Rapid initiation of buprenorphine/naloxone to optimize MAT utilization in Philadelphia

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1 Study Summary

Title	Rapid initiation of buprenorphine/naloxone to optimize MAT utilization in Philadelphia
Short Title	Rapid initiation of BUP/NX
Study overview	The proposed research will evaluate the ability of a mobile, rapid induction procedure to engage individuals in ongoing medication assisted treatment. A total of 250 untreated individuals meeting criteria for opioid use disorder and at high risk of opioid overdose will be enrolled in the study. Recruitment will take place in two targeted neighborhoods of Philadelphia (Kensington and South Philadelphia) with a high prevalence of fatal and non-fatal opioid overdose. A total of 250 participants will be engaged in the research. Following informed consent and determination of eligibility, 125 individuals will be enrolled as they engage with the mobile, rapid induction team and 125 individuals will be enrolled as they seek treatment from the CRC Episcopal Hospital (serving Kensington area) or BAC/CRC Hall Mercer Community Mental Health (serving South Philadelphia). The intervention group will receive four weeks of treatment with buprenorphine /naloxone and support for treatment engagement provided by a case manager and a peer recovery specialist. All participants will be assessed at baseline and then 1- and 6-month following enrollment. The primary endpoint for the study is continued enrollment in medication-assisted treatment at 6 months post enrollment.
Study Duration	The estimated duration of study is 36 months. Individual study subject participation will last 6 months.
Study Center(s)	The University of Pennsylvania will serve as the primary project location, and all recruitment and data collection efforts will be executed by University of Pennsylvania staff members. A subcontract has been established with Prevention Point Philadelphia and Public Health Management Corporation.
Objectives	The proposed research will evaluate the ability of a mobile, rapid induction procedure to engage individuals in ongoing medication assisted treatment. The specific aims are: • Aim 1: To evaluate the impact of the mobile, transitional MAT intervention on its ability to engage participants in targeted, existing MAT treatment slots at 1- and 6-month post-enrollment. • Aim 2: To evaluate the impact of the mobile intervention on subsequent drug use and overdoses at 6-month post-enrollment. • Aim 3: To assess the acceptability and costs of the intervention. We will document the program and patient costs of delivering and participating in the intervention.
Number of Subjects	A total of 250 participants will be engaged in the research at the time they seek treatment: 125 individuals will be enrolled as they engage with the mobile, rapid induction team and 125 individuals will be enrolled as they seek treatment from the BAC/CRC (treatment as usual).

Main Inclusion and Exclusion Criteria	**Inclusion Criteria:** • Must be 18 years of age or older • Opioid overdose in the prior 12 months • Meet criteria for opioid use disorder • Resident of Philadelphia • Willingness and ability to participate in study procedures **Exclusion Criteria:** • Inability to comprehend or complete study procedures • Plans to relocate during study time frame • Diagnosis of serious liver disease (LFT >3x normal ranges) • Currently in medication assisted treatment (MAT) for substance use disorder • Pregnancy or lactation • Moderate to severe alcohol or benzodiazepine use disorder
Intervention	• The intervention consists in a rapid initiation of buprenorphine/naloxone, counseling, peer support and case management as a method for linkage to long-term, evidence-based medication assisted treatment. • Inductions will be initiated in the individual's home community, either on our mobile medical facility or via home visits. • The mobile team will be led by a nurse practitioner (able to prescribe buprenorphine/naloxone in PA) and include a peer recovery specialist (PRS), and a case manager. The team will rapidly confirm opioid use disorder and risk of overdose, complete informed consent, and begin induction procedures for a "transitional" (one month) course of buprenorphine/naloxone treatment. During this time, the dedicated case manager and PRS will work with the participants to help them become engaged in existing medication assisted treatment programs. • The type of ongoing treatment will be determined on an individual basis and will include options of methadone maintenance, buprenorphine/naloxone treatment, or extended-release naltrexone (XR-NTX).
Statistical Methodology	• Comparison on engagement rates in ongoing opiate use disorder treatment at the two time points (1- and 6-months) using a repeated measures logistic regression model, incorporating the propensity score (to correct for non-randomized trial) • Evaluate the change in substance use and severity of addiction using a repeated measures model to compare the groups on the ASI drug composite score at months 1 and 6. • Compare of the number of overdoses per participant between groups using repeated measures Poisson regression models, if there is sufficient variability in the number of overdoses reported. If a low rate of overdoses causes convergence issues for the Poisson model, we will classify participants as having no overdoses versus at least one, and compare the groups using repeated measures logistic regression models. • Evaluation of the sensitivity of our main analyses to the presence of missing data by performing a sensitivity analysis, in which we will obtain estimates of the group effect under various non-ignorability assumptions, using selection models to examine the effects of missing data, using logistic regression models, and incorporate the predicted probabilities into a weighted analysis of the main hypotheses.
Data and Safety Monitoring Plan	The study will be monitored by the PIs and co-investigators, and Philadelphia Department of Public Health Institutional Review Board, as well as by regulatory committees at the University of Pennsylvania (i.e., IRBs, OHR) and Center for Studies of Addiction Data Safety Monitoring Board (Penn DSMB). During the course of the study, safety and data quality monitoring will be performed on an ongoing basis by the Principal Investigator and the study staff.

