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# Protocol

**Title of the project:** A Pilot Implementation Project of Methadone and Suboxone® for Injecting Drug Users in Ho Chi Minh City, Vietnam

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## Abstract

HIV continues to spread around the world and new infections in Asia are one of the most important areas for prevention among drug using populations. There is strong and consistent evidence from several countries that while injection drug users (IDU) continue to be a source of new infections, treatment of opiate addiction is an effective prevention measure against further spread. Among those IDU already infected, substance abuse treatment can improve access and adherence to HAART therapy and promote sustained viral suppression. The proposed project will take place at the Go Vap HIV clinic in Ho Chi Minh City (HCMC), Vietnam. Vietnam is an original PEPFAR country and has experienced a major HIV epidemic that has been propelled by injection drug use. While the country has begun the scale up of methadone maintenance treatment (MMT), coverage remains inadequate and the rate of expansion of new treatment programs clearly needs to be accelerated to have meaningful impact on the epidemic. For heroin (and other opiate) dependent individuals, methadone maintenance has limited availability and there are currently no buprenorphine/naloxone (Suboxone®) treatment programs in Vietnam. This newer medication has the possibility of making treatment available to more patients because of the efficiency of three times per week dosing and given the high prevalence of HIV among drug users in HCMC, fewer interactions with antiretroviral medications. The current project will support and evaluate the expansion of drug treatment to both HIV positive and negative IDUs as a model prevention program. The project will begin with the implementation of a comprehensive training program on addiction and Medication Assisted Treatment (MAT). Following this training the project will introduce MMT at the Go Vap clinic. At month 18, daily methadone will continue to be available and new patients will be given the opportunity to be treated with Suboxone® progressing from daily to thrice weekly observed treatment. All participants also will be engaged in behavioral drug and risk counseling. During the project, the study project enrolling up to 500 IDUs into MAT treatment program co-located with the Go Vap clinic. The investigators are not proposing a comparison between methadone and Suboxone®. Both are safe and effective medications. The project will demonstrate feasibility and evaluate participant, clinic, and community factors that promote or inhibit program implementation. The study will measure costs and identify factors that are associated with treatment success for each medication and for positive and negative participants. Importantly, the program is being implemented in partnership with the Provincial AIDS Committee of HCMC and will contribute to their goal of expanding access to both drug abuse and HIV treatment.


## Objectives

### Overall objectives

The proposed project will evaluate the implementation of a Medication Assisted Treatment (MAT) program (both methadone and buprenorphine/naloxone) integrated within an HIV treatment setting. This will be the first project to establish and evaluate the implementation a buprenorphine/naloxone (Suboxone®) treatment program in Vietnam. Following project start-up, the investigators will enroll a total of up to 500 injection drug users using structured community-based outreach strategies. All subjects will be enrolled in the integrated MAT program that will include drug and risk counseling, and for those who are HIV positive, HIV treatment. At one year following enrollment, participant's treatment success will be assessed based upon retention in MAT treatment, continued drug use, criminal behavior and employment. For those who are HIV positive the study will also assess medication adherence and suppressed HIV viral load. The study will carefully assess barriers to implementation and, using qualitative methods, measure awareness and perceptions of the program among local community-based organizations, governmental agencies, and drug users. The

medication assisted treatments will use well established protocols and will be monitored by investigators from the HCMC team, EXPERTISE FRANCE and University of Pennsylvania Center for Studies of Addiction (PennCSA).
Importantly, the work represents a collaboration between the Provincial AIDS Committee (PAC) of HCMC, EXPERTISE FRANCE, the French led initiative to expand access to HIV prevention and treatment services, and the PennCSA all of whom will support the implementation and evaluation to be done by the HCMC clinical and research team. The goal of this collaboration will be to conduct implementation research in a resource limited setting with a high prevalence of intravenous drug use and HIV infection. The current project proposes to establish the feasibility of the use of Suboxone®. Primary measures will consist of facilitators and barriers to implementation and retention in MAT generally and Suboxone® treatment specifically. The following specific aims will be evaluated:

- Establish a new integrated MAT treatment program within and HIV treatment setting in HCMC.
- Evaluate barriers and facilitators to implementation of integrated MAT/HIV treatment.
- Evaluate patient retention and medication adherence in integrated MAT/HIV Care.
- Estimate the costs and benefits of MAT treatment strategies.

**Primary outcome variable(s)**
1) Qualitative assessment: acceptability, barriers, and facilitators to implement medication-assisted treatment for opiate addiction within an HIV-treatment setting; 2) Treatment retention at 6 and 12-month follow-ups; 3) Treatment adherence: Methadone, Suboxone®, HIV treatment, counseling sessions; 4) Cost-effectiveness ratios calculated at the end of the study

**Secondary outcome variable(s)**
1) Drug use and severity of addiction assessed by the ASI scores; 2) Risk taking behaviors: scores from the RAB at 6 and 12-month follow-ups

## Background

The significance of the proposed study lies in its focus on providing data that can be used to facilitate and expand the public heath response to a very serious epidemic of HIV/AIDS among opiate dependent drug users in Ho Chi Minh City (HCMC), Vietnam. As described below, Vietnam is experiencing a significant AIDS epidemic fueled in large part by injection drug use. An important component of the response to this epidemic has been the initiation and initial scale up of methadone treatment. The significance of the proposed project lies in the potential to demonstrate strategies that can help to expand an integrated HIV and drug treatment system in Vietnam and to contribute to the attainment of the country's national plan for HIV prevention. The proposed project will carefully evaluate the implementation of a Medication Assisted Treatment (MAT) program that is fully integrated with PEPFAR supported HIV treatment. The project will also be the first to evaluate the feasibility and acceptability of buprenorphine/naloxone treatment in Vietnam.
Clearly, the significance of the work is rooted in the AIDS epidemic in Vietnam. HIV prevalence in Vietnam is estimated at 0.53% (WHO) and the number of PLWHAs reported is 290,000 (UNAIDS 2009). Vietnam is still at a concentrated stage with a high HIV prevalence amongst injecting drug users (IDUs) and female sex workers (FSWs). As a result, Vietnam's national prevention strategy focuses on harm reduction pilot interventions targeting drug

injection and high-risk sex. Current interventions include education, needle and syringe exchange programs, social marketing of condoms, voluntary counseling, and testing, and STI diagnosis and management. Methadone maintenance therapy (MMT) for IDUs started as a pilot program in 2008 in Haiphong and HCMC, two of the highest prevalence provinces for injecting drug use. In HCMC, where 51.8 % of IDUs are HIV positive (HCMC Provincial Aids Committee PAC, 2009), MMT pilot program started in three districts in May 2008 (district 4, 6 and Binh Thanh). On December 2009, 784 patients were under MMT and 235 were receiving ARV. 30% of patients under MMT are HIV+ (HCMC PAC, 2009). A conference held in HCMC on July 2009 concluded positively on the results of the pilot program in terms of 1) Improvement of drug adherence for patients receiving ART; 2) Improvement of social rehabilitation; and, 3) Decrease in drug use (heroin) and risk of HIV transmission. According to interviews conducted and information provided by HCMC health authorities, there are around 15,000 active drug users in the City. Heroin appears to be the main drug used but opium is also widely consumed (mostly among ("old addicts") and there is a rapid spread of methamphetamine use, frequently through intravenous (IV) route. Consequently, the HIV transmission rate due to needle sharing is high. Between 50% and 70% of drug users are also infected with HCV and an elevated rate of tuberculosis has been reported.

