on the risk-related behaviors of both the educators and the peers whom they educate. Providing peer educator training to IDUs may efficiently cultivate sustainable protective behavioral norms related to injection and sexual risk among the IDU educators' social networks. Prior studies have demonstrated that peer educator programs can realize such normative changes, and it is hypothesized in this study that these normative changes will be reflected in significant reductions in the rates of HIV transmission among the peer educators and the members of their social networks.

1.1.1 Social Influence and Behavior Change

Social influence processes can have powerful effects on behavior and present an important avenue for HIV prevention research. There is extensive literature on the role of social influence in behavior change.¹¹ Peers may influence each other's sexual behaviors through social comparison processes, fear of social sanctions, information exchange, socialization of new group members, modeling and reinforcement, and social interactions that provide opportunities to meet new sex partners.^{12,13} Some HIV behavior change models include social influence components.^{14,15} The community-wide HIV risk reduction observed among gay men in San Francisco suggests that social influence can be an important approach to behavioral risk reduction.¹⁶ In a study of behavior change among injection drug users in four countries (Brazil, Thailand, Scotland, and the U.S.), Des Jarlais and colleagues found that talking about AIDS with drug-using friends was consistently associated with reduction in self-reported injection and sexual risk behaviors.¹⁷

One social influence strategy that has been widely applied in HIV prevention interventions is outreach. Outreach programs are designed to access "hard-to-reach populations," such as IDUs and their sexual partners, who might not otherwise be exposed to interventions.¹⁸ IDUs in San Francisco reported that outreach workers were their most frequent source of information on bleach for disinfecting needles.¹⁹ Several studies suggest that street

outreach is effective in reducing IDUs' risk behaviors.^{20,21} Actively involving individuals from the target population in HIV outreach and education activities can significantly reduce their risk behaviors. One study found that women who discussed risk reduction with friends and neighbors reported significant long-term sexual risk reduction.²² Kelly and colleagues found similar results using this approach with the chronically mentally ill.²³

1.1.2 Predictive Peer Network Characteristics

Social network characteristics have been demonstrated to predict HIV risk-related behaviors. Needle sharing, cessation of drug use, and relapse have been found to be associated with personal network characteristics, such as gender composition, size, role function, and the perceived closeness of network members.^{24,25, 26} These findings suggest that peer networks represent a compelling context for HIV prevention among IDUs.

Building upon this evidence, the Stop AIDS for Everyone (SAFE) study, conducted in Baltimore, Maryland, USA, used an experimental study design for delivering a psycho-educational AIDS prevention intervention to injection drug-sharing networks.²⁵ 293 participants for the SAFE study were recruited from the AIDS Link to Intravenous Drug Users (ALIVE) study (N=642, 1991-95), a prospective study of the natural history of HIV infection in injection drug users, which began in 1988²⁷ These participants were 18 years or older, reported sharing drugs in the prior six months, had a drug sharing network, and were not enrolled in other prevention studies. The study used trained paraprofessionals recovering from addictions to administer a six-session, cognitive-behavioral intervention. Participants were randomly assigned to either the psycho-educational, risk-reduction counseling sessions (experimental condition) or the usual two-session HIV-test counseling (control condition). One hundred and eighty-nine participants were assigned to the experimental condition as 'index' participants who were asked to bring members of their drug network to the clinic for the intervention. Of these 189 participants, 145 brought at least one member of his/her drug network, 78 groups began the sessions, 66 completed at least four sessions, and 57 completed all six sessions. Of the 145 participants who brought in at least one member of his/her drug risk network, the five-month follow-up rates were 94% for the indexes and 88% for the controls. The 18-month follow-up rates were 71% and 70%, respectively.

Experimental indexes were significantly more likely than control indexes at the three-month follow-up to report reduction in drug-related HIV risk behaviors. At the 18-month follow-up, HIV-uninfected index participants in the experimental condition reported significantly less frequent needle sharing compared to those in the control condition (OR=2.83, p=0.03) and less frequent injecting of heroin and cocaine than in the control condition (OR=2.74, p=0.06). In multiple logistic regression models of HIV-uninfected participants, controls were more than twice as likely as experimental subjects to report needle and cooker sharing in the prior six months.

This study suggests that drug networks are sufficiently stable to be identified and be the focus of a clinic-based network intervention. The intervention had long-term effectiveness for modifying drug risk behaviors among HIV-uninfected individuals, and was effective for both clinic- and street-recruited participants. The intervention had

limitations in that it did not appear to reduce sexual risk behaviors, nor was it effective in reducing the risk behaviors of HIV-infected participants.

The SHIELD (Self-Help In Eliminating Life-threatening Disease) study conducted in Baltimore, Maryland, USA sought to introduce health education, communication skills, and risk reduction strategies, as well as to encourage a pro-social identity among participants. The intervention emphasized the interdependence of HIV risk, protection of oneself and one's family, friends, and community, and promoted individual practice and peer advocacy of health protective behaviors as a means of mutual HIV protection. The intervention encouraged participants to introduce safer sex and drug norms to their social networks by conducting outreach education among their drug and sex network members and others in their community.

The SHIELD study was built upon lessons learned from the SAFE study. One of the lessons was that it would be more feasible and efficient to train specific members of a network to disseminate protective information than to try to recruit and work with an entire risk network. Therefore, the SHIELD study sought to train individuals in the drug-using community to promote HIV prevention messages within their networks and neighborhoods. The study used cognitive and affective process strategies from current theories of behavior change,^{28, 29, 30} and added a social component derived from theories of social influence, social diffusion, and social identity. The social component emphasized superordinate goals of caring for one's family, friends, and community, as well as for oneself, through practice and advocacy of health protective behaviors. The study used an outreach-oriented approach for the distribution of HIV prevention materials, and to influence norms surrounding sexual and drug risk behavior among injection drug users' referent peer networks. Index participants were recruited in Baltimore, Maryland, USA, through targeted snowball sampling. Participants were randomly assigned to either a 10-session experimental intervention, which included training in teaching risk reduction to others, or a 10-session attention control condition. With 2:1 random assignment, the 180 experimental and 93 controls recruited 305 network members of whom 20% were HIV positive and 43% were female. The study analyses were based on an intent-to-treat model. Both index participants and network members were scheduled to be administered a survey at baseline, eight months and 18 months. In an unadjusted analysis, there were statistically significant associations between assignment to the intervention condition and decreased frequency of injecting heroin and cocaine at follow-up (OR=2.28, chi-square=4.05), and cessation of injection drug use (OR=2.55, chi-square=3.80). There was a marginally significant association between being in the experimental condition and self-reported reductions in frequency of injecting with a contaminated needle. After adjusting for age, gender, race, employment, arrest history, and HIV serostatus, experimental participants were over three times more likely than control participants to report greater reduction in the three drug risk behaviors at six-month follow-up (OR=3.05, CI= 1.82-3.32, N=115). After adjusting for age, gender, race, employment, arrest history, and HIV serostatus, participants in the experimental condition were more than four times as likely as control participants to report increased use of condoms with a casual partner (OR=4.2, CI=1.23-15.91, N=189).

These results suggest that peer education and advocacy by IDUs to their network members should be an effective method of reducing HIV-related sexual and drug risk behaviors among injection drug using communities.

1.2 Study Rationale

Network-based interventions have been shown in randomized trials to produce sustained behavioral risk reduction among IDUs²⁵. Although these results are promising, it is unknown if self-reported behavior change is correlated with reducing rates of HIV transmission. The purpose of the proposed study is to determine the efficacy of a peer-educator, network-oriented intervention to prevent HIV transmission among substance users and their risk network members. The proposed study is based on the previous SAFE and SHIELD interventions, which used a social influence approach and a small group training strategy to alter behavioral norms by using peers as change agents to introduce safer sex and drug norms to their social networks. The proposed intervention trains peer educators to provide outreach, education, and HIV prevention materials and information, such as distribution of condoms and information on where to access cookers, alcohol, cotton swabs and bleach kits to their HIV risk network members. By leveraging social influence processes to alter norms related to risk behaviors, it is anticipated that this intervention can realize sustainable reductions in HIV risk behaviors and in HIV transmission. As research indicates that peer networks are an important reference group for substance users cross-culturally, it is expected that the intervention will be appropriate in diverse settings and cultures.¹⁷ Furthermore, prior research suggests that the intervention can be tailored to the social and cultural context of a site without compromising the integrity of the intervention.⁸

The principal aim of this study is to determine the efficacy of a network-oriented peer education intervention to prevent HIV transmission through the reduction of risk behaviors known to be associated with HIV among HIV-uninfected IDUs and members of their HIV risk network. It is hypothesized that a network-oriented, peer educator intervention will lead to changes in network norms that favor condom use and needle hygiene, and lead to sustained risk reductions and reductions in HIV incidence. It is also anticipated that training individuals to conduct HIV prevention education in their networks and in the community represents a more feasible, sustainable, and ultimately cost effective strategy than more traditional individually-focused prevention interventions.

2.0 STUDY OBJECTIVES AND DESIGN

2.1 Primary Objective

To determine whether the peer-educator intervention reduces the rate of HIV infection among injection drug users and members of their HIV risk network

2.2 Secondary Objectives

1. To determine whether the intervention reduces reported injection and sexual HIV risk behaviors in index participants and/or network members

2. To determine whether the intervention changes substance use network norms for injection and sexual HIV risk practices
3. To determine whether the intervention effects on injection and sexual HIV risk behaviors differ between index and network participants, or by HIV status in each study arm
4. To determine whether the intervention effect on behaviors identified as important mediators of the intervention is similar at both sites

2.3 Study Design

This is a Phase III, multi-site, two-arm, randomized, controlled study of a network-oriented peer education training intervention for the prevention of HIV infection through reduction of HIV risk behaviors among HIV-uninfected IDUs and members of their HIV risk networks. (See study design and randomization schema on page 3.)

IDUs will be recruited using street and community outreach methods in Chiang Mai and Chiang Rai, Thailand, and Philadelphia, Pennsylvania, USA. Outreach workers will supply basic information about the study in geographic areas and settings frequented by drug users and will encourage these individuals to seek screening at a local study site. Individuals who present at the study clinic will undergo informed consent for screening, a screening eligibility survey, and HIV counseling and testing. Individuals will be asked to return to the clinic in one week for their HIV test results, post-test counseling and further screening. Those who are HIV-uninfected, who meet preliminary eligibility requirements, and are willing to participate, will undergo informed consent for the study. These persons are referred to as **index participants** throughout the protocol. Each index participant will then be asked to recruit at least two members of his/her sex and/or drug HIV risk network over a one-month period. These HIV risk network members are referred to as **network members** throughout the protocol. HIV-infected and un-infected network members are eligible for enrollment. HIV-infected network members will not contribute to the primary efficacy analysis, although they will contribute to secondary endpoint analyses. Inclusion of HIV infected network members will ensure that the networks enrolled broadly represent the IDU populations at the study sites. It will also help preserve the confidentiality of the HIV status of each participant. These network members will be offered referrals to support services as described in Section 8.4.1. Adjustments will be made to the study sample size in the event that the number of HIV-infected network members enrolled could substantially reduce the study's ability to detect an intervention effect. See Section 7.3.4 for details on the recruitment process.

The two sites proposed for this study have substantially different baseline rates of seroincidence. Traditionally, the rationale for combining data from different settings is to achieve both sufficient power and generalizability. With respect to power, the current design attains most of its strength from the higher seroprevalence site. However, the results of a single site protocol cannot be convincingly generalized, particularly for behavioral interventions where cultural setting is arguably a significant modifier of effect. If the intervention is implemented in Thailand and Philadelphia and the overall relative risk after adjusting for site is statistically significant, then the analysis of

behavioral mediators of the intervention effect can provide a scientific basis for claiming the intervention is effective in different settings. For this reason, the intervention will be implemented in these two sites.

Index participants will be randomized in a 1:1 ratio with their network members to one of two study arms. Index participants and network members in both study arms will receive enhanced HIV counseling aimed at risk reduction in conjunction with HIV testing (see Section 4.2). In addition, index participants randomized to the experimental arm will receive six two-hour peer educator-training sessions in groups of up to 12 over a period of four weeks. The training sessions will focus on skills building with respect to risk-reducing behaviors and the promotion of such behaviors to network members (see Section 4.1). There also will be a one-hour booster training session held for the index participants after their six and 12-month follow-up assessments. Network members in the experimental arm are expected to receive indirect benefits through their interactions with their index participants. Average network HIV incidence rates will be compared across the two arms of the study.

All participants will be administered a risk behavior survey at screening prior to provision of risk reduction counseling to measure baseline risk behavior and a questionnaire to assess perceived network norms. In addition, to assess the network characteristics and intensity of intervention delivery by the index, both indexes and network members will be administered questionnaires about the frequency and duration of contact and types of discussions between them.