2 Introduction

The information that follows constitutes the research protocol for the Rapid initiation of buprenorphine/naloxone to optimize MAT utilization in Philadelphia study. This study will be conducted in compliance with the provisions set forth in this document. This study will also be conducted in full accordance with all applicable University of Pennsylvania Research Policies and Procedures, Good Clinical Practice Standards and all applicable Federal and state laws and regulations including *45 CFR 46*, 21 CFR Parts 50, 54, 56. All episodes of noncompliance will be documented.

The proposed research will test a mobile intervention designed to initiate treatment and link individuals with opioid use disorder and a high risk of overdose to ongoing medication-assisted treatment (MAT). Despite the high prevalence of opioid use disorder and elevated rate of fatal and non-fatal overdose in Philadelphia, over 20% of MAT capacity goes unused. The proposed intervention will rapidly initiate treatment with buprenorphine/naloxone and provide one-month of medication coverage, peer support and case management sharply focused on linkage to ongoing MAT (i.e., methadone, buprenorphine/naloxone, extended-release naltrexone). Several critical barriers to treatment (stigma, time, and distance) will be minimized by rapidly initiating MAT in the individual's home environment.

In 2016, a total of 63,632 Americans died of a drug overdose and opioids were involved in 66.4% of these cases (42,249 overdose deaths) (Seth, Scholl et al. 2018). At present, opioid-related overdoses are the leading cause of accidental death in the country with a mortality rate that has quadrupled since 2000 and increased by 44.1% from 2015. In Pennsylvania, between July 2016 and September 2017, the CDC Enhanced State Opioid Overdose Surveillance system reported an 81% increase of the ED visits for suspected opioid overdoses. Statewide, there were 4,627 overdose deaths in 2016, an increase of 44.1% from 2015, the second highest rate of increase of any state during this reporting period (Centers for Disease Control and Prevention 2018). In Philadelphia, in 2017 there were 1,217 drug overdose deaths. Medical examiner reports indicate that 88% involved opioids, including prescription opioids, heroin, and fentanyl (City of Philadelphia, 2018). The increasing presence of fentanyl is directly associated with the escalating numbers of fatalities and in 2017, fentanyl was found in over 80% of the opioid fatalities. The 2017 the age-adjusted opioid-related death rate (59.8 per 100,000) was more than twice that found in New York City and greater than any of the other largest cities in the country. Conservative estimates suggest that there are 70,000 individuals using heroin in Philadelphia and approximately, 50,000 who misuse opioid prescription medications. According to the DEA, the heroin sold in Philadelphia has the highest purity and the lowest price in the country. A bag of heroin in Philadelphia is now cheaper than a pack of cigarettes. Philadelphia is an urban epicenter of the opioid epidemic in the United States.

There is no demographic that remains unaffected by the opioid crisis in Philadelphia (City of Philadelphia, 2018). The age adjusted mortality rates have increased for all categories of age, race and gender. The highest rates of increase over the past two years have occurred for women (49% increase) and 15 to 24-year old (62% increase). Using the City of Philadelphia Department of Health and Human Services' integrated data system (CARES), analyses of fatal overdoses during the past 5 years indicated that 70% were males, 63% white, and 27% were ages 25 to 34. Importantly, 41.4% of these individuals had contact with at least one service of the Philadelphia Behavioral Health System within the 6 months of their death and 26.4% within 1 month of their death.
Geographically, the opioid epidemic has affected all neighborhoods in the City. Of relevance to this application, the two areas of highest concentration for fatal overdoses are the Kensington and South Philadelphia. These are the target areas for the proposed intervention. It is also important to note that nearly 75% of fatal overdoses took place in private residences. The proposed intervention will be accessible to those with stabile as well as unstable housing.

2.1 Responses to the epidemic

Beginning in the mid 1970's, efforts directed at reducing the problems associated with drug use were led by the criminal justice systems. The United States' "War on Drugs" resulted in changes in law and enforcement policies leading to almost 3% of the US adult population being under some form of criminal justice supervision by the early 2000's (Peters, Young et al. 2017). These policies created a system of mass incarceration and relied on ineffective abstinence-only approaches, resulting in harmful consequences and in huge economic and human costs (Belenko, Hiller et al. 2013). One of the consequences of these failed policies has been the neglect of evidence-based treatment approaches and systems.

Scientific and medical communities have advocated for increasing the availability of evidence-based pharmacotherapeutic approaches (Volkow, Frieden et al. 2014, Blum, Gold et al. 2016). In 2017, the US Department of Health and Human Services declared a public health emergency and announced a 5-point strategy to combat the opioid crisis. The strategy included improving access to evidence-based treatment and recovery services, promoting use of naloxone to prevent overdose, strengthening the understanding of the epidemic through better public health surveillance, providing support for cutting edge research on pain and addiction, and advancing better practices for pain management (US Department of Health and Human Services 2018). The opioid epidemic is a complex public health issue that should be addressed with multifaceted approaches including harm reduction and evidence-based treatment of the opioid addiction.