To date, there has been no large-scale expansion of drug treatment or harm reduction programs for drug users. Compulsory admission to a rehabilitation center is still the main method used by Vietnamese authorities to fight against drug use and nationally, about 20,000 persons are currently enrolled in such centers. However, five pilot outpatient clinics (OPC) with access to methadone have been recently opened in HCMC, with the technical assistance of CDC and Family Health International (FHI) and funding from the American President's Emergency Plan for AIDS Relief (PEPFAR). For the past three years EXPERTISE FRANCE, the French led initiative to expand access to HIV prevention and treatment services, has been working with Government and Non-Government Organizations in Vietnam to establish an integrated HIV/drug treatment capacity. The PI of this application (O'Brien) has worked closely with many of the investigators from the EXPERTISE FRANCE group for over 20 years and his Center, the Penn Center for Studies of Addiction has been a leader in conducting and participating in research to show that drug treatment is HIV prevention (Metzger, Woody, and O'Brien, 2010).

**Drug Treatment as HIV Prevention**

The research literature of the past 20 years provides a strong "proof of concept" that methadone treatment is an effective HIV prevention intervention. Specifically, individuals who participate in methadone treatment have been found to significantly reduce the frequency of their opiate use (Haverkos 1998; Hubbard et al. 1989; Ball et al. 1988; Ball and Ross 1991; Hubbard et al. 1997; Gowing et al. 2006; Hartel et al. 1998; Lawrinson et al. 2008;). This finding has been observed when methadone patients have been compared to their community counterparts who are not in treatment (Capplehorn and Ross 1995; Metzger et al. 1993; Qian et al. 2008) and when patient's opiate use during treatment has been compared to their pre- and post-treatment use (Ball et al. 1988). Further, significantly lower rates of opiate use have been observed when patients with regular methadone program attendance have been compared to those with poor attendance (Wong 2003), and when patients receiving minimal ancillary services were compared to those receiving more intensive services (McLellan et al. 1993; Avants et al. 1999). Consistent with the observed reductions in opiate use, available data suggests that methadone patients participate in 40 to 60 percent fewer instances of opiate injection and needle sharing events. This finding has been reported in cross-sectional, prospective and retrospective designs comparing methadone patients to heroin users who are

not in treatment (Hubbard et al. 1997; Capplehoren and Ross 1995; Booth et al. 1996; Kwiatkowski 2001; Qian et al. 2008) and in studies focused on measuring changes in cohorts of methadone patients during treatment (Avants et al 1999; Gossop et al. 2002). Findings have also been reported showing significantly lower rates of injection among patients who remain in treatment when compared to patients who left treatment (Metzger et al. 1993; Thiede et al. 2000). Perhaps most importantly, from a public health perspective, research has documented strong associations between methadone participation and lower rates of HIV prevalence and incidence. Heroin users who remained in methadone treatment during periods of rapid HIV transmission in their surrounding communities were found to have a dramatically lower prevalence of infection (CDC 1984; Novick et al. 1986; Barthwell 1989; Novick et al. 1990; Blix et al. 1991). HIV prevalence rates have also been correlated with length of time in treatment. In both prospective and retrospective studies, the incidence of new HIV infections has been found to be significantly associated with participation in (Metzger et al. 1993; Hartel et al. 1998; Wong et al. 2003) and duration of, methadone treatment (Moss et al. 1990; Serpelloni et al. 1994; Hartel et al. 1998). Although no randomized controlled trials have yet been conducted (due primarily to ethical concerns regarding the random assignment of individuals to no treatment or other treatment modalities), the consistency of findings from the observational and case controlled studies cited here provide a preponderance of evidence suggesting that sustained treatment with methadone is strongly associated with protection from HIV infection (Metzger et al. 1998; Sorensen et al. 2000; Farrell et al 2005; Sullivan et al. 2005; Metzger et al. 2010).

**ARV Treatment as HIV Prevention**

The second tool to reduce HIV transmission among drug users is the use of HAART. Indeed, an undetectable viral load is associated with a very low risk of HIV transmission. Recent results (Wood et al 2009) have shown a dramatic decrease in HIV transmission in the community of drug users where a high coverage of ART was reached. Therefore, there is a consensus on the positive impact of linking MAT and HAART in the treatment of HIV-infected drug addicts (Roux et al. 2008; Roux et al. 2009). The treatment of addiction leads to a significant improvement in adherence, with ARV adherence being required for antiviral efficacy and reduction of transmission. In this respect, the objective of HCMC health authorities to improve and expand access to opiate substitution treatment is extremely important and supported by data.

**Medication Assisted Treatment for opiate addiction**

The current project will evaluate the implementation of methadone and Suboxone®. Our work is guided by an understanding that no single treatment strategy can meet the needs of all opiate dependent drug users. The investigators believe methadone to be a safe and effective method for MAT when prescribed by trained clinicians and in conjunction with meaningful counseling. However, the exclusive use of methadone has several drawbacks. First, its full agonist effect raises overdose risks, especially in a context of poor access to drug treatment. This lack of access to treatment can increase the likelihood of diversion and fatal overdoses. Secondly, the metabolic interactions of methadone with ARVs may decrease the effectiveness of methadone by decreasing methadone blood levels and requiring significantly higher methadone dosages to achieve effects equal to those without ARVs. Finally, as mentioned earlier, it is a medication that requires daily administration. For these reasons, it would be most useful to complement the current system of care with buprenorphine/naloxone (Suboxone®). Buprenorphine, a partial agonist with a ceiling effect of agonist activity and a partial antagonist effect (on kappa receptors), reduces considerably the overdose risks (2). The addition of naloxone (full opiate antagonist) to buprenorphine leads to a major decrease in

misuse, especially in a population that almost exclusively uses full agonists (heroin, opium): injection or snorting of Suboxone® causes very unpleasant opioid withdrawal syndromes, discouraging diversion. On the opposite, when buprenorphine is used sublingually, as it should, naloxone is not absorbed, and buprenorphine exerts its full substitution effect. Suboxone® has also been shown to have fewer interactions with ARV medications and requires fewer dose adjustments when the medications are taken together. Finally, another important characteristic of Suboxone® is that it allows for three times per week dispensation instead of daily administration, reducing the staff and infrastructure needs as well as the costs.

**Behavioral Drug and Risk Counseling**

Behavioral Drug and Risk Counseling (BDRC) was developed in 2005 by Marek Chawarski, Ph.D., and colleagues at Yale University. This approach is rooted in evidence-based cognitive behavioral counseling approaches and is highly structured, manual driven, and prescriptive, and focuses on a limited set of immediate problem areas. In BDRC, the counselor guides the participant through the initial stages of the recovery process. The counselor does this by using explicit contracting procedures to engage the participant in a comprehensive recovery program that involves medication, counseling, clean and sober activities, and lifestyle changes that promote sustained abstinence. Additional prescriptive BDRC components include education about opiate addiction as a chronic medical condition and optimal use of all treatment components (e.g., sessions or meetings with counselors, doctors, nurses) and other available resources (e.g., psychiatric, medical, social work, community resources) to maximize the effectiveness of the treatment. Finally, BDRC puts strong emphasis on HIV prevention including education about drug- and sex-related HIV risks and effective HIV prevention strategies. BDRC combines behavioral contracting with an Information-Motivation-Behavioral Skills (IMB) model for reducing HIV risk behaviors and illicit drug use that is grounded in social cognitive theory (Bandura 1997) and supported by empirical findings in numerous studies and populations (Avants et al. 2004; Carey et al. 2000; Peipman et al. 2001; Bryan et al. 2000; Fisher and Fisher 2000; Fisher et al. 1999; Kalichman et al. 2001; Carroll et al. 2004). The intensive HIV risk reduction interventions provided in BDRC, that includes a personalized assessment of risk (i.e., identification of personal, social and environmental factors associated with risky behaviors) in conjunction with education and training in skill-building and self-control, may lead to greater reductions in both drug and sex related HIV risk behaviors than the more limited, brief counseling provided in many clinics, as supported by findings of a recent clinical trial with methadone maintained patients (Sorensen and Copeland, 2000) and a meta-analysis regarding the effectiveness of HIV risk reduction interventions during drug abuse treatment (Pendergast et al, 2001). BDRC emphasizes a medical model of treatment for drug dependence and is highly complementary to and compatible with regular MAT. Because early abstinence achievement is associated with longer term treatment success, BDRC uses short-term behavioral contracts to help the patient achieve an initial period of abstinence, take maintenance medications regularly, and as prescribed, activate the patient behaviorally to reduce behaviors associated with HIV transmission (Schottenfeld et al. 2005). The accomplishment of specific, short-term behavioral goals early in treatment promotes the patient's experience of therapeutic success and counters the patient's belief that his/her actions will not lead to success in accomplishing goals. Short-term behavioral goals target a limited number of domains, including achieving an initial period of abstinence, increasing activities (primarily vocational, social, or recreational) that are not related to drug use, and reducing HIV risk behaviors (e.g., fostering consistent condom use, avoiding casual sexual encounters, avoiding IDU or needle or equipment sharing) (Chawarski et al. 2003). BDRC teaches cognitive and behavioral strategies for promoting behavioral change, including identifying antecedents of drug use,