Index participants and network members will have follow-up visits every six months. The study duration will be approximately 48 months. Enrollment is expected to take approximately 30 months. Participants will be followed for a minimum of 18 months and a maximum of 30 months at each site. Every six months, participants will be administered surveys designed to assess the following: HIV risk behavior; network characteristics; the intensity of the intervention delivery; social harms experienced that may be associated with study participation; and intervention contamination in the control arm (i.e. sources of exposure to HIV prevention-related messages and materials). In addition, perceived network norms will be assessed annually. The behavioral risk survey will be administered prior to risk reduction counseling by an individual other than the person who administered the counseling. Behavioral risk survey interviewers will be blinded to the study arm of the participants.

To enhance retention, participants will be contacted in-between their scheduled six-month follow-up visits to update their locator information (e.g., address, telephone number, name and address of family members) confirm or re-schedule their next follow-up visit and reinforce instructions to contact the study site to update locator information. Also, any difficulties experienced in contacting participants at these timepoints will serve to trigger timely mobilization of outreach efforts to ensure that participants are located in time for their next scheduled follow-up visit. The contacts may be conducted in-person at the study site, via telephone, or via street/home outreach.

3.0 STUDY POPULATION

HIV uninfected IDUs (index participants) and members of their HIV risk network (network members) irrespective of their HIV status, will be included in this study. Participants will be

enrolled in the study according to the criteria in Sections 3.1 and 3.2. They will be recruited as described in Section 3.3 and 3.4 and assigned to a study intervention arm as described in Section 7.4. Conditions for withdrawal from the study are described in Section 3.7.

3.1 Inclusion Criteria

3.1.1 Index Participants

Individuals must meet all of the following criteria to be eligible for inclusion in the study as an **index participant**:

- Of legal age to independently provide written informed consent for research
- Provide written informed consent for screening and study participation
- Report having injected drugs at least 12 times in the last three months
- Been out of treatment for at least 3 months and have relapsed.
- HIV ELISA negative on specimen obtained within 60 days prior to randomization
- Willing and able 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.

3.1.2 Network Members

Individuals must meet all of the following criteria to be eligible for inclusion in the study as a **network member**:

- Of legal age to independently provide written informed consent for research
- Recruited for the study by an eligible index participant
- Have injected drugs with and/or had sex with the relevant index participant within the three months prior to screening
- Provide written informed consent for study participation

3.2 Exclusion Criteria

3.2.1 Index Members

Individuals who meet any of the following criteria will be excluded from the study as an **index participant**:

- Prior or concurrent enrollment in the last 6 months in another HIV behavioral or biomedical prevention study
- Appearance of psychological disturbance or cognitive impairment that would limit the ability to understand study procedures, as determined by clinic staff
- Any other condition that, in the opinion of the investigator, would make participation in the study unsafe, or otherwise interfere with the study objectives
- Enrollment as a network member or index participant in another network of HPTN 037

3.2.2 Network Members

Individuals who meet any of the following criteria will be excluded from the study as **network members**:

- Appearance of psychological disturbance or cognitive impairment that would limit the ability to understand study procedures, as determined by clinic staff
- Any other condition that, in the opinion of the investigator, would make participation in the study unsafe, or otherwise interfere with the study objectives
- Enrollment as a network member or index participant in another network of HPTN037

3.3 Recruitment Setting

Study participants will be recruited from the following HPTN sites:

Philadelphia, Pennsylvania, USA

IDUs in Philadelphia will be recruited from neighborhoods with high concentrations of drug use, drug sales, and diagnosed AIDS cases. Guided by an established network of community gatekeepers, field staff will identify prospective index participants using van-based street outreach. Volunteers will be scheduled for a screening visit at one of two office-based locations, either the West Philadelphia research offices of the Treatment Research Center or the North Philadelphia field site. It is anticipated that for this study, approximately 28 participants (seven index participants and 21 network members) per month will be entered into the study at these sites during the 30-month enrollment phase.

These recruitment strategies were utilized in a prospective vaccine preparedness cohort study (VPS II) and a New HIVNET IDU Study conducted in Philadelphia. The primary objectives of the VPS II were to examine the incidence of HIV infection among women at heterosexual risk and to expand the number of injectors at high risk. Recruitment began in July 1999 and over 6 months 222 HIV uninfected IDUs were enrolled. After six months of follow-up, participants had a 94% retention rate and an incidence of HIV infection of 3.8 per 100 person years. At the close of the study (12 months of follow-up), HIV incidence was 2.04 per 100 person years and retention, 93%. Recruitment for the HIVNET NEW IDU Study began in August 1997 and over 10 months 262 HIV-uninfected injection drug users at high-risk of HIV infection, defined as not in methadone treatment and not using needle exchange, were enrolled. Follow-up was for 15 months. To be eligible, injectors had to have visible signs of recent injection and report injecting at least three days per week during the prior three months. Recruitment and follow-up were conducted from the study's mobile assessment unit and from drug detoxification programs. At 6 months there was a 93% retention rate and an HIV incidence rate of 2.5 per 100 person years. After 15 months, the retention rate was 88% and the incidence of HIV infection was 1.8 per 100 person years at risk.

Chang Mai and Chang Rai, Thailand

IDUs in Thailand will be recruited using street outreach in the cities of Chiang Mai and Chiang Rai, Thailand and from the Northern Drug Dependence Treatment Center (NDTC), which is located about 15 kilometers north of Chiang Mai and Chiang Rai and services both cities. This center is an inpatient facility operated by the Department of Medical Services, Ministry of Public

Health. Patients are admitted for a maximum stay of 21 days; approximately 25% of patients leave against medical advice. It is estimated that the relapse rate among injection drug users is 90% within one year and based on re-admission data is over 50% within the first three months following discharge (personal communication Dr. Jaroon Jittiwutikarn, NDTC Director). It is anticipated that approximately 60 participants (15 index and 45 network members) per month will be entered into the study at these sites during the 30-month enrollment phase.

The NIDA HIV Prevalence Study (*1 R01 DA11133-01A1*) enrolled 1,865 substance users from the Northern Drug Dependence Treatment Center. The prevalence of HIV infection among the 879 injection drug using participants in the NIDA study was 35.2% with the use of injection drugs associated with HIV infection. As of November, 2001 in the ongoing, two-year, follow-up incidence phase of the same NIDA-funded study retention is 81%; however, follow-up rates are rising after additional staff were hired to assist with tracing. The study is on-going. HIV incidence in the cohort (through November 30, 2001) is 7.99 per 100 person-years among the IDU in follow-up. Only individuals who have been out of treatment for at least three months and have relapsed will be recruited for participation as index participants.

3.4 Recruitment Process

Approximately 440 networks will be enrolled in Chiang Mai and Chiang Rai, Thailand, and approximately 220 networks will be enrolled in Philadelphia, Pennsylvania, USA. Each network will consist of an HIV-uninfected index participant and an average of three network members. Therefore, approximately 2,640 participants will be enrolled in the study during a 30-month enrollment period. (See the study design and randomization schema on page 3.)

Screening of each index and his/her network members will take place over a period of up to 60 days. This study will largely employ a street outreach-based approach to participant recruitment. Prospective index participants will be first identified by targeting specific geographic areas, that is, outreach will be conducted in areas in the cities of high drug use. The outreach workers will also identify other settings or organizations frequented by drug users. In these geographic areas and settings outreach workers will disseminate information about the study, provide verbal and written descriptions of the studies to prospective participants, and will encourage prospective index participants to participate in screening activities at a local study site. Prospective participants will also be informed that, if the study does not apply to them, they should pass the information on to other individuals.

Outreach workers will be trained to not 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 will be selected from the community and must be knowledgeable about the community’s dynamics and trained on basic methods of rapid assessment procedures in order to target areas of high drug use. They will also be trained, as part of the study, in methods of approaching and communicating with potential participants, personal safety, and confidentiality.

Prospective index participants who present at the study site will be offered HIV counseling and testing and receive a brief introduction to the study. Indexes that are interested in participating will be asked to provide written informed consent for screening. A sample of the consent form can be found in Appendix III. After providing informed consent for screening, volunteers will undergo an

eligibility screening survey. If at any time during screening, they are found to be ineligible, screening will be discontinued; however, HIV counseling and testing will be offered to all persons who present for screening. The survey will include questions about recent injection drug use and the size and structure of their risk networks. Participants who meet initial study screening eligibility criteria will be administered a baseline risk behavior survey and then undergo enhanced risk reduction counseling and HIV testing. Participants will be scheduled for a visit to return for their HIV test result and post test counseling in one week. HIV-uninfected, prospective, index participants are eligible for enrollment and will be offered further screening and asked to provide study consent. A sample of the consent form can be found in Appendix IV. HIV-infected, screening participants are not eligible for enrollment as indexes but will be offered referrals to support services as described in Section 8.4.1.

After consent for study participation, prospective index participants will be asked to supply the initials, ages, and brief physical descriptions of the people with whom they inject drugs and of their sexual partners. Participants will then be provided with individual cards marked with their identification number, to facilitate the recruitment of their network members. There will be no identifying information on the cards to indicate participation is in a HIV study or drug use. The prospective index participants will be asked to give the cards to network members and to encourage each network member to bring his or her card with them to the local study site to serve as their identification for participation in screening. (Note: Index participants will only be able to recruit as network members those individuals they have identified at their screening.) For 30 days following each prospective index participant's post-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.

For prospective network members to participate in the screening process they must either present at a local study site with a card bearing their prospective index participants' ID number, or match the description provided by the index during his or her screening survey in terms of age, gender, frequency of contact with the index, duration of relationship with the index, and residential distance from the index. Prospective network participants will then be asked to provide study informed consent. Individuals who provide study consent will complete the network member screening survey, the baseline risk behavior survey, and will participate in HIV risk reduction counseling and testing. 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 results for eligibility. Network participants will be able to enroll only once in the study. Once an individual is enrolled in the study as a "network member", he/she will be unable to enroll as an index, or in any other study network.

It is important to note that, throughout screening, the study staff will clearly explain and emphasize to participants that although they themselves may screen eligible for the study, the final decision regarding enrollment will depend on the other network members who are eligible for the study. This will be determined after all network members have been screened.

3.5 Enrollment of Networks and Randomization

Prospective index participants will be asked to return to the study clinic approximately 30 days after their initial post HIV test counseling visit, to learn of their eligibility status. Index participants in networks that contain at least two eligible and consenting network members will be randomized

along with their network members to either the experimental or control arms. At this point participants will be officially enrolled in the study. Study staff will then contact network members to confirm their enrollment status.

If fewer than two prospective network members identified by an index have presented for screening, been found to be eligible, and provided study consent within the 30 days following the index participant's post-test counseling visit, the index participant and any network members that may have presented for screening will be considered ineligible for the study. (Note: If identified 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.

3.6 Participant Retention

Once a participant has enrolled in the study, the study site will make every reasonable effort to retain him/her for the duration of the study. Retention rates of at least 90 percent annually are targeted. Study site staff are responsible for developing and implementing local standard operating procedures to achieve this high level of follow-up.

To enhance retention, sites will collect detailed locator information for each participant and will update this information quarterly, develop and implement comprehensive protocols for follow-up, perform field visits when participants are unable to come to the local sites for visits, and implement remote access protocols, when feasible, for participants who move away from study sites. Examples of procedures to enhance participation in the intervention phase and retention during the follow-up phase will include any of the following as locally appropriate:

- Collection of complete locator information
- Use of appointment cards
- Dissemination of thank-you letters after enrollment
- Use of self-addressed postcards for notification of address changes
- Reminder letters and calls before appointments
- Immediate multi-faceted follow-up on missed visits, including calls, letters and home visits
- Searches of local resources to locate participant (e.g. post office check)

3.7 Participant Withdrawal

Participants may withdraw from the study for any reason at any time. The investigator also may withdraw participants from the study in order to protect their safety and/or if they are unwilling or unable to comply with required study procedures. See Section 5.6 for assessments to be performed if possible for participants, who withdraw. Participants also may be withdrawn if the sponsor or regulatory authorities terminate the study prior to its planned end date. Indexes who do not complete the peer education training will continue in the study and will complete all follow-up visits as scheduled, as will their network members.

4.0 BEHAVIORAL INTERVENTIONS

4.1 Experimental Peer Education Intervention

The experimental intervention is a cognitive-behavioral and social influence peer educator training program comprised of theory-based exercises and activities, and outreach training. The intervention addresses knowledge, attitudes, intentions, and social influences aimed at reducing sexual and drug risk practices among the participants and their network members. As networks are important sources of informational, emotional, and material support across cultures, it is anticipated that this intervention will be appropriate across a range of cultures. It is expected that the program will be adapted to individual contexts and cultures but retain comparability across sites and cultures.

The intervention will be delivered in six two-hour sessions by two facilitators to groups with a maximum of 12 index participants, as described below. These sessions will occur within a four-week time frame and will focus on skills building and practicing promotion of HIV prevention messages among the indexes' network members. The first four sessions will be offered in the first two weeks, and the final two sessions will occur in Weeks 3 and 4. The 4-week course of the intervention should afford participants opportunities to rehearse their newly acquired peer education skills with the members of their risk networks and to share some of their experiences with other members of their peer-education training group. During the training sessions, experimental group index participants will be encouraged to apply their newly acquired skills with the members of their risk networks. Every effort will be made to maintain a stable group membership for the duration of the peer educator training intervention, but it will not be necessary to maintain the same membership for participation in the booster sessions.