An important response to the opioid epidemic in Philadelphia has been the rapid scale up of naloxone access and training. When administered correctly and in time, can prevent death from opioid overdose. Different approaches for naloxone deliveries have been extensively examined and have concluded in the efficacy of the widespread coverage of naloxone to reduce overdose (Rowe, Santos et al. 2015, Kirane, Ketteringham et al. 2016, Wagner, Bovet et al. 2016, Fairbairn, Coffin et al. 2017, Faulkner-Gurstein 2017). In Philadelphia, naloxone has become widely available and has been used to reverse over 7,000 overdoses in 2017.

Although an effective tool for fatal overdose prevention, naloxone is not a treatment of opioid addiction or a prevention for future overdose. In fact, a recent publication showed that non-fatal overdose is the highest risk factor for subsequent fatal overdose (Caudarella, Dong et al. 2016). Consistent with these findings, the above map displaying the incidence of naloxone use is nearly identical to the one displaying the incidence of fatal overdose in Philadelphia. These findings support the importance of linking individuals to effective opioid addiction treatment after an overdose.

2.2 Medication Assisted Treatment

Opioid use disorder, or opioid addiction, is a chronic relapsing disease defined as the loss or reduced control of the use of substance and is expressed through persistence of this use despite the accumulation of negative consequences in health, social, financial, and family life (Auriacombe, Serre et al. 2018). Opioid addiction is most effectively treated as a chronic disease which cannot be cured and requires long-term management strategies (McLellan, Lewis et al. 2000, American Society of Addiction Medicine 2014).

It is well-established that medication-assisted treatment for opioid use disorder, either with methadone, buprenorphine/naloxone, or, naltrexone is safe and effective in reducing and suppressing opioid use, improving health outcomes, and reducing all cause and overdose mortality (Mattick, Breen et al. 2014, Nielsen, Larance et al. 2016). More recently, extended-release naltrexone (XR-NTX) has been approved by FDA for the treatment of opiate use disorder. For those who initiate treatment, the effectiveness of XR-NTX appears comparable to methadone and buprenorphine/naloxone (Morgan, Schackman et al. 2018).

Despite overwhelming evidence of efficacy and perceived potential to impact the opioid epidemic, it is estimated that less than 20% of the individuals with opioid use disorder have access to medication-assisted treatment and less than 10% actually receive treatment (CDC 2018) (Wu, Zhu et al. 2016). Several barriers have been identified and can include financial (lack of insurance coverage, inability to pay), regulatory (limited treatment capacity, waivered physicians), geographic (limited providers, treatment access), attitudinal (stigma, negative attitude towards medication assisted treatment), and logistic (lack of transportation, hours of operation) (Huhn, Tompkins et al. 2017, Sharma, Kelly et al. 2017). The strict regulatory environment and the often-long waiting list to access outpatient methadone clinic is a major barrier to treatment engagement and has helped to promote the expansion of buprenorphine/naloxone treatment that is primarily delivered in physician offices (Stancliff, Joseph et al. 2012). Increased access to buprenorphine treatment was shown to dramatically reduce the overdose rate in France (Auriacombe, Fatseas et al. 2004, Fatseas and Auriacombe 2007, Dupouy, Palmaro et al. 2017), and studies have shown a link between buprenorphine prescriptions and reduced rates of opioid overdose (Knudsen 2015, Knudsen, Havens et al. 2017).

The overall mortality in buprenorphine/naloxone treatment has been shown to no different than methadone treatment (Auriacombe, Franques et al. 2001, Kelty and Hulse 2017), and buprenorphine is safer than methadone during the 4-week period of induction (Kimber, Larney et al. 2015, Sordo, Barrio et al. 2017). Because buprenorphine is a partial agonist for mu opiate receptor and a kappa opiate receptor antagonist, the medication has a ceiling effect protecting from overdose (Fatseas and Auriacombe 2007). Increasing access to buprenorphine might raise concerns regarding diversion, however, previous studies have shown that illicit buprenorphine was not

linked with opioid overdose (Bretteville-Jensen, Lillehagen et al. 2015) and its use can enhance access to buprenorphine treatment (Cunningham, Roose et al. 2013, Fox, Chamberlain et al. 2015).

2.3 Interventions to increase utilization of existing MAT

Surprisingly little scientific attention has been devoted to evaluating interventions to increase the utilization of MAT. Several studies have focused on engaging individuals while they were in hospital (Sittambalam, Vij et al. 2014) or in the emergency department (D'Onofrio, O'Connor et al. 2015, D'Onofrio, Chawarski et al. 2017). These protocols have shown evidence of successful initial buprenorphine treatment engagement (21% to 74%) but without follow-up support after leaving the hospital, these rates were not sustained after 6 months. However, not all the individuals who experienced non-fatal overdose go to the hospital or, if admitted, may leave prior to the delivery of any effective intervention or referral. A recent qualitative study in out-of-treatment opiate users showed that when they got insurance coverage (mostly Medicaid), they more likely to choose the treatment available in their local community (Huhn, Tompkins et al. 2017). Community-based buprenorphine treatment intervention within harm reduction facilities (i.e. needle exchange program) was the most appealing strategy (Fox, Chamberlain et al. 2015, Fox, Sohler et al. 2017). Another approach that has been reported was based on community outreach. This project used peer-recovery specialists to engage opiate users at high-risk for overdose and link them to methadone treatment. They found that 76% initiated screening but only 54% stayed in treatment after 1 month (Scott, Grella et al. 2018). A similar strategy used a mobile unit and targeted individuals encountered at drug use venues (Daniels, Salisbury-Afshar et al. 2014) and linked the opiate users to local buprenorphine providers after helping them with insurance coverage. This program was able to link 49% of the participants to ongoing treatment but there was no measure of status at six months.