needle sharing, and high-risk sexual behaviors, and learning strategies to avoid high risk situations or cope without engaging in these behaviors. Skill building exercises (e.g., regarding condom use) are used within sessions to learn and practice new skills, and patients are encouraged to practice these skills outside the session in their natural environment (Avants et al. 2004; Margolin et al. 2003; Kamb et al. 2000; NIMH MHPT 2000; Carroll et al. 1997). Findings addressing the efficacy of BDRC are beginning to emerge in the literature. Of relevance to this application is a pilot study of BDRC enhanced treatment in Malaysia (Chawarski et al, 2007). After a 2-week buprenorphine induction and stabilization period, heroin dependent individuals (n= 24) in Muar, Malaysia were randomly assigned to Standard Services (physician administered advice and support, and weekly, non-contingent medication pick-up) or BDRC enhanced services (nurse delivered, manual-guided BDRC, and abstinence-contingent take-home buprenorphine). Both groups significantly reduced HIV risk behaviors during treatment ($p< 0.05$), and the proportion of opiates-negative urine tests increased significantly over time for both groups ($p< 0.001$). However, reductions were significantly greater in the BDRC enhanced services group ($p< 0.05$), with this group achieving higher overall proportions of opiate negative urine toxicology tests (87% vs. 69%, $p= 0.04$) and longer periods of consecutive abstinence from opiates (10.3 weeks vs. 7.8 weeks, $p = 0.15$) (Chawarski et al, 2007). More recently the results of a three-arm randomized, placebo-controlled trial were reported. In this trial, 126 opiate dependent individuals in Malaysia were randomized to received either buprenorphine, naltrexone, or placebo (Schottenfeld, Chawarski, and Mazlan, 2008). All participants received BDRC counseling. Subjects in all groups showed significant declines in drug and sexual risk behaviors while drug use outcomes were superior for the buprenorphine group. Because of its suitability for use in settings that do not have professional therapists, as well as for its potential efficacy, manual guided BDRC is being used as the counseling platform provided to patients in various research and clinical settings in Malaysia and in the HIV Prevention Trials Network (HPTN) protocol 058 in Thailand and China evaluating the efficacy of buprenorphine for reducing HIV transmission. Preliminary data from the first year of implementation in Thailand (N=50) shows a high rate of attendance and acceptability for the BDRC counseling. Sixty-three percent of the subjects attended all their scheduled sessions and 86% attended 75% or greater of their scheduled sessions.

**Innovation**

Although standard methods of evaluation of program implementation are proposed in this application, this effort represents the first time a buprenorphine/naloxone (Suboxone®) treatment program will be introduced in Vietnam. Its location within an HIV treatment setting represents another important and innovative feature of the work. The project is built upon two distinct prevention strategies — 1) effective drug treatment for prevention of infection among those who begin the study as HIV negative; and 2) sustained viral suppression through the effective treatment of those who begin the project already infected. The cost of integrated drug and HIV treatment has not been well examined and this also represents a unique feature of the proposed project and will provide an opportunity to gauge the public health relevance of the program. The goal of the current project is not to compare methadone with Suboxone® but to demonstrate the feasibility of the use of both medications within an HIV treatment setting and to document the barriers and facilitators to their implementation.

## Study design

**Phase**

Not Applicable

**Design**
This is an open-label follow-up study. The project proposes to enroll up to 500 opiate dependent individuals entering Medication Assisted Treatment (Methadone or buprenorphine/naloxone) at Go Vap Clinic, HCMC, Vietnam. All participants who appear to meet inclusion criteria and who express interest in drug treatment will be invited to be screened for participation in the research. The investigators expect that around 40% of them will be also HIV-positive and so will receive appropriate treatment. All participants will receive BDRC sessions (weekly for 12 weeks, monthly thereafter until week 52).

**Study duration**
The first 18 months, only methadone will be available as MAT at Go Vap Clinic as Suboxone® is not available in Vietnam. The introduction of the Suboxone® treatment will follow the establishment of the methadone program at Go Vap, designed to facilitate the implementation of Suboxone®. At Month 18, the investigators plan to begin Suboxone® treatment. They anticipate that enrollment of up to participants in methadone treatment will occur for 24 months after the first participant's enrollment and they plan to enroll up to 300 new participants in Suboxone® treatment during the subsequent 36 months.

**Resources necessary for human research protection**
All participants who appear to meet inclusion criteria and who express interest in treatment will be invited to be screened for participation in the research. Participants who express interest in the study will meet with one of the research staff and be engaged in a conversation explaining the details of the study. Subjects will have the opportunity to have all their questions answered and will be given time to discuss the study with family members or others with whom they choose to discuss their participation. Staff will be very clear that participation is voluntary, and individuals may withdraw from the study at any time without consequence to their treatment participation. For those who meet inclusion criteria for treatment, detailed informed consent procedures will outline the nature of participation, risks and benefits, and the schedule for data collection and compensation. Potential participants will then be given a detailed description of the research procedures and all remaining questions will be answered. Subjects will be reminded that they are free to decline or stop participation at any time. The consent form and related discussions will make it very clear that a critical feature of the study is the ability to follow study participants for one year whether they remain in their treatment program. The consent will indicate permission from the participant to contact them even if they leave treatment. The locator data collection form includes contact information on specific individuals with whom the participant expects to maintain contact and for whom contact permission is granted by the participant. Following the completion of informed consent procedures, subjects will be sign the study consent form and will be assessed and screened for eligibility using the following inclusion and exclusion criteria.
The Go Vap Clinic is currently an HIV treatment facility supported by the CDC. The project will implement MAT for opiate addiction within this HIV treatment settings. All participants will receive all treatment they need at the Go Vap Clinic. The Doctors, nurses, psychologists and counselors will receive intense training and supervision. The counseling intervention has minimal risk associated with participation. Study resources are focused on maximizing the protection of confidentiality. The Go Vap clinic has a private room where research assessments can be completed.
The Principal Investigator and Co-Investigators have certifications of completion for required education on the protection of human research participants. Staff who have responsibility for

the conduct of the study and/or direct contact with human study participants will complete certification requirements on ethical principles involved in the conduct of human subject's research by completing the on-line training module on the CITI website, or its equivalent. The PI and the local PI will ensure that all project staff are oriented to the study procedures during their training period. The local Principal Investigator at the HCMC site, Dr. Le Truong Giang was appointed as the local PI by the local health authorities and has considerable experience supervising research implementation and data collection. He will assist Dr. O'Brien in the direct supervision of the data collection sites. Protocol monitoring will ensure that the research protocol specified is being followed without unauthorized deviations. Special emphasis will be placed on ensuring that the consent process is being completed properly and that adverse events are being properly reported. Weekly meetings will be held by the local PI to monitor the safety and progress of the trial. These meetings will involve the Principal Investigator, Investigators, and project personnel. This will help to ensure standardized application of the protocol and will serve as an ongoing mechanism by which project staff and investigators will communicate to maintain a consistently high quality of study conduct. Concerns identified will be addressed through training and retraining of personnel. Dr. O'Brien will have regular conference calls with the investigators and study staff in HCMC. In addition, Dr. O'Brien will be available by e-mail and Internet telephony.