The focus of the intervention will be to encourage outreach and peer education within the index participants' personal risk networks. Goal setting activities in the intervention sessions will be focused on promoting HIV prevention among the network members enrolled in the study; however, index participants also will be encouraged to disseminate prevention information to non-study participant members of their networks. As the intervention is focused within the network, the risk of contamination due to possible interactions between experimental group index participants and control group network members is expected to be small. Nonetheless, as described in Section 7.2.3, the expected intervention effect has been adjusted to account for this.

Prior studies have suggested that contamination is unlikely to pose a major threat to study validity, largely because the social networks of IDUs tend to be naturally structured so that there would be a decreased opportunity for interaction and overlap of network members assigned to the experimental arm versus the control arm. Data from injectors in Baltimore, Philadelphia, and Northern Thailand suggest that HIV risk networks among injectors tend to be small. In the SHIELD study of 804 injectors, the average number of risk network members was five, with a mean relationship duration of 17 years and a median of 12 years. Prior research also suggests that HIV and HIV prevention is not a common topic of spontaneous conversation among injecting populations, which would also decrease the likelihood of contamination across study arms.

The intervention is designed to promote the dissemination of outreach-related materials and information to the members of the index participants' social networks. One training module

component focuses on the indexes specifically tailoring and rehearsing their outreach efforts to their specific network members. Impediments to talking to these specific individuals will be assessed during the intervention sessions, and indexes will be trained in strategies to overcome these impediments.

Efforts will also be made to assess the exposure of study participants to HIV prevention-related messages and materials and to ascertain the sources of this information. Included in the follow-up surveys will be detailed questions about whom participants talked to about HIV, about the HIV prevention materials they received, and about the sources of those materials. Participants will also be tested on their level of recognition of logos affiliated with the experimental arm intervention. This information should help assess the extent to which control arm participants were exposed to elements of the experimental arm intervention.

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. 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.

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.

4.1.1 Facilitator Selection and Training

Intervention group facilitators will be local residents proximal to the target population. Study staff will recruit former IDUs or individuals who have experience with the target population. Facilitators must have a good understanding of participants' worldview and health beliefs. They must be able to fully understand the dimensions of family and interpersonal relationships, sex roles, drug use history and the openness with which sex and drug use are discussed in the selected study sites. A highly scripted, culturally specific intervention manual will be followed, based on the SHIELD manual. A four-day facilitator training on facilitation, group processes, ethical guidelines, social cognitive and social influence models of behavioral change will be held in during the first three months of study preparation. As part of their training, the facilitators will be made aware of gender roles and norms in the specific site context and how these shape the sexual decision-making process. They will be given a variety of teaching materials on AIDS, drug use and practices, AIDS risk factors, safer sex practices and group counseling; and will also be provided with a referral list for services such as employment training, detoxification and rehabilitation programs and HIV counseling centers to refer study participants who may request or need additional professional help.

4.1.2 Booster Sessions

Within 1 month following their 6-month and 12-month follow-up assessments, index participants will meet in small groups with a maximum of 12 participants for a one-hour booster session. These booster sessions will afford the indexes additional opportunities to troubleshoot, share their outreach experiences and lessons learned, improve their outreach communication styles, and maintain their motivation to promote HIV prevention among network members and in the community. It will not be necessary for experimental group index participants to attend the booster sessions with the same group of participants with whom they attended their peer educator training; however, the same groups will be reformed for the booster sessions, whenever possible.

4.2 Enhanced Risk Reduction Counseling and HIV Testing Intervention

Indexes and network members in the study will be offered two enhanced counseling sessions in conjunction with HIV testing. Each counseling session will involve a 10-to 15-minute client-centered, interactive approach that focuses on: 1) increasing the participant's perception of personal risk, 2) supporting participant initiated protective behavioral changes, and 3) focusing on the pursuit of small, achievable steps toward reducing personal risks.

Every effort will be made to have participants see the same counselor for both their pre- and post-HIV test sessions at each HIV testing timepoint. The first counseling session will be offered directly prior to the phlebotomy for HIV antibody testing at study screening and at each follow-up visit for HIV testing. 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. Counselors will receive intensive training from study coordinators and experts experienced with this approach before offering counseling to any study participants.

All counseling sessions and disclosure of test results will be offered in private rooms with only the counselor and the participant present, to ensure the maintenance of participant confidentiality. The following guidelines will be followed:

- No one but the participant will be notified of his/her HIV status in the post-test counseling session.
- It is solely the right and choice of the participant to disclose his/her HIV status to others.
- Counselors will discuss potential consequences of participant disclosure of serostatus during the post-test counseling session.
- 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. Even with such a request, the desired information will only be directly released to the participant.

The two-session, HIV-test and interactive risk reduction counseling will be modeled after the two-session, brief counseling arm offered in Project RESPECT, described below. This counseling model was selected as the HIV counseling and testing model for this study because it has been proven effective in increasing condom use and prevention of new STIs. Because it is well documented, use of this model will help to standardize the delivery and quality of the counseling and testing offered throughout the study.

Project RESPECT was a multi-center, randomized, controlled trial of 5,758 heterosexual HIV-uninfected participants who presented for STI examinations in five US public STI clinics.³¹ Participants were randomized to one of three individual face-to-face HIV/STI prevention counseling intervention arms: Arm 1 received a four session counseling intervention, involving four behavioral theory-based sessions; Arm 2 received a brief counseling intervention involving two sessions based on CDC's client-centered, interactive HIV prevention counseling model; and Arm 3 received didactic messages, involving two brief, information-only sessions.

In both the four-session enhanced and two-session brief counseling interventions, participants self-reported 100% condom use was higher ($p < .05$) at three and six months post intervention, compared to participants who received didactic messages. In addition, 30% fewer participants had new STDIs ($p = .002$) in both counseling interventions than did participants in the didactic message group.

The brief counseling approach utilized in Project RESPECT placed a strong emphasis on condom use as a means of HIV risk reduction. The approach used in this study will be modified to also feature counseling about risk reduction relevant to injection drug use. This will include counseling about the use of clean needles and the importance of not sharing needles and other injection equipment.

5.0 STUDY PROCEDURES

An overview of the visit procedures schedule is provided in Appendix II. Detailed instruments to guide standard study procedures across sites will be provided in the Study Specific Procedures (SSP) Manual. Presented below is additional detail on visit-specific study procedures for index and network participants.

5.1 Screening (-60 to -1 Days)

Determination of the final eligibility of networks will take up to 60 days. Written informed consent for screening will be obtained before any screening procedures are initiated and study consent will be obtained prior to initiation of any study procedures. As noted in the study design and randomization schema on page 3 and in Section 3.4, for participants who do not meet the study eligibility criteria, the screening process will be discontinued when ineligibility is determined, however HIV counseling and testing will be available to all persons who present for study screening.

5.1.1 Screening of Index Participants

At the initial screening visit, prospective index participants will undergo the following:

- Written informed consent for screening
- Collection of locator information
- Eligibility screening survey
- Baseline HIV risk behavior survey (prior to counseling)
- HIV pre-test and risk reduction counseling
- HIV testing

Prospective index participants will be asked to return in one week for their second counseling session and their HIV test results and to undergo further eligibility screening. Those who test HIV positive are not eligible for further screening and will receive post-test counseling and referrals as described in Section 8.4.1. Those who test HIV-negative and are otherwise eligible for further screening will undergo the following:

- Confirm identity and update locator information
- Written informed consent for the study
- HIV test results and post-test counseling
- Collection of identifying information for network members
- Baseline questionnaire (to assess network norms and frequency and duration of contact and types of discussions with network members. Note: These assessments can be completed at any visit prior to randomization.)

As part of the network member recruitment process, prospective indexes' will be provided with individual cards marked with an identification number and participants will be asked to give the cards to their relevant network members identified to the study staff.

5.1.2 Screening of Network Members

Individuals who were provided with identification cards by the index participants and identified as members of their HIV risk network will be able to drop-in at the local study site to

participate in study screening for 30 days following the index participant's post-test counseling session.

Screening of network members is expected to take place over two visits. During the first visit, prospective network members will undergo the following:

- Written informed consent for the study
- Eligibility screening survey
- Baseline behavioral risk survey
- HIV pre-test and risk reduction counseling
- HIV testing

During the second visit, network members will receive their HIV test results, post test counseling, and appropriate referrals. In addition, network members will be administered baseline questionnaires to assess network norms and frequency and duration of contact and types of discussions with their index members. Note: These assessments can be completed at any visit prior to randomization.

5.2 Study Enrollment/Randomization of Index and Network Members (Day 0)

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 randomized to the experimental arm 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.

5.3 Follow-up Visits

Follow-up visits are scheduled to take place every six months from enrollment/randomization until the study end date; however, they may take place any time within the period extending from 14 days prior to the target date to 30 days after the target date. Visits that do not take place during this period are treated as interim visits (see Section 5.5). Post-test counseling visits will occur 7 to 14 days after HIV testing. For the purposes of scheduling follow-up visits, a single "Day 0" enrollment/randomization will be assigned to all network members.

Participants will undergo the following:

- Identity confirmation
- Update locator information
- Risk Behavior Survey Note: *The risk survey must be administered prior to the delivery of HIV counseling, by a staff member who has not previously provided HIV counseling to the participant and is blinded to participant's study arm assignment.*
- Enhanced risk reduction counseling

- HIV testing according to Appendix I
- Follow-up questionnaire (to assess the intensity of the intervention delivery by the index in indexes themselves and network members (duration of contact and types of discussions), intervention contamination in the control arm, and perceived network norms (every 12 months))
- Social harms assessment
- Reiteration of study site contact information and instructions to contact the site for additional information about the study and/or HIV counseling, if needed, prior to the follow-up HIV post-test counseling visit.

Note: Network members identified as HIV infected at baseline and index participants and network members identified as HIV infected after enrollment will remain in follow-up and undergo all scheduled assessments except HIV testing.

5.3 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, during which (at a minimum) their HIV test results will be disclosed and HIV post-test counseling and appropriate referrals will be provided.

5.4 Locator contacts

Locator contacts are scheduled to take place in between participant's scheduled six-month follow-up visits; therefore, all participants will be in contact with study staff quarterly throughout follow-up. The contacts in between the scheduled follow-up visits may take place via any modality that the study site deems appropriate for the local study population. Locator information, which includes the address and telephone number of each participant, and contact information for friends and family members will be updated.

5.5 Interim Visits

Interim contacts and visits may be conducted at participant request at any time during the study. Locator information will be updated and interim HIV counseling and testing will be provided as needed in response to participant reports of potential exposure to HIV. All interim contacts and visits, and the results of all interim HIV tests will be documented in participants' study records and on applicable case report forms.

5.6 Study Endpoint Assessment for Participants Who Withdraw

Participants who withdraw from the study (see Section 3.7) will be asked to participate in an end-of-study assessment of their HIV status. In the last six months of the study, site staff will initiate contact with these participants who withdrew from the study and they will be asked to undergo HIV counseling and testing only.

6.0 SOCIAL HARMS

Because of the purely behavioral nature of the intervention, no "biological" adverse experiences directly attributable to the intervention are anticipated. Such events have not been identified in the SHIELD study in Baltimore, nor in the NIDA-funded cohort study of injection drug users conducted by Johns Hopkins University and Research Institute for Health Sciences of Chang Mai of Chang Mai (RIEHS) in Thailand. However, given the illegal status of drug use, the social stigma that surrounds injection drug use and perceptions of drug users held by many members of the communities in which the study will be conducted, there are potential social harms that could occur purely as a result of participation in a study targeting injection drug users. These could include discriminatory treatment and violence associated with possible disclosure of participants' drug or sex-related behaviors or of their HIV serostatus.

In Philadelphia, all activities involving participants will be conducted in venues that mask the criteria for study participation. It is impossible and unwise to think that the primary purpose of the study can be kept secret (i.e., a prevention study for IDUs) from the community, including the police. An appropriate working relationship with the local law enforcement agency, which recognizes the urgent need to prevent HIV in this population, has been established. Such relationships have assisted our outreach staff whose presence in the community is understood and respected. Site staffs do not disclose the names of participants to anyone other than members of the field research staff and have strict policies regarding the situations in which discussions of participants can take place, such as staff meetings on topics of recruitment and follow-up. All interview and laboratory data are securely stored in a confidential manner with no identifying information other than study number. All identifying information is stored in a separate and secure area and does not include study numbers. All computerized information is password-protected and encrypted when saved. Over the past 13 years, this site has enrolled and followed over 3000 IDUs without any instances of police intrusion or unwanted disclosure of personal information of any type.