While MAT treatment capacity continues to expand, primarily through increasing numbers of buprenorphine/naloxone providers (Substance Abuse and Mental Health Service 2016), there is growing recognition of the need for more effective strategies to link opiate users to treatment. In February 2017, the Pennsylvania Department of Drug and Alcohol programs in partnership with the PA Department of Health, established a strategy for improving patient engagement in substance abuse treatment following hospital-based treatment for opioid overdose. This strategy is called the “Warm Handoff”. Overdose survivors who are treated in the emergency department (ED) receive counseling and a physician’s referral to be transferred directly from the ED to a drug treatment facility. The warm handoff is completed by a Peer Recovery Specialist who supports the patient and will accompany him/her to appointments for ongoing treatment following hospital discharge (Department of Drug and Alcohol Programs 2018). This strategy is being scaled up and has potential to improve the rate of completed referrals for individuals seen in the ED and needing substance abuse treatment services. No data is yet available on the efficacy of this approach.

2.4 MAT engagement in Philadelphia

The City of Philadelphia Behavioral Health System has established Behavioral Assessment Centers (BAC) and Crisis Response Centers (CRC) as the point of entry into MAT. In cases of emergency related to addiction-related crisis, CRCs operate 24 hours a day, 7 days per week and do emergency evaluations to help determine the most appropriate level of care and services and provide linkages to these programs. BACs provide urgent assessments for addiction services during working hours. In many cases, they will help link individuals using opioids to a community-based MAT provider as appropriate. The Philadelphia Behavioral Health System outpatient MAT capacity is 8,707 slots, as of March 13, 2018, 1,846 (21%) MAT slots were still available (21%).

3 The proposed study

3.1 Project overview

The proposed project will build upon and incorporate many of the same principles that have proven important to the success of the buprenorphine/naloxone program established by Prevention Point Philadelphia (PPP), a primary partner in this proposal. This treatment program, known as the “Stabilization, Treatment and Engagement Program” (STEP) is fully integrated within the PPP needle-exchange program that has been operational since 1991 (Bachhuber, Thompson et al. 2018). The STEP program was designed to provide treatment access to users of the syringe exchange program. Individuals identified at exchange sites throughout the City were screened at PPP’s clinical offices in Kensington. Following assessment and a mandatory training, individuals would meet with the program’s physician and receive an initial one-week prescription for buprenorphine/naloxone. Weekly visits and prescription refills were required for the first month. The STEP program has been able to successfully engage 124 opiate users in long-term buprenorphine maintenance treatment with a retention of 65% at 6 months and 56% at 12

months. More than 90% of those who remained in treatment at 12 months were opiate-abstinent (Bachhuber, Thompson et al. 2018). Importantly, and in contrast to many other programs in the City, the STEP program has a waiting list of nearly 200 individuals.

The proposed project incorporates the concept of rapid initiation of MAT and consequently, the rapid control of withdrawal symptoms. A mobile team (Nurse Practitioner, Certified Peer Recovery Specialist, and a Case manager) will provide medication, counseling and treatment engagement support for one month. During this time, individuals will be linked to community MAT providers with unused capacity.
We will determine the economic value of the mobile intervention relative to treatment as usual from the perspective of the City of Philadelphia's Department of Public Health. Dr. Julie Becher, a Health Economist in the HIV Prevention Research Division, Department of Psychiatry, Perelman School of Medicine at the University of Pennsylvania, will lead this portion of study activities with consultations with colleagues at the Center for Health Economics of Treatment Interventions for Substance Use Disorder, HCV, and HIV (CHERISH). The results of this analysis will inform future policy decisions regarding implementation of this novel, mobile strategy for rapid initiation of MAT as a method for engagement in long-term evidence-based treatment. If the intervention in this study shows positive economic value, the City of Philadelphia's Department of Public Health may scale-up the intervention to reach more people throughout the city that may be at risk of opioid overdose. Enhanced interventions may require a greater amount of resources than alternative methods of more basic interventions or the usual standard of care. However, resource-intensive interventions may be justified through the achievement of better outcomes resulting from administering enhanced procedures.