## Characteristics of the study population

### Target population

All individuals who are 18 or more years of age and who meet the DSM-5 criteria for opiate use disorder with or without HIV co-morbidity are considered eligible for the study.

### Subjects at Penn

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### Subjects at Sites Other than Penn

Up to 500

### Accrual

All participants who appear to meet inclusion criteria and who express interest in drug treatment will be invited to be screened for participation in the research. Participants who express interest in the study will meet with one of the research staff and be engaged in a conversation explaining the details of the study. Subjects will have the opportunity to have all their questions answered and will be given time to discuss the study with family members or others with whom they choose to discuss their participation. Staff will be very clear that participation is voluntary, and individuals may withdraw from the study at any time without consequence to their treatment participation. For those who meet inclusion criteria for treatment, detailed informed consent procedures will outline the nature of participation, risks and benefits, and the schedule for data collection and compensation. Potential participants will then be given a detailed description of the research procedures and all remaining questions will be answered. Subjects will be reminded that they are free to decline or stop participation at any time. The consent form and related discussions will make it very clear that a critical feature of the study is the ability to follow study participants for one year whether they remain in their treatment program. The consent will indicate permission from the participant to contact them in the community should they leave treatment. The locator data collection form includes contact information on specific individuals with whom the participant expects to maintain contact and for whom contact permission is granted by the participant. Following the completion of informed consent procedures, subjects will be

signing the study consent form and will be assessed and screened for eligibility using the following inclusion and exclusion criteria.

**Key inclusion criteria**

- 18 or more years of age
- Meets DSM-5 criteria for opiate use disorder
- Positive urine drug screen for heroin or other opiates
- Interested in methadone maintenance or Suboxone® treatment for opiate use disorder
- Injected heroin within past 30 days by self-report, documented by "tracks" or puncture marks
- Willingness and ability to give informed consent and otherwise participate
- Provision of adequate locator information

**Key exclusion criteria**

- Clinically significant cognitive impairment, schizophrenia, paranoid disorder, bipolar disorder
- Known neurological, cardiovascular, renal, or other medical disorder that is likely to impair or make the patient's participation hazardous
- Physiologically dependent on alcohol, benzodiazepines, or other sedative type drugs
- Pending legal charges with likely incarceration within next 12 months

**Vulnerable Populations**

| | |
|---|---|
| | Children (refer to SOP 501 for definition of children) Form |
| | Pregnant women (if the study procedures may affect the condition of the pregnant woman or fetus) Form |
| | Fetuses and/or Neonates Form |
| | Prisoners Form |
| X | Other |
| | None of the above populations are included in the research study |

***Populations vulnerable to undue influence or coercion***

Injecting drug users are considered a vulnerable population due to the risks, both perceived and real, created as they identify themselves as engaging in illegal activity through the use of illegal drugs. Care will be taken to ensure that they are treated with respect and consideration throughout the study process. All research procedures will be conducted within the participant's methadone treatment program, an environment considered protective of the rights of drug users and supportive of their health and welfare. All data will be stored in a safe and confidential manner at the Go Vap Clinic, HCMC, Vietnam.

**Subject recruitment**

Recruitment will utilize street outreach, publicity, and a modified respondent driven sampling strategy (snowball method), where IDUs who participate in screening are encouraged to bring their IDU friends to the study site. Outreach workers will primarily carry out recruitment activities. These staff 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 research staff from the community and must be knowledgeable about the community's heath care and drug treatment resources as well as the local criminal justice response to drug users. They will be trained, as part of the study, in methods of approaching and communicating with potential participants, personal safety, and the importance of maintaining confidentiality. Outreach workers will identify and develop strategies for accessing venues

frequented by drug users. In these geographic areas and settings, outreach workers will disseminate general information about the project verbally and via written materials as approved by the IRB. They will provide information on available drug treatment resources in the community and encourage prospective participants to participate in screening activities at the study site.
All participants seeking treatment for opiate dependence at Go Vap Clinic will be invited to take part in the study. The study will be explained to the participant during the intake process.

**Subject compensation**
Yes

***If there is subject compensation, provide the schedule for compensation per study visit or session and total amount for entire participation, either as text or separate document***
Participants will receive the equivalent of US$5 (104,084 VND) for each data collection visit, that is, at baseline, 6- and 12-month visits, for a total of an equivalent of US$15 (312,252 VND).

**Study Procedures**
**Procedures**
All participants who express interest in participating in the study and consent to participate will receive MAT, BDRC and HIV treatment if needed.

**Methadone Treatment:** The project will implement a standard treatment protocol in accordance with evidence-based practice and Vietnamese policy. As mentioned previously, the program will be co-located in the Go VAP HIV treatment clinic site where care and treatment services for HIV/AIDS patients are provided: consultation, ART dispensation, home-based care, counseling and testing, social services, TB/HIV care, help groups, vocational training (for eligible patients). The site will be staffed with the following clinical professionals: 2 doctors; 2 pharmacists; 2 nurses; and 5 counselors. Importantly the methadone treatment process will incorporate the following features:

- Dosage of methadone will follow the Ministry of Health guidelines
- Treatment will be started with low doses (usually 20-30 mg)
- The dose will be increased slowly (usually 5-10 mg every 3 days) to reduce the risk of overdose
- Most patients not receiving ARVs will be able to be managed on 60 mgs/day

In practice, higher doses are often necessary, particularly in patients on ART. In case of difficulties, doctors in charge seek advice from the city technical working group, with whom regular meeting are hold. Clinical consultation will also be available from the Investigative team for this research. Supervision of the prescribing physician will be provided by the on-site PIs and co-investigators, Drs. Le Truong Giang, and Lisa Huang. Patients receiving methadone will attend the Go Vap program daily. All oral methadone doses are consumed daily under direct observation by the pharmacist. Random observed urine samples are obtained at least twice per month tested for opiates and other drugs commonly abused in Vietnam.
Methadone will be provided by the Central Procurement Company (Ministry of Health), with strict control from agents from both organizations regarding quality and quantity of the methadone delivered. Monthly reporting of methadone use and request for next month's supply are sent to the Pharmaceutical Department of the HCMC Health Department for control and approval. Used bottles of Methadone are destroyed according to a process approved and controlled by the Environmental and Natural Resources of the city.

**Buprenorphine/Naloxone (Suboxone®) Treatment**: At month 18, the investigators plan to begin Suboxone® treatment and enroll up to 300 new patients during the subsequent 42 months. The introduction of Suboxone® following the establishment of the methadone program at Go Vap is designed to facilitate implementation. The project will be expanding an existing MAT center and not establishing a new and distinct Suboxone® clinic. Importantly, the same entry point will be used to provide access to care and psychosocial support for HIV-positive IDUs. The clinical management of patients on Suboxone® will follow guidelines established and used successfully in the long-term treatment arm of the HPTN 058 (Lucas et al, In Press). Manuals for clinical management will be modified and translated for use in this project. Reckitt Benckiser, the manufacturer of Suboxone®, has agreed to donate the medication for this project.