Since 1999, the Chiang Mai site has enrolled almost 1,000 IDUs and has followed 400 IDUs of different ethnic groups from varying geographic areas in northern Thailand. The site team has established good relationships with drug users, communities, non-governmental organizations (NGOs), and governmental organizations, including law enforcement agencies, throughout the years. The research team includes staff from a regional drug-dependence treatment and rehabilitation center of the Thailand Ministry of Public Health. Researchers from RIEHS, under the auspices of the Thailand Ministry of University Affairs, serve as interviewers and counselors from the communities, including hill tribe groups. Information on participants obtained from interviews in the form of paper questionnaires and laboratory tests are stored in separate and secure filing cabinets without any personal identifiers except numeric study numbers. All computerized information is password-protected and encrypted. The Chiang Mai site has never experienced any intrusion, harassment, or information request from law enforcement agencies or communities regarding identities of any participant IDUs. However, this site is not protected by a Certificate of Confidentiality, which is not recognized by the laws governing Thailand. However, all cognizant public agencies are fully briefed about the site's work and the importance of protecting the confidentiality and identity of all research participants. In 10 years of conducting HIV research in marginalized populations in Thailand, there have been no negative experiences in this regard.

Additional information about protections against social harms can be found in Section 8.5.

6.1 Monitoring of Social Harms

In order to prevent against adverse social events, “social harms” will be monitored closely throughout the study. At each follow-up visit, a series of structured questions will be used to probe for interpersonal, legal, housing and healthcare problems that have occurred as a result of study participation. All subjects will be also be reminded of the importance of reporting problems to study staff between regularly scheduled visits and instructed on how to contact study staff should problems occur during intervals between visits. When problems are identified, additional data regarding the severity and resolution will be described and recorded on a separate reporting form and will include a description of actions taken by the participant, the site staff, and others to resolve or respond to the problem. The nature and frequency of these social impact reports will be monitored by the protocol team as they occur. In addition, these data will be routinely reviewed by the DAIDS Prevention Data and Safety Monitoring Board (DSMB).

7.0 STATISTICAL CONSIDERATIONS

7.1 General Design

This is a Phase III, multi-site, two-arm, randomized, controlled study of a network-oriented peer-education training intervention for prevention of HIV infection through reduction of HIV risk behaviors among HIV uninfected IDUs and members of their HIV risk networks. All participants in the study will receive enhanced HIV counseling and testing at screening and semiannually during follow-up. Indexes in the intervention arm receive a six-session peer education training intervention, plus a booster session at six and 12 months, with a maximum of 12 indexes. Indexes in the control arm receive no additional training. Primary and secondary endpoints will be measured on each participant - indexes and network members - every six months for a maximum of 30 months.

7.2 Study Endpoints

7.2.1 Primary Endpoint

Incident HIV-1 infection in IDU peer networks (indexes and network members) as determined by the seroconversion algorithm in Appendix I.

7.2.2 Secondary Endpoints– Self reported HIV Risk Behaviors

Self- reported HIV risk behaviors for indexes and network members, as follows:

- Frequency of injection drug use, by drug
- Frequency of sharing of injection equipment (needles, cookers, cotton, and rinse water)
- Number of people injection equipment shared with
- Frequency of properly disinfecting injection equipment.
- Entering into drug treatment
- Cessation of injection drug use.
- Number of sex partners
- Frequency of condom use during sex

7.2.3 Secondary Endpoints – Community Norms

- Self-reported behaviors: Network norms will be measured by aggregating the self-reports within networks of the HIV risk behaviors listed above
- Psychometric measures of perceived network group social norms
- Self-reports of frequency of peer discussions of risk behaviors
- Self-reports of frequency of encouragement by network members to reduce HIV risk
- Perception of peer risk behaviors

7.2.4 Potential Effect Modifiers, Confounders and Covariates

7.2.4.1 Individual Risk Factors

- Alcohol use
- Demographics
- Non injection drug use

7.2.4.2 Network Risk Factors

- Network size
- Change in network composition
- Marker of exposure to intervention (tag phrase to measure contamination across arms)

7.3 Sample Size and Accrual

Sample size estimates are based on a group, randomized design, where all members of a network are randomized to the same arm. The sample size required with a group-randomized design is increased depending on the strength of correlation between outcomes within a network, relative to an individually randomized design.

Sample size computations use the formulation given by Donner et al³², where the total number of participants per arm required in a design with clusters of size n is given as:

$$T = \frac{(Z_a + Z_b)^2 (P_E (1 - P_E) + P_C (1 - P_C)) (1 + (n - 1)k)}{(P_E - P_C)^2}$$

where Z_a, Z_b are standardized Normal quantiles for type I error α and power $1 - \beta$, P_E and P_C are, respectively, the cumulative probability of seroconversion in the experimental and control arms, and k is analogous to an intraclass correlation coefficient.

The number of networks required per arm is then T/n .

k can be expressed as:

$$k = \frac{P_1^* + P_0^* - (P^n + (1 - P)^n)}{1 - (P^n + (1 - P)^n)}$$

where P_1^* and P_0^* are the probabilities of network concordance, i.e. the probability all and none of the members of network seroconvert, respectively. The numerator of k measures the difference between the actual concordance among clusters and the expected concordance rate under the assumption of independence, i.e. k measures how much agreement exists in a cluster beyond the amount expected by chance.

7.3.1 Power for seroincidence endpoints

Philadelphia has established a seroincidence rate of 2 per 100 person-years and the current rate established in Thailand among IDU is 10.4 per 100 person-years, although in the sample size computations a conservative 8% rate is used. One-third of the networks will enroll in Philadelphia and two-thirds in Thailand.

Sample size computations are made using the following assumptions:

- Mean seroincidence rate: 6% per year for pooled sites, 8% per year for the Thai sites.
- Loss to follow up 10% per year
- 30 months recruitment, minimum 18 months follow up, maximum 30 months)
- 90% power, 5% Type I error

The formula above is used, substituting for P_E and P_C estimates \bar{P}_E and \bar{P}_C , the average probability of seroconverting during the study on the experimental and control arms. These estimates take loss to follow-up and differential length of follow-up into account.

Table 1: Sample size requirements for two-arm group randomized network study

Rate	Effect	\bar{P}_E	\bar{P}_C	k	Total/arm	Networks /arm	Total/arm	Networks/arm
					Mean per network = 4		Mean per network = 3	
6%	33%	7.8%	11.6%	0.1	1671	418	1542	515
				0.2	2057	515	1800	600
				0.3	2442	611	2057	686
6%	40%	7.1%	11.6%	0.1	1112	278	1026	343
				0.2	1368	343	1197	400
				0.3	1625	407	1368	457
8%	33%	10.4%	15.3%	0.1	1246	312	1150	384
				0.2	1534	384	1342	448
				0.3	1821	456	1534	512
8%	40%	9.4%	15.3%	0.1	828	208	765	255
				0.2	1020	255	892	298
				0.3	1211	303	1020	340

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 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 people per network

(HIV-uninfected peer leader and three 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 networks per arm.

Enrolling 343 networks per arm implies a total study enrollment of approximately 2,736 participants: approximately 110-120 networks per arm in Philadelphia (900 total participants) and 220-230 networks per arm in Thailand (1,800 total participants).

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 networks per arm; 80% power is achieved with 191 networks.

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

7.3.2 Power for Behavioral Endpoints

One third of the networks will be enrolled in Philadelphia, approximately 110 networks per arm; the remainder will be enrolled in Thailand, approximately 220 per arm. Due to the lower seroincidence in the Philadelphia site, it will not be possible to assess the effect of the intervention at that site using primary outcome information. Differences in secondary outcomes of self-reported behavioral outcomes will be assessed to evaluate the intervention at the Philadelphia site (as well as in Thailand).

For behavioral endpoints, assuming repeated measurement at each visit and a conservative average of 15 visits per network [average number of visits per participant = 5, average number of members = 4, loss to follow-up/year = 10%], the formula above can be used to estimate the power for change of behavior within the networks. P_{Exp} and $P_{Control}$ are the probabilities of a behavior in the previous six-month period. As shown in Table 2 below, there is adequate power to detect 10% behavioral change among networks at the Philadelphia site, depending upon the prevalence in the control arm and the correlation within networks.

Table 2: For network aggregates: Sample size requirements for testing proportions with repeated measurements: cluster size=15

P_{Exp}	$P_{Control}$	k	Networks/arm	
			Power: 80%	Power: 90%
40	50	0.1	62	83
		0.2	98	131
		0.3	134	179
30	40	0.1	57	76
		0.2	90	120
		0.3	123	164
20	30	0.1	47	63
		0.2	74	99
		0.3	101	135
10	20	0.1	32	43
		0.2	50	67
		0.3	69	92

Similarly, for testing behavioral change amongst the network indexes, sample size estimates have been computed for repeated measures from the five visits of the index participant: Table 3 shows adequate power at the Philadelphia site for detecting 15% behavioral change in the networks depending on the correlation within networks and the prevalence in the control arm.

Table 3: For network indexes: Sample size requirements for testing proportions with repeated measurements: cluster size=5

P Experimental	P Control	k	Networks/arm	
			Power: 80%	Power: 90%
35	50	0.1	47	63
		0.2	60	81
		0.3	74	99
25	40	0.1	42	56
		0.2	54	72
		0.3	66	88
15	30	0.1	24	45
		0.2	33	57
		0.3	43	70
10	20	0.1	55	74
		0.2	71	95
		0.3	87	116

There is close to 90% power for detecting 10% change in behavior in the networks' aggregates in the Philadelphia. There is close to 90% power for detecting 15% behavior change in the network indexes at the Philadelphia site.

7.3.3 Power for Assessment of Intervention Effect on Behavior

In the event of a successful trial outcome based on the primary endpoint, an analysis of behavioral correlates addresses the question of whether the behavioral changes observed at both sites make it plausible that the intervention is effective in both sites, Thailand and Philadelphia. This analysis has two distinct stages. During the first stage, behaviors that are most important mediators of the intervention effect on HIV seroincidence will be established. Explicitly, these are behavioral measures that, when added to the model of the effect of the intervention on seroincidence, 1) have significant coefficients in the expected direction and 2) substantially reduce the size of the intervention effect. They are thus correlated with seroincidence and substantially account for the observed intervention effect. This argues the plausibility of a behavior being a partial surrogate of the treatment effect.^{33,34,35} Behaviors meeting these criteria will then be used in the second stage of the analysis, which would examine whether the difference in behavior change observed between the intervention and control arms is preserved in the two sites. Power calculations are only provided for the simplest case of a dichotomous outcome, where the analysis reduces to a 2x2 table of behavior proportions by site and arm. The null hypothesis states that the relative behavior change at each site is the same. Under the alternative, the behavior change between arms is different at the sites; formally, the test boils down to a test for a non-zero interaction term.

Presented in Table 4 below are the 80% power boundary probabilities for the given sample size of the trial, expressed as cell probabilities. Power computations are based on use of generalized linear models for binomial data. For these calculations, the sample size is taken as fixed by the requirement for adequate power for the primary endpoint, at 343 networks of size 4 per arm, and it is assumed 2/3 of the networks are in Thailand.

It is expected that the probabilities for behavioral endpoints will be in the range of 20-80%, so power computations are over this range. The upper bound is the probability for the intervention arm at the Philadelphia site that, if it were true, there would be 80% probability of detecting it was not the same behavior reduction as seen in Thailand. For example, in the first row of the table below, it is assumed that a behavior has 80% prevalence in the control arm in both the Philadelphia and Thailand sites at the conclusion of the trial. It is assumed that, in the intervention arm in Thailand, the prevalence of this behavior is halved to 40%. The null hypothesis is that the same is true in Philadelphia. If the true prevalence in Philadelphia were 60% or 26%, there would be 80% power to detect this. Three scenarios are considered in Table 4: prevalence is the same in Philadelphia and Thailand; prevalence is lower, and prevalence is higher in Philadelphia.

Table 4: Analysis of behavioral correlates: bounds on probabilities for which the trial has 80% power to detect differences in behavior change in Philadelphia vs. Thailand.

Scenario	Thailand, Control P_{00}	Philadelphia, Control P_{01}	Thailand, Intervention P_{10}	Philadelphia, Intervention		
				Null P_{11}	Lower Bound	Upper Bound
Equal site prevalence	0.8	0.800	0.40	0.400	0.264	0.605
	0.5	0.500	0.25	0.250	0.160	0.392
	0.2	0.200	0.10	0.100	0.058	0.173
Lower Philadelphia Prevalence	0.8	0.600	0.40	0.300	0.195	0.460
	0.5	0.375	0.25	0.188	0.117	0.299
	0.2	0.150	0.10	0.075	0.042	0.132
Higher Philadelphia Prevalence	0.8	0.850	0.40	0.425	0.281	0.642
	0.5	0.625	0.25	0.312	0.202	0.485
	0.2	0.250	0.10	0.125	0.074	0.211

The alternatives that there is reasonable power to detect seem useful; that is, they represent clinically relevant differences that are neither too small nor too broad.