3.2 Innovation

Rapid induction with buprenorphine/naloxone in the community is the core innovation of the proposed research. By reducing time and geographic barriers to treatment and the control of withdrawal symptoms, the intervention will provide a one-month opportunity to link participants to an appropriate, ongoing treatment provider. This use of MAT is an innovation designed to minimize common barriers to treatment engagement. The use of buprenorphine will also allow for the transition to other MAT strategies that may be more appropriate for the individual, including methadone maintenance treatment, buprenorphine treatment, or treatment with extended-release naltrexone. The ability to engage individuals with opioid use disorder in their home environment is another important innovation of the proposed research. The mobile engagement team will include a Nurse Practitioner, a Case manager, and a Certified Peer Recovery Specialist and will begin inductions on the mobile medical unit or in the individual's home. The mobility of the team is an innovation allowing easy access to individuals who indicate interest in treating their opioid use disorder. We will assess treatment status at six months post enrollment as our primary outcome measure. With the permission of the participant, the CARES Integrated Data Systems Service Utilization database will be available to identify involvement with drug treatment and other services provided by the City prior to and following the enrollment in the study.

3.3 Collaborations

The proposed project will be led by investigators from the University of Pennsylvania (Metzger, Kampman, Becher, and Lynch) with over 60 years of collective experience in community-based substance use research in Philadelphia. These investigators have had close and longstanding collaborations with investigators from TRI and Prevention Point Philadelphia.

- **Prevention Point Philadelphia (**https://ppponline.org **):** Prevention Point Philadelphia (PPP) was founded in 1991 as an underground syringe exchange organization. Over the years, PPP has evolved into a multi-service public health organization serving the most hard-to-reach populations in the toughest neighborhoods of Philadelphia. PPP was founded as a community-based SEP to address the high incidence of HIV and hepatitis C infection among people who inject heroin. Its core services now include harm reduction through syringe distribution and exchange, overdose education and naloxone distribution, provision of HIV and hepatitis C virus testing, HIV care, housing, and assistance with social services. In 2008, responding to client interest in addiction treatment and perceived lack of access by clients and program staff, PPP created a buprenorphine maintenance treatment program called the Stabilization, Treatment, and Engagement Program (STEP) that was fully integrated within the SEP. This program targets current SEP participants who express interest in cessation of heroin use. PPP will hire and support to the mobile intervention staff and maintain responsibility for the integrity of the mobile treatment and engagement service modeled after the STEP program. Jose Benitez and David Barclay have decades of

clinical and administrative experience in MAT delivery and will provide clinical leadership for the mobile team.

- **TRI Center on Addictions at PHMC (**https://www.tresearch.org **):** The Treatment Research Institute (TRI) was founded in 1992 as a 501(c)(3) not-for-profit organization in Pennsylvania. TRI's core mission has been to apply research to improve substance abuse policies and programs. TRI is committed to the development, evaluation, and dissemination of solutions designed to address issues related to substance use. As an independent treatment outcome evaluator, TRI has an extensive history of integrating its proven outcome assessment methods, measuring service delivery, and implementing evidence-based practices into clinical treatment programs nationally and internationally. TRI's research focuses on integrating clinical care across the various sectors affected by substance use problems, including healthcare, criminal justice, education, and community-based services. TRI is highly regarded in the substance use and mental health fields and has a reputation as a leader in translating research into practical applications. TRI is also known as the 'home' of the Addiction Severity Index (ASI), one of the most widely used assessment tools in the field. Instruments developed by TRI are among the most widely utilized by clinicians, researchers, and justice systems throughout the world. In June 2017, TRI merged with Public Health Management Corporation's R&E Group, becoming the TRI Center on Addictions at PHMC (TRI-CA). The investigators to be involved in theis project (Dugosh, Festinger, and Cos) have extensive experience in treatment research with a particular focus on MAT. They will participate in the trainings and will help to manage the implementation of the research and maintain primary responsibility for the recruitment, follow-up, and assessment of individuals seeking treatment at the participating BAC/CRCs--the Treatment as Usual Group.
- **Center for Health Economics of Treatment Interventions for Substance Use Disorders, HIV, and HCV (CHERISH** https://cherishresearch.org **):** CHERISH is an NIH-funded multi-institutional research center devoted to developing and disseminating economic evidence that informs substance use treatment policy and HCV and HIV care for people who use substances. The Center serves as a national resource to increase the impact of substance use economic research. Its infrastructure is designed to enhance existing research projects, promote state-of-the art economic research methods, and improve the ability of substance use economic researchers to communicate with decision makers and address changes in today's healthcare system. CHERISH will provide the research team with training and consultation in documenting the time and resources required to deliver and monitor the intervention, as well as potential downstream cost offsets associated with effective treatment.
- **Penn Injury Science Center** (https://www.penninjuryscience.org): The Penn Injury Science Center is funded by a grant from the Centers for Disease Control and Prevention and brings together university, community, and government partners around injury and violence intervention programs with the greatest potential for impact. The Center promotes and perform the highest quality research, training and translation of scientific discoveries into practice and policy, in order to reduce injuries, violence and their impact to our region, the US, and locations around the world. The Center's diverse group of scientists, students, and staff are centrally co-located on the University of Pennsylvania campus in Philadelphia and represent 6 Penn Schools, 12 other Penn Institutes and Centers, 2 Level 1 Trauma Centers, and 3 Research Laboratories. The Center will provide consultation and support in geospatial analyses and mapping. Specifically, the Center will provide guidance on the initial location of the mobile treatment engagement unit.
- **Philadelphia Department of Public Health (PDPH):** This project has been planned and will be implemented in close cooperation with the Philadelphia Department of Public Health. We will work closely with Kendra Viner, PhD, MPH and Jeffrey Hom, MD who co-manage the Opioid Surveillance, Epidemiology and Prevention Program (OSEPP) at PDPH. This program focuses on collecting, analyzing, and reporting epidemiological trends in opioid abuse, including both fatal and nonfatal overdoses, use of addiction treatment services (e.g., detoxification, MAT), opioid prescribing practices, and medical consequences of drug use (HIV, hepatitis). All work is done in close collaboration with the Medical Examiner's Office (MEO), which investigates and conducts comprehensive toxicology testing on all victims of fatal overdoses. OSEPP also conducts several prevention efforts, including managing community-based naloxone distribution programs, educating providers, pharmacists, and the public about opioid overdose prevention and reversal, and training primary care providers in screening and diagnosis of opioid misuse. We will also work closely with Lia Pizzicato, MPH who created the city's first Opioid Misuse and Overdose Report (https://hip.phila.gov/DataReports/Opioid) by building relationships with and securing timely information from the Medical Examiner's Office, the Fire Department, the Police Department, and all major Philadelphia area emergency departments.