Suboxone® tablets are administered sublingually, placed under the tongue until they are dissolved. For doses requiring the use of more than two tablets, participants are instructed to either place all the tablets at once or alternatively (if they cannot fit in more than two tablets comfortably) place two tablets at a time under the tongue. Either way, the participant should continue to hold the tablet under the tongue until they dissolve; swallowing the tablet reduces the bioavailability of the drug.

To aid clinicians in determining the appropriate dose during the first two-to-three days, the study will use the Clinical Opiate Withdrawal Scale (COWS), an instrument measuring validated items of physical signs or symptoms of withdrawal, such as gooseflesh, vomiting, and sweating, to objectively assess withdrawal in both treatment arms (Wesson and Ling, 2003). The total score gives an index of the participant's withdrawal intensity and can be administered over time to track changes and adjust dosing. On day one, the clinician will wait until the participant shows at least mild opiate withdrawal by monitoring with the COWS. If the score indicates at least mild withdrawal (the higher the score the more severe the withdrawal), the clinician will give 4 mg for the first dose. COWS will be repeated in one hour; patients will receive further dosing as described below.

Dosing will begin with a titration over a period of two to three days under supervision in the Go Vap clinic using the COWS as described above. On the first day of treatment, patients will initially receive a 4 mg dose of buprenorphine/Naloxone (expressed as the amount of buprenorphine) to be taken sublingually. Most participants will begin with a total first day's dosage of 8 mg. On Day 2, up to 16 mg may be given. Up to 32 mg may be given on Day 3 and thereafter until three-times-weekly dosing begins. The induction strategy is primarily dependent on three factors: 1) time since last opiate use; 2) type of opiate (e.g., long, or short-acting) used; and 3) degree of physical dependence. Therefore, each dosing schedule will be tailored to the individual participant.

Individuals will come to the study site daily for direct observation of dosing until they have stabilized (for up to three weeks). After induction and stabilization, participants will be asked to come to the site for dosing three-times-weekly. The target dosage schedule for individuals whose daily dose was 16 to 24 mg/day is expected to be 32/32/48 mg administered on a three-times-weekly schedule (e.g., M/W/F); this is also the maximum three-times-weekly dosage. On rare occasions, for individuals who require more than 24 mg/day (i.e., 26, 28, 30, or 32 mg/day), it is unlikely that the 32/32/48 mg dosage schedule will be adequate. For those individuals, as well as for others who received 24 mg or less per day but for whom the 32/32/48 mg three-times- weekly schedule is not adequate, dosing may be continued daily through Week 52 of the study, with take-home doses administered for those days on which in-clinic dosing is not possible (e.g., 32 mg on M/Tu/W/Th/F/Sat with a take-home 32 mg dose on Sun).

When dosed daily, the maximum agonist effects of buprenorphine will likely occur in a dosage range between 16 to 24 mg/day for most individuals. While increased dosages may not produce corresponding increases in agonist effects, they may extend the duration of buprenorphine-induced blockade of concurrently administered opiates. In one study, individuals maintained on 8 mg/day of buprenorphine solution were shown to tolerate a 72-hour dose omission well (Essenberg et al, 1997; Lucas et al, In Press).

**Behavioral Drug and Risk-Reduction Counseling Visits (BDRC):** At the enrollment visit, participants will be scheduled for the 12 weekly counseling sessions. Approximately every four weeks, participants will be asked to provide urine for drug testing during the counseling visits for the first year of enrollment. Women will have pregnancy testing approximately every four weeks during counseling visits. Monthly counseling sessions will be scheduled approximately every four weeks beginning at week 16 through week 52. At each of these sessions, participants will be asked to update their locator information and provide urine for drug and pregnancy testing (for women in the substitution treatment arm only). Monthly counseling sessions can also be combined with dispensing and follow-up visits.

**Implementation Research Strategy:** To assess implementation and costs, the study will collect data from the individual study participants, from the program staff, and from the PAC and MOH of HCMC. The project wants to document the extent to which the program achieves the intended goals at the individual level as well as documenting aspects of the process that facilitate implementation. The investigators will use a mixed methods approach that includes both qualitative and quantitative data collection. Direct comparison of outcomes between methadone patients and Suboxone® patients is not the purpose of this project. The project will not randomly assign patients to their treatments. In fact, the project will examine the response to treatment to look for patient characteristics that are associated with success in each modality.

**Assessments:** As described below, the assessment interviews for each participant will include: 1) the locator questionnaire; 2) a brief study specific questionnaire that will be used to capture relevant socio-demographic data, health status, medical and drug treatment history and living situation and family relationships; 3) the Addiction Severity Index (ASI), 4) the Risk Assessment Battery (RAB); 5) the ICD-10; and, 6) the WHO Quality of Life (QOL) scale. At monthly intervals, urine specimens will be collected for testing evidence of continued drug use and blood will be collected for HIV testing at baseline, 6 and 12 months. Research staff will also collect data from the program records regarding clinic attendance and methadone dosage and will keep a log of all counseling sessions attended, their duration and copies of all session content checklists.

All assessments will be completed by trained research staff (not clinicians or counselors) at baseline, and again at 6-, and 12-month post-enrollment. Importantly, assessments will be completed on those who remain in treatment as well as those who leave the program. The investigators anticipate follow-up rates exceeding 90% after 12 months.

Locator Data Collection: A basic philosophy of the research approach to be implemented is that follow-up begins at recruitment and enrollment. Thus, a detailed contact sheet (Locator Form) will be completed for all subjects as part of the baseline assessment. This locator form will be updated at each subsequent assessment visit. Participants in the research will also be asked to call or visit the research office in the clinic whenever they have questions about assessment schedules or have updates to provide regarding changes in contact information. Participants will be asked to provide contact information on themselves and three additional people with whom they are most likely to stay in contact. They will also be asked about other

places where they might be able to be contacted in the future. This instrument will be modeled after the Locator form developed in Philadelphia and will be modified and translated by the investigators in Vietnam.

Study Specific Questionnaire: This questionnaire will be administered by study staff and collects demographic information (e.g., age, gender, race and ethnic identity, marital status, sexual orientation, educational level, employment status, income and income sources) and descriptive information about the subject's living situation, involvement with the criminal justice system, drug treatment, and source of needles during the last 6 months. This questionnaire will also include questions about non-study treatment services.

Addiction Severity Index (ASI): The ASI is a structured interview developed to assess the range of problems seen in drug abusers (McLellan, et al, 1980). It has been widely used in international settings for substance abuse and treatment research. It combines objective and subjective data to produce ratings of problem severity in seven areas: medical, employment and support, drug use, alcohol use, legal status, family/social relations, and psychological status. The ASI produces severity ratings and composite scores in each of seven areas, and each type of score has been assessed regarding validity and reliability (McLellan et al, 1992b). Severity ratings and composite scores have demonstrated high levels of inter-rater, test-retest, and concurrent reliability. The Treatnet version of the ASI, developed in 2007 for international studies (McLellan and Carise, 2007 - UNODC Treatnet ASI version 3.0). It will be administered at baseline, 6 and 12 months.