There are necessarily several points of scientific, rather than statistical, interpretation in the analysis of behavioral correlates. In the first stage of the analysis, there is a judgment of whether a behavioral measure is a substantial mediator of intervention effect. Given the multifaceted nature of behavior change, no single behavioral measure would be expected to fully capture any observed treatment effect.

In the second stage, power calculations are presented for a single dichotomous behavioral outcome per participant. The trial will collect repeated measure data, so there is a risk the study will ultimately be overpowered to detect interaction effects. That is, the intervention effects within each site may be different using a statistical metric, but clinically those differences may not be relevant. An alternate approach would be to establish a clinically relevant difference and reject behavioral changes as the same using an objective standard.

7.3.4 Issues in Sample Size Computation

It is possible that indexes or network members assigned to the experimental group will interact with those assigned to the control. This may attenuate the differences between networks and lead to an underestimation of the effect of the intervention. To take this in account, the study has been powered to detect a decrease of 40% (i.e. a relative risk of 0.6), even though in the SHIELD study, unadjusted OR in excess of 2.0 and adjusted OR as high as 3.0 were observed in behavior change. See Section 4.1 for additional information regarding the possibility of contamination.

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.

7.4 Random Assignment

Individuals found eligible for participation in the study as an index will be randomized to one of the two study groups in a ratio of 1:1 along with their networks. The randomization will be stratified on study site and blocked (with random sequences of block sizes) within study site to ensure that the assignment sequence is not predictable and yet ensure that balance between experimental and control assignments is maintained within each study site over the entire period of recruitment.

7.5 Analysis Plan

7.5.1 Primary Analysis

- HIV seroincidence

Comparison of HIV seroincidence in the two arms will be based on 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 analysis of seroincidence rates per arm will be repeated for the Thailand site alone.

7.5.2 Secondary Analysis – Behavioral

- HIV drug and sexual risk behaviors
- Psychosocial measures of network norms

Both incidence and rates of each risk behavior will be compared between arms using GEE³⁶ and Mixed Linear Models (MLE). Perceived norms reported by index and network members will be analyzed using GEE³⁷, MLE and methods for repeated measurement of ordered categorical responses.

Comparisons will be made between arms for

1. Network aggregates - overall, between sites,, and within sites
2. In network indexes alone, overall, between sites, and within sites

3. Between indexes and networks – overall, between sites, and within sites
4. Between HIV infected and uninfected network members – overall, between sites, and within sites.

Covariates adjusting for type and frequency of injected drug, alcohol use, drug treatment, and network characteristics, in addition to demographic variables, will be considered.

7.5.3 Secondary Analysis – Behavioral Correlates

Partial behavioral surrogates will be identified using the methods referenced in Section 7.3.3. As described there, models with behavioral measures as outcomes and using site and intervention arm as covariates will examine whether the intervention effects on behavior are similar at both sites.

7.6 Interim Monitoring Process

The duration of the study will be approximately 4 years. It is estimated that the enrollment period will be approximately 30 months. Study conduct will be monitored regularly by the HPTN Study Monitoring Committee (SMC) with a focus on issues relating to quality of study conduct, such as overall and site-specific rates of recruitment, adherence to study interventions and visit schedules, and retention. The sample size may be adjusted after 12 months if it is apparent that the mean number of HIV-uninfected network members enrolled is insufficient to achieve adequate power.

The study will also be monitored by the DSMB. Administrative data will be reviewed every 6 months during the first 18 months of the study. Primary and secondary endpoint data will be monitored annually. Sequential monitoring methods will be used to develop boundary guidelines for early termination.

The randomization code will be maintained by the research biostatistician at the HPTN Statistical and Data Management Center. At each interim efficacy analysis, the chairman of the DSMB will be given a sealed envelope with the randomization code enclosed. The DSMB will be encouraged to conduct unblinded reviews of efficacy data.

8.0 HUMAN SUBJECTS CONSIDERATIONS

8.1 Ethical Review

This protocol, the template informed consent forms contained in Appendices III through V will be reviewed and approved by the HPTN Protocol Review Committee (PRC) and DAIDS Prevention Science Review Committee (PSRC) with respect to scientific content and compliance with applicable research and human subjects regulations.

The protocol, site-specific informed consent forms, participant education and recruitment materials, and other requested documents – and any subsequent modifications – also will be

reviewed and approved by the Institutional Review Boards/Ethical Committees (IRBs/ECs) bodies responsible for oversight of research conducted at the study sites.

Subsequent to initial review and approval, the responsible local IRBs/ECs will review the protocol at least annually. The investigator will make safety and progress reports to the IRBs/ECs at least annually and within three months of study termination or completion. These reports will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others. In addition, all detailed results of DSMB reviews of the study will be provided to the IRBs/ECs.

8.2 Informed Consent

Written informed consent will be obtained from each study participant. Each study site is responsible for developing study informed consent forms for local use, based on the templates in Appendices III through V, which describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations. The study site also is responsible for translating the template forms into local languages and verifying the accuracy of the translation by performing an independent back-translation.

IDUs with obvious psychiatric impairment that limits their ability to understand and retain study procedures will be excluded from enrollment (see Section 3.2). Those who are disoriented due to acute effects of drugs or alcohol at the time of screening will be asked to return at a later time. These determinations will take place before any formal study procedures begin and be recorded in a recruitment log. While the informed consent form will be reviewed in its entirety, emphasis will be made on the key aspects of participation in the study and the risks. Individuals will be encouraged to ask questions. In addition, in order to determine that each individual understands the content of the consent form, individuals will be administered a brief consent quiz designed to test the participants' understanding of the study requirements, risks, expectations, and his/her rights as a volunteer. Participants will be provided with a copy of their informed consent form. Informed consent will be an ongoing process and reviewed with participants as needed during follow-up. Study staff will document the informed consent process including issues discussed with the volunteer as described in the Study-Specific Procedures Manual (SSP).

8.3 Risks

Study participants may experience discomfort associated with blood sample collection. Blood sample collection may be associated with pain during blood drawing and subsequent bruising, or in very rare instances, local infection.

Participants may become embarrassed, worried, or anxious when completing their HIV risk assessment and/or receiving HIV counseling. They also may become worried or anxious while waiting for their HIV test results. Trained counselors will be available to help participants deal with these feelings.

Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others and that social harms may result (i.e., because participants could become known as HIV-infected or at "high risk"

for HIV infection). For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities. In addition, names of study participants who develop HIV may be required by state or local officials under health department regulations providing for reporting of communicable diseases, partner notification, and/or contact tracing (see Section 8.6). Finally, reporting names of study participants who report (in the context of a counseling session or via response to a questionnaire) an intention to harm self or others, current or recent child abuse, or current or recent statutory rape may be required by state or local officials.

8.4 Benefits

There may be no benefit to participants in this study. However, the study may provide information that could benefit participants and others in the future. Participants will receive free HIV counseling and testing throughout the study and, although the study cannot provide medical care and other services to participants, study staff will refer participants to other organizations for these services. In particular, participants who are found to be infected with HIV will be referred to available medical services, other psychosocial services, and research studies for HIV-infected persons.

The study will provide information on whether the proposed behavioral intervention reduces the incidence of HIV infection compared to standard counseling and testing. If the intervention is effective, it could be disseminated internationally as a useful strategy for preventing HIV transmission.

Participation in this study may help participants remain HIV-uninfected through reinforcement of HIV risk reduction. During the study, participants will receive the most current information and counseling about how to avoid HIV, as well as periodic testing for HIV infection. In addition, study site staff may provide risk reduction materials, such as condoms and lubricants, as applicable, to study participants.

8.4.1 Access to Care

This study provides for periodic HIV-related behavioral risk assessment as well as testing for HIV infection. Study staff will be trained to refer participants to such services as STI treatment, drug treatment and/or other psychosocial services, as applicable to the participant. In the event of HIV infection, study staff will refer participants to appropriate medical and psychosocial services, as well as monitor their access to follow-up care.

In Philadelphia, participants who test HIV positive at screening and during follow-up will first be provided supportive counseling by the research staff at the time of the post-test visit. If necessary, community-based counseling will be arranged. Network members who test HIV positive at screening will be offered follow-up in the same manner as other network members, and great care will be taken to prevent the disclosure of their serostatus. Although treatment options are discussed during the post-test session, often several follow-up sessions are required in order to assist the participant to become engaged with a medical care provider. Subjects are also made aware of research opportunities that are available to them during these visits. Research staff will schedule appointments with medical care providers selected by the participant and will arrange

transportation, if necessary. Treatment options include the Immunodeficiency Clinic at the Hospital of the University of Pennsylvania, the community-based services of Philadelphia Fight, or the treatment provided by the Department of Public Health of the City of Philadelphia.

In Thailand, participants who test HIV positive at screening and during follow-up will be provided supportive counseling services during the post-test counseling sessions by the research staff who are certified HIV counselors. Network members who test HIV positive at screening will be offered followup in the same manner as other network members, and great care will be taken to prevent the disclosure of their serostatus. HIV infected participants will be referred during post-test counseling to provincial hospitals or district AIDS fund clinics. Appropriate prophylactic and symptomatic treatments will be provided by these referred centers according to Thailand Ministry of Public Health Guidelines. If requested by participants, transportation and other social services will be provided regarding the referral. Contact addresses and phone numbers of community support groups and agencies for HIV-infected persons will be provided to the participants. Participants who are trained as peer educators will be encouraged to participate in local HIV prevention activities beyond the duration of research by arranging connection with HIV prevention community network organizations in northern Thailand.

Participants who complain of physical health problems will be referred to local government outpatient clinics, where care is provided at very low charge of Baht 30 (U.S. \$0.75). For participants with STI symptoms, referrals will be made to the Communicable Disease Control, Region 10 STI clinics, where care is provided free of charge. For network participants who are determined to be HIV-infected at baseline or for participants who seroconvert during the course of the study, referrals will be made to the HIV care service at Chiang Mai University Hospital to link participants with an on-going source of care.

8.4.2 Incentives

The level of compensation that will be provided will be determined in consultation with the local Community Advisory Board (CAB) and approved by the local IRB. Participants will be reimbursed for the costs of lost work, transportation and other costs associated with study visits. Index participants will be given a one-time payment for recruitment of eligible network members. The specific amount of reimbursement will be specified in the informed consent.

8.5 Confidentiality

All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with limited access. All laboratory specimens, reports, data collection, process, and administrative forms will be identified by a coded ID number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link

participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

All HIV test results will be kept strictly confidential, all counseling and blood draws will be conducted in private rooms, and study staff will be required to sign agreements to preserve the confidentiality of all participants. Study staff will never inform network members of the serostatus of other members of their group, but counselors will provide general messages about the prevalence of HIV in the study population in the interests of emphasizing harm reduction.

Participants' study information will not be released outside of the study without the written permission of the participant, except as necessary for monitoring by NIAID and/or its contractors (e.g., the DAIDS monitoring contractor), representatives of the HPTN CORE, SDMC, and/or Central Lab (CL), and US or in-country government and regulatory authorities.

8.5.1 U.S. Federal Protections

A Certificate of Confidentiality that applies to all U.S. study sites will be obtained prior to initiation of screening from the Department of Health and Human Services. The Certificate of Confidentiality states that study staff may not be compelled to disclose study-related information by any U.S. Federal, State or local civil, criminal, administrative, or legislative agency, or other proceedings. The Certificate thus serves to protect the identity and privacy of study participants at the Philadelphia site.

8.6 Communicable Disease Reporting Requirements

Study staff will comply with all applicable local requirements to report communicable diseases identified among study participants to local health authorities. Participants will be made aware of all reporting requirements during the study informed consent process.

8.7 Study discontinuation

The study may be discontinued at any time by the sponsors NIAID, the HPTN, or US or in-country government or regulatory authorities.

8.8 Community Preparedness

Each study site will develop strategies to increase community awareness, knowledge and acceptance of this study, particularly among populations most likely to be targeted for study enrollment. Each study site will convene and provide logistical support for a Community Advisory Board (CAB). The CAB will meet regularly and information will be sought to preemptively address concerns likely to arise during the study. In addition, the CAB will also be asked to comment on study related informational and educational materials including procedures and documents related to the informed consent process.

9.0 LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT

9.1 Local Laboratory Specimens

Eight mL of blood will be collected from each participant for HIV testing and stored at the local laboratory at screening and every six months thereafter.

Each study site will adhere to standards of Good Laboratory Practice, the HPTN Manual of Operations, and local standard operating procedures for proper collection, processing, labeling, transport, and storage of specimens to the Local Lab (LL). Specimen collection, testing, and storage at the LL will be documented using the HPTN Laboratory Data Management System (LDMS).

9.2 Laboratory Quality Assurance

The HPTN CL has established a proficiency testing program at each study site. CL staff also will conduct periodic visits to each site to assess the implementation of on-site laboratory quality control procedures, including proper maintenance of laboratory testing equipment, use of appropriate reagents, etc. CL staff will follow-up directly with site staff to resolve any quality control or quality assurance problems identified through proficiency testing and/or on-site assessments.