3.4 Study Objectives

The proposed research will evaluate the ability of a mobile, rapid induction procedure to engage individuals in ongoing medication assisted treatment. Individuals meeting criteria for opioid use disorder and at high risk of opioid overdose will be enrolled in the study. Recruitment will take place in two targeted neighborhoods with a high prevalence of fatal and non-fatal opioid overdose. A total of 250 participants will be engaged in the research at the time they seek treatment. Following informed consent and determination of eligibility, 125 individuals will be enrolled as they engage with the mobile, rapid induction team and 125 individuals will be enrolled as they seek treatment from the BAC/CRC. All participants will be assessed at 1- and 6-month following enrollment. These assessments will provide data able to address each of the three aims.

Aim 1: To evaluate the impact of the mobile, transitional MAT intervention on its ability to engage participants in targeted, existing MAT treatment slots at 1- and 6-month post-enrollment.

Aim 2: To evaluate the impact of the mobile intervention on subsequent drug use and overdoses at 6-month post-enrollment.

Aim 3: To assess the acceptability and costs of the intervention. We will document the program and patient costs of delivering and participating in the intervention.

Assessments will also provide data on factors that are considered to be important determinants of retention in treatment—duration of opioid use; prior number of treatment attempts; frequency of recent use; and, depression. In addition to age, gender, and race these variables will be used in the proposed propensity analyses.

3.5 Rationale for Study Design

3.5.1 Why no Randomization?

In the proposed project, individuals will contact our mobile team after learning about the opportunity to begin a rapid induction with buprenorphine/naloxone. As described in more detail later, awareness of the intervention will precede contact with the research team via social media, targeted advertisement, and word of mouth. This is an important feature of the research since we want to be able to measure the acceptability and demand for such a strategy. We believe that it would not be ethical to randomly assign individuals at this point to an alternative treatment option that would require additional time and referral to a different location to initiate screening and intervention. As an “open label” trial, any randomization process would also become widely known among potential participants and contaminate the perception of the mobile team as able to reliably initiate rapid treatment engagement.

3.5.2 Why buprenorphine/naloxone for rapid treatment initiation?

For this study, we choose to use buprenorphine/naloxone to initiate treatment. Buprenorphine, the active treatment agent in the buprenorphine/naloxone medication, is a partial mu-opioid receptor agonist with greater affinity than heroin, morphine or other prescription opioids (Johnson, Strain et al. 2003, Orman and Keating 2009, Hser, Evans et al. 2016). It provides anti-withdrawal and anti-craving effects for up to 36 hours on a single dose. As a partial agonist, the slower onset of effect diminishes the patient’s perception of euphoria (Mammen and Bell 2009, Dennis, Naji et al. 2014), while its safety profile, long half-life and binding duration make it useful for both short term use, tapering, and long-term opioid maintenance (Soyka 2015). Effectiveness has been demonstrated across diverse samples (Thomas, Fullerton et al. 2014). The initiation of treatment with buprenorphine is safer than with methadone and unobserved induction is widely adopted and has been shown to be as safe as supervised initiation (Lee, Vocci et al. 2014). A recent Cochrane review showed no difference in retention at any duration with supervised compared to unsupervised dosing in retention in treatment at 1-month and at 3-month follow-up, no difference in abstinence at the end of treatment and no difference in diversion of buprenorphine (Saulle, Vecchi et al. 2017).

Study participants who will receive buprenorphine/naloxone will be provided with information, counseling, and support for selection of ongoing treatment options including methadone maintenance (MMT), extended-release naltrexone (XR-NTX), or continued treatment with buprenorphine/naloxone (Baser, Chalk et al. 2011, Hartung, McCarty et al. 2014).

3.6 Study Timeline

As shown in the Table below, following start-up activities (approvals, hiring, training, and data collection preparations), recruitment activities (community awareness) will start in month 5 and implementation of the intervention will begin in month 6 and continue for 18 months.