Risk Assessment Battery (RAB): The RAB provides a brief self-report measure of drug use, injection-related risk behavior, and sexual risk and uses the preceding six months as the time interval of interest. The RAB takes an average of 10 minutes to complete. There are 38 closed-ended items that cover issues of recent substance use and frequency of use, needle sharing and cleaning, and condom use. The nine drug-use risk items include questions concerning whether the participant injected drugs, whether they shared needles, the number of people with whom they shared needles, the number of visits to a location where drugs are used with others present, the number of times they shared rinse water, cookers, or cottons, and the frequency of back loading. There are eight sex-risk items, which include sexual orientation, number of partners (male and female), frequency of exchanges of sex for drugs, drugs for sex, sex for money, money for sex, and the consistency of condom use. Scores from the RAB have able to discriminate between cocaine and opiate abusers as well as those who seroconverted from those who remained seronegative (Metzger et al, 1993; Navaline et al, 1994). The RAB has been used in various international settings including Brazil, Russia, Ukraine, Georgia, Israel, and China. Translation and cultural adaptation have not been identified as serious problems primarily because the questions do not involve the understanding of complex concepts and are focused on discrete and relatively recent behaviors. The RAB will be translated into Vietnamese.

ICD-10 and ICD-10 Symptom Checklist for Mental Disorders (psychoactive substance use syndromes): The MINI ICD-10 is a short structured diagnostic interview, developed jointly by psychiatrists and clinicians in the US and Europe for ICD-10. With an administration time of approximately 15 minutes, it was designed to meet the need for a short but accurate structured psychiatric interview for multi-center clinical trials and epidemiology studies. This instrument has been translated to Vietnamese.

WHO QOL-BREF: For assessing quality of life, the World Health Organization Quality of Life (WHOQOL)-BREF will be used. Assessments will be completed at baseline, month 3, 6, 9, and 12. The World Health Organization Quality of Life (WHOQOL) project was initiated in 1991 to develop an international cross-culturally comparable quality of life assessment instrument. It assesses the individual's perceptions in the context of their culture and value systems, and their personal goals, standards, and concerns. The WHOQOL instruments were

developed collaboratively in several centers worldwide and have been widely field-tested. The WHOQOL-BREF is a self-administered, standardized instrument used as a measure of health outcome and comprises 26 items, which measure the following broad domains: physical health, psychological health, social relationships, and environment. The WHOQOL-BREF is a shorter version of the original instrument that may be more convenient for use in large research studies or clinical trials. It has been used in international settings, including the WHO collaborative study of substitution treatment (Lawrinson et al, 2008).

Urine testing: Urine drug testing will be done using rapid test kits that test for opiates, amphetamines, methamphetamines, benzodiazepines, and cannabis. These will be purchased from an approved laboratory in Vietnam. These kits provide a rapid urine test that is done on site and produces a result within five minutes. In this study, urine testing will be done monthly, with collection days being randomly selected.

HIV Testing: At the baseline visit rapid HIV testing will be used to determine HIV status and need for care. All participants who are determined to be HIV positive (two rapid positives) will be referred directly to Go Vap HIV clinic for initial assessment. All participants who test negative will be scheduled for retesting at 6- and 12-month assessment points. The test kits to be used will be WHO tested and selected in conjunction with the HCMC MOH.

Drug Abuse Treatment Cost Analysis Program (DATCAP): The cost data will be collected in Year three. This effort will be led by Dr. Julie Becher a health economist from the Penn CSA. The program-based DATCAP and Client-based DATCAP are reliable instruments widely used by substance abuse treatment programs for the collection and organization of programmatic costs and participant-based costs, respectively. The instruments, by standardizing data collection procedures, enable direct comparison of data and cost estimates across different drug treatment programs and over time (French et al. 1997). The program-based DATCAP is divided into different categories, each one pertaining to a particular area of standard universal economic resource and cost variables: personnel (e.g., percentage of time devoted to the program, annual salary, total cost of employee benefits, total overtime cost, any other personnel cost) supplies and materials (e.g., cost of medications, medical and office supplies, value of supplies and materials donated or received free of charge), major equipment (e.g., cost of all leased/rented equipment used by program, depreciation expense for equipment, value of any equipment donated or received free of charge), contracted services (e.g., cost of laboratory services, repairs and maintenance, advertising services), buildings and facilities (e.g., size of total usable space in building, percentage of that space used by the treatment program, percentage of time it was used by this program, annual lease/rental price per square foot), miscellaneous resources and costs (e.g., cost of utilities such as electricity, telephone, transportation, staff training, medical waste disposal) not recorded elsewhere. The outpatient-client based DATCAP collects information on costs incurred by participants such as expenses related to transportation, child or elder care and lost productivity while participating in the treatment program (French et al. 2004; Salome et al. 2003).

The general categories of "costs" are universal and applicable to different programs in different countries. These instruments were designed to be flexible; individual items within each category may be added or deleted depending on specific aspects of a unique drug treatment program or geographical characteristics (Salome, French, Miller, & McLellan 2003). For example, the DATCAP has been used in Australia, Spain, Romania, and a few other countries. The instrument is in the public domain and usage has not been monitored, so there is no readily available list of citations (Michael French, personal communication, August 18, 2008). Time to complete the instruments varies depending on specific characteristics of drug treatment programs and participants. These assessments are highly structured and will be completed over the course of three days of interviews conducted by Dr. Becher.

Together, these assessments will produce serologic, behavioral, and cost measures during the project period. Baseline assessments are expected to last approximately two hours. Given the number and variety of assessment modalities (interview, questionnaire, phlebotomy, pre and post-test counseling), the burden of the participants will be minimized through careful scheduling and efficient administration of assessments and small refreshments and brief breaks will be provided. Follow-up assessments are expected to take approximately one hour.

Study Retention: A series of structured activities will be used to maximize completion of follow-up appointments. These activities are considered core principles in conducting longitudinal studies and have been shown successful in many different cultural settings. The investigators believe that with the intensive and structured efforts described below, the proposed project can achieve a 90% retention rate at 12 months. Most importantly, research staff will maintain accurate and timely follow-up contact information for all participants throughout the study. A basic philosophy of the work to be implemented is that follow-up begins when the initial relationship is established, and the data is collected at the time of recruitment and enrollment. Thus, a detailed locator interview will be completed for all subjects following completion of the informed consent at the time of enrollment. This will be updated at all subsequent contacts. All future appointments for research assessments will be scheduled on a calendar at the time of enrollment. A copy of this visit schedule will be given to the participant. Ten days prior to all scheduled assessment visit, calls reminding subjects about their scheduled assessment will be completed and a note will be left in the methadone dispensing area reminding the participant about the time and location of the assessment visit. Missed calls will be noted and attempts to contact the participant will continue until contact is achieved. For those who are not able to be contacted through the clinic or by phone, staff will visit contact locations collected from the participant at the time of enrollment and updated at their most recent contact. Reminder calls will also be made on the day before the scheduled appointment. Missed appointments will be responded to immediately. At the end of each day, the designated follow-up staff will attempt to contact all the subjects who missed their appointment that day. For those who unable to be reached by phone, a reminder letter will be sent within three days. Outreach by research staff will also be used to locate missing subjects. When unable to make contact after 5 days, research staff members will implement outreach procedures, including visiting the subject's home, contacts, and common "hangouts" reported by the subject at the time of their prior visit. Subjects who are reported to be incarcerated will have a note placed in their retention file and staff will periodically update the status of the participant through contact with the friend or family member who initially reported the incarceration.