The HPTN CL will repeat HIV antibody testing on all specimens from HIV seroconverters and a random sample of stored specimens for quality assurance (QA) purposes. The CL will inform site staff of the samples selected for quality assurance testing, and site staff will ship the selected specimens to the CL. All specimens will be shipped in accordance with the HPTN Manual of Laboratory Operations and IATA specimen shipping regulations. All shipments will be documented using the HPTN LDMS.

The CL will test the specimens for HIV antibody and compare the results of their tests with the results obtained by the local labs. CL staff will follow up directly with site staff to resolve any quality assurance problems identified through this process.

9.3 Specimen Storage

Study site staff will store all plasma specimens collected in this study at least through the end of the study. All plasma specimens will be subject to possible quality assurance testing — for HIV antibody — as described in Section 9.2.

9.4 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the U.S. CDC.

10.0 ADMINISTRATIVE PROCEDURES

10.1 Study Activation

Following ethical review and approval, study sites will submit required regulatory documentation — as listed in the SSP Manual — to the HPTN CORE. CORE staff will work with study site staff to complete “protocol registration” in accordance with DAIDS procedures.

Pending successful protocol registration and submission of all required documentation CORE staff will issue a “site activation notice”. The study may not begin until a study activation notice is provided to the site.

10.2 Study Coordination

Study implementation at all sites will be directed by this protocol as well as a common SSP manual. This manual will outline procedures for conducting study visits, collecting and submitting study data, collecting and shipping specimens, and other study operations.

Study case report forms will be developed by the study team and HPTN SDMC. Data will be recorded on site and transferred to the HPTN SDMC, entered, and cleaned using the DataFax data management system. Quality control reports and queries will be routinely sent back to the site for verification and resolution.

Close cooperation between the study site investigators and coordinators, NIAID Representative, Protocol Coordinator, Biostatistician, Data Managers, and other study team members will be necessary to track study progress, respond to queries about proper study implementation, address issues in a timely manner, and assure consistent participant management, documentation, and information sharing. Rates of accrual, follow-up, and protocol compliance will be monitored closely by the study team. Representatives of the HPTN CORE and SDMC also will evaluate these rates on a regular basis.

10.3 Study Monitoring

On-site study monitoring will be performed in accordance with DAIDS policies. Study monitors will visit the site to

- Verify compliance with human subjects and other research regulations and guidelines;
- Assess adherence to the study protocol, study-specific procedures manual, and local counseling practices; and
- Confirm the quality and accuracy of information collected at the study site and entered into the study database.

Site investigators will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, case report forms), as well as observe the performance of study procedures. Investigators also will allow

inspection of all study-related documentation by authorized representatives of the HPTN CORE, SDMC, CL, NIAID, and US and in-country government and regulatory authorities. A site visit log will be maintained at the study site to document all visits.

10.4 Protocol Compliance

The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the Protocol Chair and NIAID Program Officer. All protocol amendments must be submitted to and approved by the relevant IRB(s)/EC(s) and the DAIDS Regulatory Operations Center prior to implementing the amendment.

10.5 Investigator's Records

The study site investigator will maintain and store in a secure manner complete, accurate, and current study records throughout the study. The investigator will retain all study records for at least three years after submission of the HPTU's final Financial Status Report to DAIDS, which is due within 90 days after the end of the HPTU's cooperative agreement with DAIDS, unless otherwise specified by DAIDS or the HPTN CORE. Study records include administrative documentation — including site registration documents and all reports and correspondence relating to the study — as well as documentation related to each participant screened for and/or enrolled in the study — including informed consent forms, locator forms, case report forms, notations of all contacts with participants, and all other source documents.

10.6 Use of Information and Publications

Publication of the results of this study will be governed by HPTN policies. Any presentation, abstract, or manuscript will be submitted by the investigator to the HPTN Manuscript Review Committee and DAIDS for review prior to submission.

11.0 REFERENCES

- 1 Stimson G, Des Jarlais D C, Ball A. 1998. *Drug Injecting and HIV Infection*. World Health Organization: London: UCL Press Limited.
- 2 National Institute on Drug Abuse (NIDA) and World Health Organization (WHO) Report on Street Children and Drug Abuse: Social and Health Consequences.
- 3 Needle R, Coyle S, Cesari, H. 1998. HIV Prevention with Drug-Using Populations: Current Status and Future Prospects. *Public Health Reports*. Vol. 113; Suppl 1.
- 4 Jones TS and Vlahov D. July 1998. HIV Prevention for Injection Drug Users. *JAIDS*: 18 (Suppl 1).
- 5 NIDA, Research Guide on HIV Prevention. In Press.
- 6 Academy for Educational Development: A Comprehensive Approach: Preventing Blood-Borne Infections Among Injection Drug Users, December 2000.
- 7 Ball A, Crofts N. 2001. HIV Risk Reduction in Injection Drug Users. In: Lampthey P and Gayle H (eds) *HIV/AIDS Prevention and Care in Resource Constrained Settings: Handbook for the Design and Management of Programs*. Arlington, VA. Family Health International.
- 8 Kelly JA. 1999. Community-level interventions are needed to prevent new HIV infection. *AJPH*. 89:3 299-301.
- 9 United Nations System on Preventing the Transmission of HIV Among Drug Abusers at the UNGASS meetings (June 23-25, 2001).
- 10 NIDA. A Manual to Reduce the Risk of HIV and Other Blood-Borne Infections in Drug Users: The NIDA Community-Based Outreach Model. September 2000. NIH Publ. No 00-4812.
- 11 Edwards J., Tindale R., Heath L., & Posavac E . (Eds.) 1990. *Applying Social Influence Processes in Preventing Social Problems*. New York: Plenum Press.
- 12 Fisher JD. 1988. Possible effects of reference group-based social influence on AIDS risk behavior and AIDS prevention. *American Psychologist*. 43:914-920.
- 13 Hall A & Wellman B. Social networks and social support. In S. Cohen & L. Syme (eds.) *Social Support and Health*. pp 23-41. New York: Academic Press.
- 14 Fisher, JD & Fisher, WA. 1992. Changing AIDS risk behavior. *Psychological Bulletin*. 111:455-474.
- 15 Fisher JD, Misovich SJ. 1990. Evolution of college students AIDS-related behavioral responses, attitudes, knowledge, and fear. *AIDS Educ Prev*. 1990 Winter; 2(4):322-37.

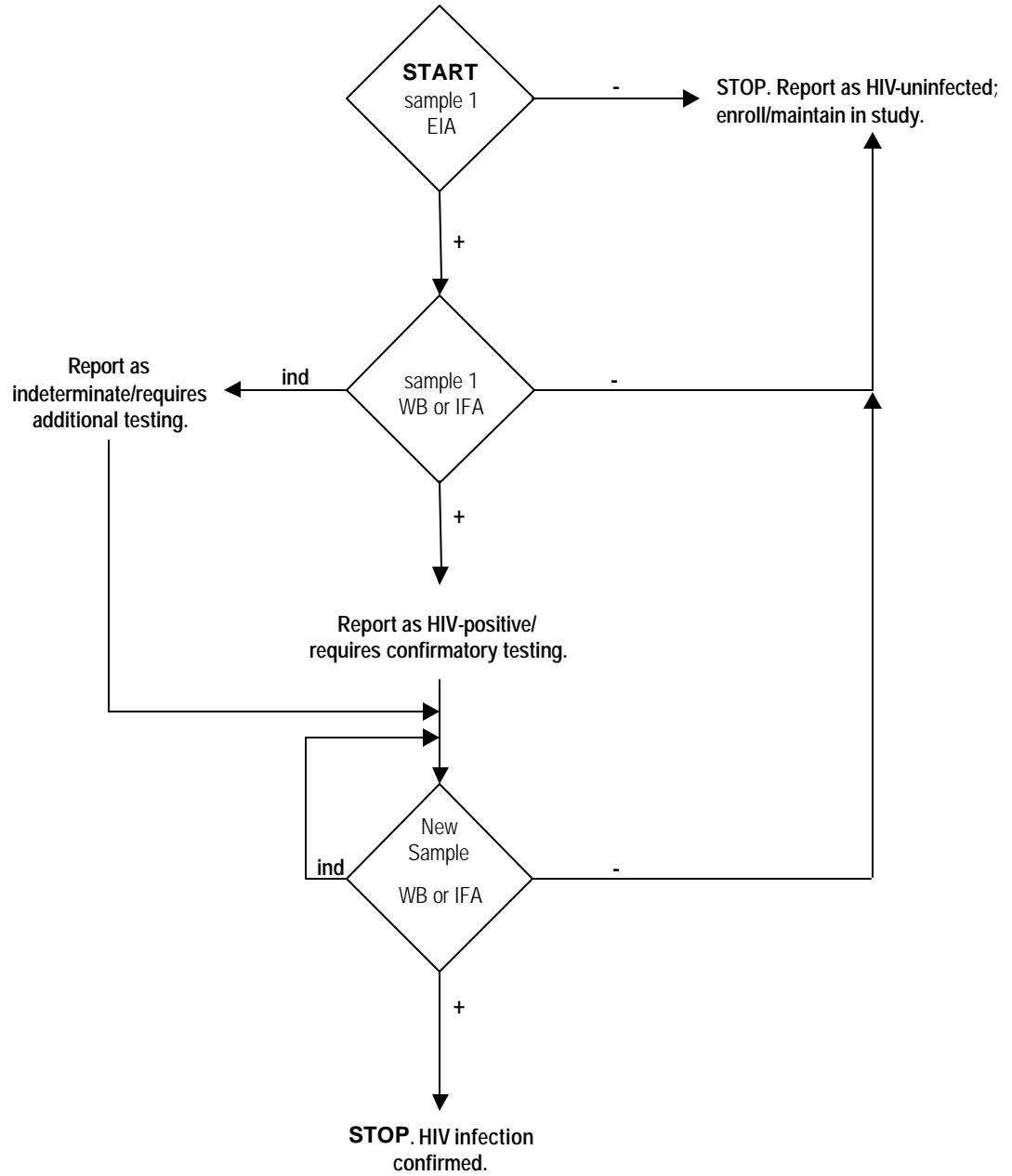
- 16 Dowsett, G.W. Sustainig. 1993. Safe Sex: Sexual practices, HIV and social context. *AIDS*. (S1), 257-262.
- 17 Des Jarlais D, Friedman SR, Friedmann P, Wenston J, Sotheran JL, Choopanya K, Vanichseni S, Raktham S, Goldberg D, Frischer M, Green S, Lima ES, Bastos FI, Telles PR. 1995. *AIDS* 9:611-617.
- 18 Reitmeijer CA, Kane MS, Simons PZ, Corby NH. 1996. Increasing the use of bleach and condoms among injecting drug users in Denver: Outcomes of a targeted, community-level HIV prevention program. *AIDS* 10(3): 291-298.
- 19 Watters JK, Estilo MJ, Clark GL, Lorvick J. 1994. Syringe and needle exchange as HIV/AIDS prevention for injection drug users. *JAMA*. Jan 12;271(2):115-20.
- 20 Needle R, Fisher DG, Weatherby N, et al. 1995. Reliability of self-reported HIV risk behaviors of drug users. *Psychology of Addictive Behaviors*. 9(4):242-250.
- 21 McCoy CB, Rivers JE, Khoury EL. 1993. An emerging public health model for reducing AIDS-related risk behaviors among injection drug users and their sexual partners. *Drug & Society*. 7:143-159.
- 22 Sikkema KJ, Heckman TG, Kelly JA, Anderson ES, Winett RA, Solomon LJ, Wagstaff DA, Roffman RA, Perry MJ, Cargill V, Crumble DA, Fuqua RW, Norman AD, & Mercer MB. 1996. HIV risk behaviors among women living in low-income, inner-city housing developments. *American Journal of Public Health*. 86(8): 1123-8.
- 23 Kelly JA., McAuliffe TL, Sikkema KJ, Murphy DA., Somlai AM, Mulry G, Miller JG, Stevenson LY, & Fernandez MI. 1997. Reduction in risk behavior among adults with severe mental illness who learned to advocate for HIV prevention. *Psychiatric Services*. 1997 48(10):1283-8.
- 24 Goehl L, Nunes E, Quitkin F, & Hilton I. 1993. Social networks and methadone treatment outcome: the costs and benefits of social ties. *American Journal of Drug and Alcohol Abuse*. 19(3):251-62.
- 25 Latkin C, Mabdell W., Vlahov D., Oziemkowska M., Celentano D. 1996. The Long Term Outcome of a Personal Network-Oriented HIV Prevention Intervention for Injecting Drug Users: The SAFE Study. *American Journal of Community Psychology*. 24:3.
- 26 Trotter RT II, Bowen AM, Potter JM Jr. 1995. Network models for HIV outreach and prevention programs for drug users. *NIDA Research Monograph*. 151:144-80.
- 27 Vlahov D, Anthony JC, Celantano D, Solomn L, Chowdhury N.1991. Trends of HIV-1 risk reduction among initiates into intravenous drug use 1982-1987. *American Journal of Drug & Alcohol Abuse*;17, 39-48.
- 28 Rosenstock, IM, Strecher, VJ, Becker, MH. 1994. The health belief model and HIV risk behavior change.(pp. 61-78). In DiClemente, Ralph J. (Ed); Peterson, John L. (Ed); Preventing AIDS; Theories and methods of behavioral interventions. *AIDS Prevention and Mental Health*. (pp. 5-24). New York, NY, USA: Plenum Press.
- 29 Bandura, A. Social cognitive theory and exercise of control over HIV infection (pp. 25-59). In

DiClemente, Ralph J (Ed); Peterson, John L. (Ed); 1994. Preventing AIDS: Theories and methods of behavioral interventions. AIDS prevention and Mental Health. (pp. 5-24). New York, NY, USA: Plenum Press.