Rapid Induction Implementation Timeline

Month	Pre Start	1 to 3	4 to 6	7 to 12	13-18	19-24	25-30	31-36
IRB Approval and CR								
CRF Finalization								
CRF Programming								
Staffing								
Training Preparation								
Training								
Recruitment								
RI Screening (ave/week)				120 (5/wk)	120 (5/wk)	120 (5/wk)		
RI Enrollment (ave/week)				42 (1.8 /wk)	42 (1.8 /wk)	42 (1.8 /wk)		
TAU Screening (ave/week)				120 (5/wk)	120 (5/wk)	120 (5/wk)		
TAU Enrollment (ave/week)				42 (1.8 /wk)	42 (1.8 /wk)	42 (1.8 /wk)		
Baseline Assessment								
Assessment 1 Mth								
Assessment 6 Mth								
Quality Monitoring								

3.7 Study Measures

All interviews will be administered by experienced research assistants trained in the administration of the proposed assessments. Following confirmation of eligibility, the mobile research assistants will complete the baseline assessment (described below). The participant assessments in this research will be sharply focused on the valid and reliable measurement of its primary endpoints i.e. ongoing treatment engagement will be the primary endpoint on which the study is powered. We will also carefully compare the two groups with respect to the rate of continued opioid use and subsequent overdoses. All assessments will be completed by trained research staff (not clinicians) at baseline, and again at 1- and 6-month post-enrollment. We anticipate follow-up rates of 95% and 90% at Month 1 and 6, respectively. We anticipate that the assessments will take approximately 45 minutes to complete.

- Physical history and examination including a blood test to evaluate the liver function.

- Locator Data Collection: A detailed contact sheet (Locator Form) will be completed for all subjects as part of the baseline assessment. We will ask participants to provide contact information on themselves and at least three additional people with whom they are most likely to stay in contact. We will also ask about other places where participants might be able to be contacted in the future. Participants will provide consent for research staff to contact individuals whose contact information they provide. Contact information will also include e-mail addresses and mobile phone numbers for texting. The locator form will be updated at each scheduled assessment visit. In addition, participants will be asked to call or visit the research staff whenever they have updates to provide regarding changes in contact information.

- DSM-5 Substance Use Disorder Checklist: This form is a listing of the eleven DSM-5 criteria for substance use disorder. We will screen for opioids, cocaine, and alcohol as each are necessary for confirmation of inclusion and exclusion criteria. A score of 4-6 is considered moderate severity and from 7-11 is considered severe substance use disorder. An opioid use disorder score of 4 or greater will be required for study eligibility. Alcohol use disorder and benzodiazepine scores of 4 or greater will be exclusionary.

- A study specific questionnaire that includes:
    - Socio-demographic Questionnaire: This brief questionnaire will be administered by research staff and will collect 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 and housing stability, history of involvement with the criminal justice system, drug use, and drug treatment history.

- Addiction Severity Index (ASI) sections for Drugs and Alcohol and Medical Status: The ASI is a structured interview developed to assess the range of problems seen in drug users. The ASI produces severity ratings and composite scores in each of seven areas, and each type score has been assessed with regard to validity and reliability. Severity ratings and composite scores have demonstrated high levels of inter-rater, test-retest, and concurrent reliability (Cacciola et al., 2008; McLellan, Cacciola, Alterman, Rikoon, & Carise, 2006; McLellan et al., 1992). The Medical and the Drug and Alcohol sections will be administered at baseline, 1- and 6-month follow-ups.

- Patient Health Questionnaire (PHQ-9): Given the important role of depression in accessing and adhering to treatments for substance use disorder and other chronic medical problems (Mahajan, Avasthi, Grover, & Chawla, 2014; Tavakkoli, Ferrando, Rabkin, Marks, & Talal, 2013), we will also assess severity of depression using the 9-item Patient Health Questionnaire (PHQ-9). This brief assessment asks participants to indicate the frequency of occurrence of each of the nine DSM-IV diagnostic criteria for depression during the previous two weeks. This instrument has been widely used in clinical research and has strong psychometric properties. The PHQ-9 will be completed at baseline and months 1 and 6.

- Urine drug screen: We will use the CLIA waived® ACON Dip-and-Read 8-panel test for THC, cocaine, opiates, amphetamines, PCP, methamphetamine, benzodiazepines, barbiturates, and buprenorphine. The urine sample will be provided using standard procedures with temperature monitoring to preclude tampering and dilution.

- HIV testing: Chembio SURE CHECK HIV 1/2® rapid-HIV test kits will be used to detect antibodies. These FDA approved and CLIA Waived kits produce results in 15 minutes from a blood drop. For those who test antibody positive, additional blood will be drawn for confirmatory testing via RNA viral load assay. We anticipate that approximately 10% of participants will test positive for HIV.