**Analysis Plan**

All data will be collected by research staff based at the Go Vap clinic. Trained staff will review all forms prior to the completion of the study visit to minimize problems associated with missing values and incorrect skip patterns. All assessments will be recorded on final version of the Case Reporting Forms (CRFs). CRFs will also be developed to capture the results of all biological assessments. All CRFs will be completed and stored using only participant identifying numbers and will not include names, addresses, or other data that could possibly be used to disclose the identity of the participant. All completed CRFs will be filed in locked cabinets by ID number. Consent forms, locator information, and other forms with personal identifiers will be securely stored separately. Research staff at the project site will be responsible for entering all data into the secure web-based data management system operated by the Data Management Unit of the University of Pennsylvania, Center for Studies of Addiction (CSA).

The data management and the quantitative analyses will be performed by the Center for Studies of Addiction data analyst, under the supervision of the PI and Dr. Kevin Lynch, the CSA Statistician. Dr. Becher will supervise the economic analyses. Prior to performing analyses, standard data screening and cleaning procedures will be applied (Tabachnik & Fidell 2001). These procedures will (1) screen the data for data-entry errors, (2) check for outliers, (3) assess the extent and pattern of missing data, and (4) check that appropriate assumptions of normality are met whenever necessary.

The planned analyses will be sharply focused on providing information able to inform the primary aims of the study.

1) *Establish a new integrated MAT treatment program within and HIV treatment setting in HCMC*. This aim will be fully documented by descriptive data focused on the numbers of patients treated by methadone and Suboxone. Data to summarize the duration of and response to treatment by patients in each of the four groupings—Methadone treated HIV-; Methadone treated and HIV+; Suboxone® treated and HIV-; and Suboxone® treated and HIV+ will be presented. The project's goal is not to compare treatment but to provide data to demonstrate that these treatments are producing results consistent with "clinical expectations" for these approaches and patient populations.
2) *Evaluate barriers and facilitators to implementation of integrated MAT/HIV treatment.* For this aim the study will carefully document the "events" or "factors" that are identified as having an influence on the ability and speed of implementation. Three stakeholder groups will be monitored—the drug using and patient population, the program staff, and the local government and non-government organizations. Data will be assembled using a monthly implementation log and formally assessed using semi-structured interview strategies.
3) *Evaluate patient retention and medication adherence in integrated MAT/HIV Care.* This aim will be critically important in documenting the success of implementation of the program. The study will carefully monitor through the baseline, 6- and 12-months assessments both retention in treatment and response to treatment. Retention will include measures of medication visit completion for expected methadone and Suboxone® administration visits as well as adherence to antiretroviral medication. Biological markers of these measures will also be collected. Results of monthly urinalyses for all participants will be reported and semiannual viral load measures for HIV positive patient will be summarized.
4) *Estimate the costs and benefits of MAT treatment strategies.* A cost-effectiveness analysis is an economic evaluation technique that may be used to evaluate multiple strategies to achieve an outcome. A cost-utility analysis is a special kind of cost-effectiveness analysis that may be used to compare strategies that affect morbidity and mortality (Gold et al. 1996; Haddix et al. 2003). One potential barrier to implementation of an enhanced intervention is the number of resources that must be devoted to administer the additional procedures. However, resource-intensive interventions may be justified through the achievement of better outcomes resulting from administering the enhanced procedures.

**Data Analyses for treatment and outcomes (Aims 1 and 3):** The sample of up to 500 participants will be split between HIV+ and HIV- participants. The participants will not be assigned at random to Suboxone® or methadone. The assignments will be based on clinical evaluation, and participants with a longer history of addiction, or with higher numbers of previous treatments, or participants who may be at risk for interactions between methadone and antiretroviral medications, will be more likely to receive Suboxone®. The investigators anticipate having about 40-50% of the sample receiving one medication, and 60-50% receiving the other, so there should be adequate numbers for analyses in each treatment stratum.

The goal of the analyses for Aims 1) and 3) is to assess the influences of participant characteristics on treatment outcome, and to examine whether characteristics of good outcome differ across treatment and HIV groups. Thus, the analyses will regard treatment (SUB or METH) and HIV status (+ve or –ve) as strata. Participant characteristics, drawn from the baseline administrations of the Study Specific Questionaire, ASI, RAB, and ICD-10 assessments, will be the explanatory variables of interest, while binary factors for treatment group and for HIV status will form four strata.
The outcomes of interest include: (1) the durations of time in treatment, and time to relapse to drug use, which will be addressed using Cox proportional hazards models and its extensions; (2) measures of psychopathology and drug or sex risk behaviors, drawn from the ASI and the RAB at the 6 and 12 month points, which will be analyzed using linear or nonlinear (e.g. logistic or ordinal) mixed effects models; (3) self-reported drug use drawn from the ASI, and monthly UDS tests, which will also be analyzed using linear or nonlinear mixed effects models; (4) overall incidence of HIV among those participants negative for HIV at baseline, which will be analyzed using a logistic regression model.
The analyses will follow the same overall analytic strategy for each set of models. First, the participant characteristics will be examined separately. For a given characteristic, the analyses will first test for heterogeneity (interaction) between the characteristic and the stratifying variables of treatment and HIV status. Two types of heterogeneity are possible: the characteristic could have effects that differ across some combination of the treatment and HIV groups (three-way interaction) or its effects may be independent of one variable but differ across levels of the other (two-way interaction). In either of these cases, stratum-specific estimates of the effects will be reported. If no heterogeneity is detected, the adjusted (pooled) estimates of effect will be reported. In each case, the estimates on an appropriate scale (e.g., odds ratios, or regression coefficients associated with interpretable changes in the level of the participant characteristic), together with appropriate confidence intervals will be reported. Once the univariate effects of the different characteristics will be assessed, multivariate models containing what appear to be the important characteristics will be performed, and these models will be implemented and reported in the same way as for the univariate models.

**Data Analyses for Economic Outcomes (Aim 4):** Standard cost-effectiveness and cost-utility analyses will compare costs and benefits of the two approaches (Gold et al., 1996; Haddix et al., 2003). The analyses will be carried out from a societal perspective which means that all costs and benefits, regardless of who pays or incurs them, will be included.
Benefits may be considered as reductions in sex risk behaviors (e.g., condom use and decreased number of partners) and less risky drug-use practices (e.g., decreased needle sharing and works sharing) during follow-up. In addition, a measure of the quality-adjusted life-years (QALYs) of sex partners saved by the intervention versus the standard of care will be estimated. Benefits will be compared to the direct and indirect costs (i.e., lost productivity) of the intervention and standard of care procedures. Relevant costs include time for the administration of the HIV counseling and testing, HIV test kits, completion of intervention questionnaires, time of staff to collect blood and follow-up assessment data and the time of participants to complete the follow-up assessments.
Incremental cost-effectiveness ratios will be computed to find the additional net cost (costs minus benefits) per outcome (e.g., cases of HIV transmission prevented or QALY saved) by administering the behavioral intervention over standard procedures. To check the sensitivity of results, univariate and multivariate sensitivity analyses, in which parameter values in the mathematical models are varied from baseline values, will be conducted.

**Data confidentiality**

| | |
|---|---|
| X | Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study. |
| X | Computer-based files will only be made available to personnel involved in the study using access privileges and passwords. |
| | Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information. |
| X | Wherever feasible, identifiers will be removed from study-related information. |
| | A Certificate of Confidentiality will be obtained because the research could place the subject at risk of criminal or civil liability or cause damage to the subject's financial standing, employability, or liability. |
| | A waiver of documentation of consent is being requested because the only link between the subject and the study would be the consent document and the primary risk is a breach of confidentiality. (This is not an option for FDA-regulated research.) |
| | Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys. |
| | Audio and/or video recordings will be transcribed and then destroyed to eliminate audible identification of subjects. |

**Subject Confidentiality**

All data will be collected by research staff at Go Vap Clinic, HCMC, Vietnam. Trained staff will review all forms prior to the completion of the study visit to minimize problems associated with missing values and incorrect skip patterns. All assessments will be recorded on final version of the Case Reporting Forms (CRFs). CRFs will also capture the results of all biological assessments. All CRFs will be completed and stored using only participant identifying numbers and will not include names, addresses, or other data that could possibly be used to disclose the identity of the participant. Research staff at the Go Vap Clinic will be responsible for entering all data into the secure web-based data management system operated by the Data Management Unit of the University of Pennsylvania, Center for Studies of Addiction (CSA). After the final data set is sealed (approximately 6 months after the final data collection session) all identifying information will be destroyed.