- 30 Catania, JA, Kegeles, S, & Coates, TJ. 1990. Towards an understanding of risk behavior: An AIDS risk reduction model (ARRM). *Health Education Quarterly*. 17: 53.
- 31 Kamb M, Fishbein M, et al. 1998. Efficacy of Risk-Reduction Counseling to Prevent Human Immunodeficiency Virus and Sexually Transmitted Diseases. *JAMA*; 280: 1161-1167.
- 32 Donner A, Birkett N, Buck C. 1981. Randomization by Cluster, *Am J Epidemiology*. 114: 906-914.
33. Freedman, L.S., Graubard, G., Statistical Validation of Intermediate Endpoints for Chronic Diseases, *Statist. Med*, 11:167-178, 1992.
- 34 Lin, D., Fleming, T, De Gruttola, V., 1997. Estimating the proportion of treatment effect explained by a surrogate marker, *Statist. Med*, 16:1515-1527.
- 35 Lin, Z, Meredith, M, Hoseyni, M, A method to assess the proportion of treatment effect explained by a surrogate endpoint, *Statist. Med*, 20:3175-3188, 2001.
- 36 Zeger SL, Liang KY. 1986. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics*; 42:121-130.
- 37 Laird, N, Ware, J. 1982. Random-effects models for longitudinal data. *Biometrics* 38:963-974.

APPENDICES

I. HIV Antibody Seroconversion Testing Algorithm II Schedule of Visits and Procedures



II. Study Visit Procedures Table

Procedures	Screening [∞]	Enrollment/ Randomization	Follow-up					
	-60 days to -1 days	Day 0	1 to 4 weeks	3 mos	6 mos	9 mos	12 mos	Follow-up visits every 6 months [*]
Screening Informed Consent (Indexes only)	X							
Screening Eligibility Survey	X							
Baseline Surveys [†]	X							
Study Informed Consent	X							
Risk Reduction Counseling	X				X		X	X
Social Harms Assessment					X		X	X
HIV Counseling and Testing [‡]	X				X [§]		X [‡]	X [‡]
Randomization		X						
Follow-up Surveys ^{**}					X		X	X
Locator Information	X		X	X	X	X	X	X
Peer Education Intervention Sessions^{††}		X	X					

[∞] Screening will occur over 2+ visits.

^{*} Follow-up visits will be scheduled every 6 months until the participants' study end date (minimum of 18 months and a maximum of 30 months). Additional contacts to update locator information will be made in between semi-annual follow-up visits (e.g. at 3, 9, 15 months, etc).

[†] Baseline surveys include assessments of HIV risk behavior, network norms, and the intensity of contacts with network members

[‡] Regardless of HIV test results, participants will complete a post-test counseling visit 7-14 days after HIV testing

[§] If EIA and WB positive, a second sample should be drawn as soon as possible or at the next scheduled visit for western blot confirmation.

^{**} Every 6 months, follow-up, surveys will include assessments of changes in HIV risk behavior, intensity of the intervention delivery by the index, and intervention contamination in the control group. In addition to these assessments, at 12-month intervals, network norms will be assessed.

^{††} Index participants randomized to the experimental arm only

Booster Sessions**				X		X	
---------------------------	--	--	--	----------	--	----------	--

III Sample Informed Consent for Screening of Index Participants

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, Version 1.0

Principal Investigators: [name and contact information for the site PI]

INTRODUCTION

You are being asked to take part in a screening process, including interviews and HIV counseling and testing. This screening process is used to determine if you are able to take part in a research study. The research study will test whether an education and counseling program can reduce the spread of HIV among drug users by changing people's behavior. The person in charge of this study at this site is _____. This study is sponsored by the U.S. National Institutes of Health (NIH).

Before you decide whether or not you want to take part in the screening process, you need to know the purpose of the screening, the possible risks and benefits, and what will be expected of you if you decide to participate. This consent form will give you information about the screening process. The study staff will discuss the screening with you. They will answer any questions that you have. After the screening has been fully explained to you, you can decide whether or not you want to participate. This process is called informed consent. If you decide to participate in the screening, you will be asked to sign this consent form or make your mark in front of someone. You will be offered a copy to keep.

At the end of the screening process, you will find out if you are eligible for the research study. If you are eligible, the study staff will fully explain the study to you and answer any questions that you have. After the study has been fully explained to you, if you decide to participate, you will be asked to sign another consent form to participate in the study.

VOLUNTARY PARTICIPATION

You must know certain things:

- Your participation in the screening process is entirely voluntary.
- You may decide not to participate in the screening or to withdraw from the screening at any time without losing the benefits of your standard medical care or other services.
- If you decide not to participate in the screening process, you can still join another research study later, if one is available and you qualify.
- Even if you agree to participate in the screening, you do not have to join the research study.

PURPOSE OF THE SCREENING

The purpose of the screening process is to determine if you are eligible for a research study that will test an education and counseling program to reduce the spread of HIV by changing people's behavior. The study will take place in the U.S. and Thailand. A total of about 2640 people will participate in the study in these two countries.

SCREENING PROCEDURES

Overview

The screening process will take about 2 months. During this time you will be asked to come to the study clinic 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, you will return to this study clinic to learn your HIV test results and receive counseling. To be eligible to participate in the research study, you must recruit at least two other people with whom you have sex or take drugs 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. These individuals must come to the clinic for screening within three weeks of the visit at which you 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. 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 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 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 decided to participate. If you are willing to participate in the research study, you will be asked to sign another consent form. 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, 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.

Screening Visit #3

The third visit will take place three weeks after you learn your HIV test result and will last only about half an hour. At this visit, you will be told whether you are eligible to participate in the research study. For you to be eligible, at least two 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.

RISKS AND DISCOMFORTS

Blood drawing may cause pain and bruising at the place where the blood is taken. Sometimes, drawing blood causes people to feel lightheaded or even faint. Getting an HIV test may cause you anxiety.

We will make every effort to protect your privacy and confidentiality while you are in this study. However, it is possible that you could have problems if people learn that you are in this study. People may think that you are infected with HIV or at risk of HIV because of sexual behavior or drug use. If you are infected with HIV, you may have problems finding or keeping a job. You may be treated unfairly by others, including your family and community.

[Sites to include/amend the following if applicable:] State regulations require the study staff here to report the names of people who test positive for HIV to the [local health authority]. Outreach workers from the [health authority] may then contact you about informing your partners, since they also should be tested. If you do not want to inform your partners yourself, outreach workers will tell them of their possible exposure to HIV, according to the confidentiality guidelines of the [health authority].

POTENTIAL BENEFITS

You may receive no direct benefit from this screening. However, the screening will provide you with information about HIV and your HIV status.

REASONS WHY YOU MAY BE WITHDRAWN FROM THE SCREENING WITHOUT YOUR CONSENT

The study staff may need to withdraw you from the screening early without your permission for the following reasons:

- The research study is cancelled by the sponsor (U.S. National Institutes of Health (NIH)), the local government or regulatory agency, or the Institutional Review Board (IRB). (An IRB is a committee that watches over the safety and rights of research subjects.)
- The Data Safety Monitoring Board (DSMB) recommends that the study be stopped early. (A DSMB is an outside group of experts who monitor the study.)
- You are not able to attend the study visits or follow the procedures required by the study.

NEW FINDINGS

You will be told of any new information learned during the course of the screening that might cause you to change your mind about continuing to participate.

COSTS TO YOU FOR YOUR PARTICIPATION

There will be no cost to you for screening visits, laboratory tests or other procedures. For each scheduled visit that you attend during the screening, you will be paid for your time and travel expenses. *[Local amount to be specified in site specific consent.]*

CONFIDENTIALITY OF RECORDS

All efforts will be made to keep your personal information confidential to the extent permitted by law. Personal information from your study records will not be released without your written permission. You will be identified by a code number known only to you and the study staff.

All information about you will be marked by this number – not your name. However, study records that could be used to identify you may be reviewed by the study sponsor and their authorized study monitors, local government or regulatory agencies, or by the [insert name of site] IRB. Your name will never be used in any publication or presentation about this screening process or about the research study.

The study staff may contact you to remind you about screening visits. When they contact you, the study staff will not tell anyone about your participation in the screening or about your HIV status.

For U.S. site: (Certificate of Confidentiality sample language)

In addition to the efforts made by the study staff to help keep your personal information confidential, we have obtained a Certificate of Confidentiality from the U.S. Federal Government. This certificate protects researchers from being forced to tell people who are not connected with this study, such as the court system, about your participation or any information that you give us for study purposes. Any publication of this study will not use your name or identify you personally.

Even with the Certificate of Confidentiality, if the study staff learn of possible child abuse and/or neglect or a risk of harm to you or others, we will be required to tell the proper authorities.

RESEARCH RELATED INJURY

If you are injured as a result of this screening process, you will be given immediate treatment for your injuries. However, you may have to pay for this care. There is no program for compensation either through this institution or the study sponsor (the U.S. National Institutes of Health (NIH)). You will not give up any of your legal rights by signing this consent form.

RESEARCH SUBJECTS' RIGHTS

Taking part in the screening process is completely voluntary. You may choose not to take part in the screening or leave the screening at any time. You will be treated the same no matter what you decide.

PERSON TO CONTACT FOR PROBLEMS OR QUESTIONS

For questions about the screening process or a research-related injury, contact:

[site insert name of the investigator or other study staff]

[site insert telephone number and physical address of above]

For questions about your rights as a research subject, contact:

[site insert name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site]

[site insert telephone number and physical address of above]

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this screening process for a research study, please sign your name or make your mark below.

Participant's Name (print)

Participant's Signature and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness' Name (print)

Witness's Signature and Date

(As appropriate)

IV. Sample Informed Consent for Enrollment of Index Participants

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, Version 1.0

Principle Investigators: [name and contact information for the site PI]

INTRODUCTION

You are being asked to take part in the research study named above. The person in charge of this study at this site is _____. This study is sponsored by the U.S. National Institutes of Health (NIH).

Before you decide whether or not you want to take part in this research study, you need to know the purpose of the study, about the possible risks and benefits, and what will be expected of you if you decide to participate. This consent form provides information about the study. The study staff will also discuss the study with you. They will answer any questions that you have. After the study has been fully explained to you, you can decide whether or not you want to participate. This process is called informed consent. If you decide to participate in the study, you will be asked to sign this consent form or make your mark in front of someone. You will be offered a copy to keep.

VOLUNTARY PARTICIPATION

It is important that you know certain things:

- Your participation in the study is entirely voluntary.
- You may decide not to participate or to withdraw from the study at any time without losing the benefit of your standard medical care or other services.
- If you decide not to participate in this study, you can still join another research study later, if one is available and you qualify.

PURPOSE OF THE STUDY

The purpose of the research study is to determine whether an education and counseling program can reduce the spread of HIV by changing people's behavior. The study will take place in the United States and Thailand. A total of about 2640 people will participate in the study in these two countries.

If you agree to participate in the study, the duration of your participation will be about a year and a half to two and a half years, depending on when you join the study.

STUDY PROCEDURES

If you agree to take part in the study, you will be assigned to one of two groups. Which group you are in is decided by chance, like tossing a coin. About half of the participants will be in each group. Participants in both groups will be asked to return to the clinic every six months for HIV counseling,

HIV testing and a questionnaire on sex and drug use. Participants in one of the groups will also be asked to participate in an additional training and education program as described below.

Follow-up visits

All participants in the study will be asked to return to the study clinic every six months after enrollment (a total of about 3 to 5 times depending on when you enroll in the study). Each follow-up visit will last about one hour. At each of these visits, you will be asked questions about your sex and drug use behaviors. You will be counseled about how to prevent HIV transmission and about HIV testing. At each follow-up visit, a sample of about 8 ml (about 2 teaspoons or local equivalent) of blood will be drawn for HIV testing. You will be told when you can return for your test results. The study staff will talk with you about the result of your last HIV test and what it means.

If, at anytime during the study, your test result shows that you are infected with HIV, the study staff will contact you in person as soon as possible. You may be asked to give another 5 ml sample of blood to confirm the result. The study staff will talk to you about your test result, how you feel about it and how to avoid passing HIV to other people. The staff will give you information on where to go for additional counseling, medical care and treatment. They will also tell you about any other research studies for which you may be eligible. You will be asked to continue in the study as scheduled.