**Subject Privacy**

*Privacy refers to the person's desire to control access of others to themselves. Privacy concerns people, whereas confidentiality concerns data. Describe the strategies to protect privacy considering the following: The degree to which privacy can be expected in the proposed research and the safeguards that will be put into place to respect those boundaries. The methods used to identify and contact potential participants. The settings in which an individual will be interacting with an investigator. The privacy guidelines developed by relevant professions, professional associations and scholary disciplines (e.g., psychiatry, genetic counselling, oral history, anthropology, psychology).*

All potential subjects will be recruited at the GoVap clinic. Research staff will speak with those interested in the study. Only research staff, not clinic staff, will collect data for the study. Clinic staff will not have access to the study data. All research assessments will be performed in private offices within the clinic. For follow-up research visits, staff will attempt to leave appointment notes for participants when they attend the clinic. For those who have left treatment, staff will use information collected on the locator form to telephone participants or mail letters to them.

**Data Disclosure**

Staff supervised by the Key Personnel will have access to the data in order to perform study duties.

**Data Protection**

| | |
|---|---|
| X | Name |
| X | Street address, city, county, precinct, zip code, and equivalent geocodes |
| X | All elements of dates (except year) for dates directly related to an individual and all ages over 89 |
| X | Telephone and fax number |
| | Electronic mail addresses |
| | Social security numbers |
| | Medical record numbers |
| | Health plan ID numbers |
| | Account numbers |
| | Certificate/license numbers |
| | Vehicle identifiers and serial numbers, including license plate numbers |
| | Device identifiers/serial numbers |
| | Web addresses (URLs) |
| | Internet IP addresses |
| | Biometric identifiers, incl. finger and voice prints |
| | Full face photographic images and any comparable images |
| | Any other unique identifying number, characteristic, or code |
| | None |

**Tissue Specimens Obtained Specimens Obtained as Part of Research***
Are Tissue Specimens being obtained for research?
No

**Tissue Specimens - Collected during regular care***
Will tissue specimens be collected during regulator clinical care (for treatment or diagnosis)?
No

**Tissue Specimens - otherwise discarded***
Would specimens otherwise be discarded?
No

**Tissue Specimens - publicly available***
Will tissue specimens be publicly available?
No

**Tissue Specimens - Collected as part of research protocol***
Will tissue specimens be collected as part of the research protocol?
No

**Tissue Specimens - Banking of blood, tissue etc. for future use***
Does research involve banking of blood, tissue, etc. for future use?
No

**Genetic testing**
If genetic testing is involved, describe the nature of the tests, including if the testing is

predicative or exploratory in nature. If predictive, please describe plan for disclosing results to subjects and provision of genetic counseling. Describe how subject confidentiality will be protected Note: If no genetic testing is to be obtained, write: "Not applicable."
N/A

## Consent

### 1. Consent Process

**Overview**

The study will be described to the participant during the intake process. Participants who express interest in the study will meet with one of the research staff and be engaged in a conversation explaining the details of the study. Subjects will have the opportunity to have all their questions answered and will be given time to discuss the study with family members or others with whom they choose to discuss their participation. Staff will be very clear that participation is voluntary, and individuals may withdraw from the study at any time without consequence to their treatment participation. For those who meet inclusion criteria for treatment, detailed informed consent procedures will outline the nature of participation, risks and benefits, and the schedule for data collection and compensation. Potential participants will then be given a detailed description of the research procedures and all remaining questions will be answered. Subjects will be reminded that they are free to decline or stop participation at any time. The consent form and related discussions will make it very clear that a critical feature of the study is the ability to follow study participants for one year whether they remain in their treatment program. The consent will indicate permission from the participant to contact them in the community should they leave treatment.

**Children and Adolescents**

N/A

**Adult Subjects Not Competent to Give Consent**

N/A

### 2. Waiver of Consent

**Waiver or Alteration of Informed Consent***

No Waiver Requested

**Minimal Risk***

NA

**Impact on Subject Rights and Welfare***

NA

**Waiver Essential to Research***

NA

**Additional Information to Subjects**

NA

**Written Statement of Research***

No

**If no written statement will be provided, please provide justification**

## Risk / Benefit

**Potential Study Risks**

Both Methadone and Suboxone® (buprenorphine/naloxone) treatment have a long history of effectiveness and safety as a therapy for opiate addiction. However, since they are highly potent drug, an improper prescription and/or their misuse can be harmful or even fatal. Some patients could experience some minor side effects such as headache, stomach pain, nausea, vomiting, constipation, warmth or tingly feeling, increased sweating, weakness, back pain, increased of anxiety and/or depression symptoms, sleep problems (insomnia) or runny nose. These symptoms usually occurred at the beginning of the treatment. Serious side effects are linked to the properties of any narcotic medicines that could slow the patient's breathing and in some case conduct to death. However, serious side effects appeared mostly with misuse/ inappropriate use of the medication or when the medication is combined with any other non-prescribed drug (alcohol, benzodiazepine). To avoid any serious side effects, the patients should strictly follow the prescription as the dose of the medication is established by the doctor on an individual basis. Clinical signs and patient-reported symptoms of either overmedication or withdrawal, along with drug craving and/or continuing illicit-opiates use, are vital indicators for achieving dose adequacy. All the doctors have received an extensive training to adequately prescribe both medications and so reduce all the serious side-effects.

There are a few risks associated with HIV testing. The participant's finger (and arm if confirmatory testing is required) may become bruised or sore following the collection of blood for the HIV testing. Also, if the tests determine that the participant is infected with HIV, they may have an emotional reaction and become depressed or angry. If this happens, the research staff will help by providing counseling and making a referral for follow-up counseling services. Although the research staff will work very hard to protect privacy and the confidentiality of the test results, it is possible that someone may discover the results of their testing. Also, participants may be embarrassed by some of the personal questions that the research staff will ask. Finally, it is possible that someone could find out about an individual's participation in the study and determine that they are in treatment for drug dependence.

**Potential Study Benefits**

Any direct benefit to individuals participating in this study can not be promised. The information gained from this study will provide information that may help to implement other programs for opiate addiction within an HIV treatment program. The HIV test will provide important information about the participants health status. For those who are determined to be uninfected with HIV, counseling will be focused on developing ways to avoid infection in the future. Although the impact of the counseling is not certain, it is possible that the counseling may help participants gain a better understanding of drug addiction. The counseling may also help participants become more successful patients in medication assisted treatment for opiate addiction and, if they are HIV infected, more adherent to their HIV treatment. Finally, the counseling sessions may give participants effective strategies to improve relationships with family and friends.

**Alternatives to Participation (optional)**

**Data and Safety Monitoring**

This study will be monitored by the principal investigator and the DSMB of the University of Pennsylvania Center for Studies of Addiction.

**Risk / Benefit Assessment**

The investigators cannot say that participation in the trial will have direct personal benefits to the participants. However, the trial procedures pose a minimal risk to participants, as they are

not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical and psychological examinations or tests. At the same time, this trial will provide information that will have potential importance in the development of enhanced medication assisted treatment outcomes.