Other Contacts

Between each of the six-month follow up visits, the study staff will contact you to remind you of your next visit and to update the contact information they have for you. Study staff may also contact the individuals whose names you provided and agreed to be in the study directly in order to find you.

Education and training sessions

Individuals assigned to the group receiving additional education and training will be asked to participate in 6 training sessions during the first month of the study. Each session will include about 8 to 12 participants and will last about two hours. Participants in this study group will also be asked to participate in two additional training sessions – one about 6 months after enrollment in the study and the other about 12 months after enrollment in the study. Each of these two training sessions will last about 1 hour. The purpose of the education and training sessions is to teach participants how to talk with their peers about reducing the risk of acquiring or transmitting HIV. The sessions will focus on changing certain behaviors that put people at risk for HIV, such as unprotected sex and sharing needles for injection of drugs. The education and training sessions may be audio taped. The reason for taping these sessions is so that the study staff can be sure they are being conducted properly. The audiotapes will not be linked to you or your voice.

RISKS AND DISCOMFORTS

Blood drawing may cause pain and bruising at the place where the blood is taken. Sometimes, drawing blood causes people to feel lightheaded or even faint. The questions about your sexual activity and drug use might make you uncomfortable or embarrassed. Getting an HIV test may cause you anxiety.

We will make every effort to protect your privacy and confidentiality while you are in this study. However, it is possible that you could have problems if people learn that you are in this study. People may think that you are infected with HIV or at risk of HIV because of sexual behavior or drug use. If you are infected with HIV, you may have problems finding or keeping a job. You may be treated unfairly by others, including your family and community.

[Sites to include/amend the following if applicable:] State regulations require the study staff here to report the names of people who test positive for HIV to the [local health authority]. Outreach workers from the [health authority] may then contact you about informing your partners, since they also should be tested. If you do not want to inform your partners yourself, outreach workers will tell them of their possible exposure to HIV, according to the confidentiality guidelines of the [health authority].

POTENTIAL BENEFITS

You may receive no direct benefit from this research study. However, information learned from this research study may help others in the future. The HIV tests will provide you with information about your HIV status. You will also learn how to avoid becoming infected with HIV.

REASONS WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT

The study staff may need to take you off the study early without your permission if:

- The research study is cancelled by the sponsor (U.S. National Institutes of Health (NIH)), the local government or regulatory agency, or the Institutional Review Board (IRB). (An IRB is a committee that watches over the safety and rights of research subjects.)
- The Data Safety Monitoring Board (DSMB) recommends that the study be stopped early. (A DSMB is an outside group of experts who monitor the study.)
- You are not able to attend the study visits or follow the procedures required by the study.
- If the study staff believe that it is unsafe for you to continue in the study for any reason.
- Other administrative reasons

NEW FINDINGS

You will be told of any new information learned during the course of the study that might cause you to change your mind about staying in the study.

ALTERNATIVES TO PARTICIPATION

If you choose not to participate in this study or are not eligible to participate, you can go to a local health center for HIV testing and counseling. Counseling that you receive may be different than counseling offered in the study.

COSTS TO YOU

There will be no cost to you for study-related visits, HIV tests or other procedures.

For each scheduled visit that you attend during the study, you will be paid for your time and travel expenses. You will also receive a one-time payment for each individual you named during screening that

comes to the study clinic (for up to 5 individuals). *[Local amount to be specified in site specific consent.]*

CONFIDENTIALITY OF RECORDS

All efforts will be made to keep your personal information confidential to the extent permitted by law. Personal information from your study records will not be released without your written permission. You will be identified by a code number known only to you and the study staff. This number – not your name will mark all information about you. However, study records that could be used to identify you may be reviewed by the study sponsor and their authorized study monitors, local government or regulatory agencies, or by the IRB. Your name will never be used in any publication or presentation about this screening process or about the research study.

All contact for follow-up visits will be handled carefully to keep your participation in this study confidential.

For U.S. site: (Certificate of Confidentiality sample language)

In addition to the efforts made by the study staff to help keep your personal information confidential, we have obtained a Certificate of Confidentiality from the U.S. Federal Government. This certificate protects researchers from being forced to tell people who are not connected with this study, such as the court system, about your participation or any information that you give us for study purposes. Any publication of this study will not use your name or identify you personally.

Even with the Certificate of Confidentiality, if the study staff learn of possible child abuse and/or neglect or a risk of harm to you or others, they will be required to tell the proper authorities

RESEARCH RELATED INJURY

If you are injured as a result of being in this research study, you will be given immediate treatment for your injuries. However, you may have to pay for this care. There is no program for compensation either through this institution or the study sponsor (the U.S. National Institutes of Health (NIH)). You will not give up any of your legal rights by signing this consent form.

PERSONS TO CONTACT FOR PROBLEMS OR QUESTIONS

For questions about this study or a research-related injury, contact:

[site insert name of the investigator or other study staff]

[site insert telephone number and physical address of above]

For questions about your rights as a research subject, contact:

[site insert name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site]

[site insert telephone number and physical address of above]

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name or make your mark below.

Participant's Name (print)

Participant's Signature and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness' Name (print)

Witness's Signature and Date

(As appropriate)

V. Sample Informed Consent for Screening and Enrollment of Network Members

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, Version 1.0

Principle Investigators: [name and contact information for the site PI]

INTRODUCTION

You are being asked to take part in the research study named above because someone that you know asked you to participate. The research study will test whether an education and counseling program can reduce the spread of HIV by changing people's behavior. The person in charge of this study at this site is _____. This study is sponsored by the U.S. National Institutes of Health (NIH).

Before you decide whether or not you want to take part in the research study, you need to know the purpose, about the possible risks and benefits, and what will be expected of you if you decide to participate. This consent form will give you information about the research study. The study staff will discuss the study with you. They will answer any questions that you have. After the study has been fully explained to you, you can decide whether or not you want to participate. This process is called informed consent. If you decide to participate in the study, you will be asked to sign this consent form or make your mark in front of someone. You will be offered a copy to keep.

VOLUNTARY PARTICIPATION

You must know certain things:

- Your participation in the research study is entirely voluntary.
- You may decide not to participate in the study or to withdraw from the study at any time without losing the benefits of your standard medical care.
- If you decide not to participate in the study, you can still join another research study later, if one is available and you qualify.

PURPOSE OF THE STUDY

The purpose of the research study is to determine whether an education and counseling program can reduce the spread of HIV by changing people's behavior. The study will take place in the United States and Thailand. A total of about 2640 people will participate in the study in these two countries. If you agree to participate in the study, the duration of your participation will be about a 1 ½ to 2 ½ years, depending on when you join the study.

STUDY PROCEDURES

Screening and enrollment

If you agree to participate in the study, your first visit will proceed today, if you are willing. You will first be asked some questions about yourself to see if you are eligible to take part in the study. Some people may not be eligible based on the responses to these questions. You will also be asked questions

about your sexual and drug use practices. The study staff will talk with you about HIV, how it is transmitted and what you can do to protect yourself and others from becoming infected. The study staff will draw a sample of about 8 ml (about 2 teaspoon or local equivalent) of blood from your arm for HIV testing. You will be told when you can return to the clinic for your HIV test result. You must receive your test result to be eligible for the research study. You will be asked to provide information on where the study staff can contact you. You will be given an appointment to return to the study clinic in six months.

Your final eligibility for participation in the study depends on whether the person who referred you to the study is also eligible. The study staff will contact you at the address or telephone number that you provide to inform you whether you are eligible and have been enrolled in the study. If so, they will also confirm the date of your next study visit.

Follow-up visits

You will be asked to return to the study clinic every six months after enrollment (a total of about 3 to 5 times depending on when you enroll in the study). Each follow-up visit will last about one hour. At each of these visits, you will be asked questions about your sex and drug use behaviors. You will be counseled about how to prevent HIV transmission and about HIV testing. At each follow-up visit, a sample of about 5 ml (about 1 teaspoon or local equivalent) of blood will be drawn from your arm for HIV testing. You will be told when you can return for your test results. The study staff will talk with you about the result of your last HIV test and what it means.

If, at anytime during the study, your test result shows that you are infected with HIV, the study staff will contact you in person as soon as possible. You may be asked to give another 5 ml sample of blood to confirm the result. The study staff will talk to you about your test result, how you feel about it, and how to avoid passing the virus to other people. They will provide you information on where to go for additional counseling and help. They will refer you for medical care and treatment. They will also tell you about any other research studies for which you may be eligible. You will be asked to continue in the study as scheduled.

Contact visits

Between each of the six-month follow up visits, the study staff will contact you to remind you of your next visit and to update the contact information they have for you. Study staff may also contact the person, who referred you for participation in the study, directly in order to find you.

RISKS AND DISCOMFORTS

Blood drawing may cause pain and bruising at the place where the blood is taken. Sometimes, drawing blood causes people to feel lightheaded or even faint. The questions about your sexual activity and drug use might make you uncomfortable or embarrassed. Getting an HIV test may cause you anxiety.

We will make every effort to protect your privacy and confidentiality while you are in this study. However, it is possible that you could have problems if people learn that you are in this study. People

may think that you are infected with HIV or at risk of HIV because of sexual behavior or drug use. If you are infected with HIV, you may have problems finding or keeping a job. You may be treated unfairly by others, including your family and community.

[Sites to include/amend the following if applicable:] State regulations require the study staff here to report the names of people who test positive for HIV to the [local health authority]. Outreach workers from the [health authority] may then contact you about informing your partners, since they also should be tested. If you do not want to inform your partners yourself, outreach workers will tell them of their possible exposure to HIV, according to the confidentiality guidelines of the [health authority].

POTENTIAL BENEFITS

You may receive no direct benefit from this research study. However, information learned from this research study may help others in the future. The HIV tests will provide you with information about your HIV status. You will also learn how to avoid becoming infected with HIV if you are uninfected with HIV. If you are infected with HIV, you will learn how to avoid infecting other people.

REASONS WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT

The study staff may need to take you off the study early without your permission if:

- The research study is cancelled by the sponsor (U.S. National Institutes of Health (NIH)), the local government or regulatory agency, or the Institutional Review Board (IRB). (An IRB is a committee that watches over the safety and rights of research subjects.)
- The Data Safety Monitoring Board (DSMB) recommends that the study be stopped early. (A DSMB is an outside group of experts who monitor the study.)
- You are not able to attend the study visits or follow the procedures required by the study.
- If the study investigator believes that it is unsafe for you to continue in the study for any reason.

NEW FINDINGS

You will be told of any new information learned during the course of the study that might cause you to change your mind about staying in the study.

ALTERNATIVES TO PARTICIPATION

If you choose not to participate in this study or are not eligible to participate, you can go to a local health center for HIV testing and counseling. Counseling that you receive may be different than counseling offered in the study. You may also have to pay for your HIV testing.

COSTS TO YOU

There will be no cost to you for study-related visits, HIV tests, or other procedures.

PAYMENT FOR SCHEDULED VISITS

You will be compensated for each scheduled visit that you attend during the study. You will receive payment only for time and travel expenses. *[Local amount to be specified in site specific consent.]*

CONFIDENTIALITY OF RECORDS

All efforts will be made to keep your personal information confidential to the extent permitted by law. Personal information from your study records will not be released without your written permission. You will be identified by a code number known only to you and the study staff.

All information about you will be marked by this number – not your name. However, study records that could be used to identify you may be reviewed by the study sponsor and their authorized study monitors, local government or regulatory agencies or by the IRB. Your name will never be used in any publication or presentation about this screening process or about the research study.

All contact for follow-up visits will be handled carefully to keep your participation in this study confidential.

For U.S. site: (Certificate of Confidentiality sample language)

In addition to the efforts made by the study staff to help keep your personal information confidential, we have obtained a Certificate of Confidentiality from the U.S. Federal Government. This certificate protects researchers from being forced to tell people who are not connected with this study, such as the court system, about your participation or any information that you give us for study purposes. Any publication of this study will not use your name or identify you personally.

Even with the Certificate of Confidentiality, if the study staff learn of possible child abuse and/or neglect or a risk of harm to you or others, they will be required to tell the proper authorities

RESEARCH RELATED INJURY

If you are injured as a result of being in this research study, you will be given immediate treatment for your injuries. However, you may have to pay for this care. There is no program for compensation either through this institution or the study sponsor (the U.S. National Institutes of Health (NIH)). You will not give up any of your legal rights by signing this consent form.

PERSONS TO CONTACT FOR PROBLEMS OR QUESTIONS

For questions about this study or a research-related injury, contact:

[site insert name of the investigator or other study staff]

[site insert telephone number and physical address of above]

For questions about your rights as a research subject, contact:

[site insert name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site]

[site insert telephone number and physical address of above]

SIGNATURE PAGE

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name or make your mark below.

Participant's Name (print)

Participant's Signature and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness' Name (print)

Witness's Signature and Date

(As appropriate)