- Economic evaluation: The cost-effectiveness of the intervention will be performed using data collected with questionnaires widely used for cost-effectiveness analyses.
  - Drug Abuse Treatment Cost Analysis Program (DATCAP): The program-based Drug Abuse Treatment Cost Analysis Program (DATCAP) is a reliable instrument widely used by substance abuse treatment programs for the collection and organization of programmatic costs. The instrument, by standardizing data collection procedures, enables 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/mobile unit 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 (French et al. 2004; Salome et al. 2003). The general categories of resources are universal and applicable to different programs in different locations. This instrument was 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). 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 instrument varies depending on specific characteristics of drug treatment programs. This assessment is highly structured and will be completed over the course of a few days by Dr. Julie Becher and study staff.
  - Non-Medical and Other Services Form (NSMOS): This questionnaire was adapted from the Treatment Services Review (McLellan et al., 1992; Cacciola et al., 2008) for patients receiving substance abuse treatment. It is designed to capture all medical and social services received by the participant between study visits. The NSMOS counts substance abuse treatment, medical services, employment visits, legal services, family services and psychological/emotional. It takes 5 to 10 minutes to complete. The Non-Medical and Other Services Form (NSMOS) will be used to collect information from participants on

their healthcare utilization. This information will enable us to estimate costs incurred by the City of Philadelphia's Department of Public Health. Participants will be asked about the medical services and other relevant resources they have utilized between assessments. More specifically, participants will be asked about: visits and number of visits to an emergency room (not admitted to hospital); admittances (number and duration) to hospitals to detoxify from drugs or alcohol, or for other reasons; participation and number of days in outpatient treatment program for drug or alcohol problems; admittance (number and duration) in a residential program to detoxify or for other services; receipt, type, and prescribed dose, of medication to treat alcohol use disorder, opioid use disorder, or mental health disorder; care (number of times) received by a psychiatrist or psychologist, counselor or social worker; number of visits to a medical office and number of visits with a doctor; amount spent out of pocket on healthcare (including prescriptions); and coverage and type of health insurance. Study staff will administer this form at each assessment. Time to complete will vary by participant.

3.8 Study Endpoints

3.8.1 Primary end-point

Treatment engagement is the primary endpoint in this study.

- Confirmation of enrollment in MAT: Assessments will collect self-report of participation in MAT at the time of assessment as well as during the intervening time-period. We will also collect confirmatory documentation from the identified treatment provider. Permission to contact the treatment provider will be included in the consent and a specific release of information form signed by the participant will be included in the request for confirmation.
- CARES Integrated Data Systems Service Utilization: Participants enrolled in this study will provide consent to allow the Health Department to review their records of utilization of city services prior to and following enrollment in the study.

3.8.2 Secondary Study Endpoints

- Evaluate the impact on the number of overdose and evaluate the change in substance use and severity of addiction using a repeated measures model to compare the groups on the ASI drug composite score at months 1 and 6.
- Cost evaluation: We will determine the economic value of the mobile intervention relative to treatment as usual from the perspective of the City of Philadelphia's Department of Public Health. Dr. Julie Becher, a Health Economist in the HIV Prevention Research Division, Department of Psychiatry, Perelman School of Medicine at the University of Pennsylvania, will lead this portion of study activities with consultations with colleagues at the Center for Health Economics of Treatment Interventions for Substance Use Disorder, HCV, and HIV (CHERISH). The results of this analysis will inform future policy decisions regarding implementation of this novel, mobile strategy for rapid initiation of MAT as a method for engagement in long-term evidence-based treatment. If the intervention in this study shows positive economic value, the City of Philadelphia's Department of Public Health may scale-up the intervention to reach more people throughout the city that may be at risk of opioid overdose. Enhanced interventions may require a greater amount of resources than alternative methods of more basic interventions or the usual standard of care. However, resource-intensive interventions may be justified through the achievement of better outcomes resulting from administering enhanced procedures.

4 Study Population and Duration of Participation

4.1 Duration of Study Participation

The duration of study participation including screening/baseline assessments to follow-up will be 6 months.

4.2 Total Number of Subjects

A total of 250 participants will be engaged in the research at the time they seek treatment: 125 individuals will be enrolled as they engage with the mobile, rapid induction team and 125 individuals will be enrolled as they seek treatment from the BAC/CRC (treatment as usual).

4.3 Inclusion Criteria

Participants must meet the following criteria for enrollment:

- Must be 18 years of age or older
- Opioid overdose in the prior 12 months
- Meet criteria for opioid use disorder
- Resident of Philadelphia
- Willingness and ability to participate in study procedures

4.4 Exclusion Criteria

- Inability to comprehend or complete study procedures
- Plans to relocate during study time frame
- Currently in medication assisted treatment (MAT) for substance use disorder
- Evidence of serious liver disease (LFTs > 3 x the upper limit of normal)
- Pregnancy or lactation
- Moderate to severe alcohol or benzodiazepine use disorder

There will be no exclusion based on gender or race/ethnicity. The participants to be recruited are expected to reflect the demographics of previous data provided by Philadelphia Department of Health on individuals who overdosed in the city of Philadelphia. Both men and women will be recruited for this study as both are affected by opioid epidemics. No gender restrictions are to be followed at recruitment. According to the available data, we are expecting enrolling about 30% of females. Minority populations will not be excluded. We are expecting enrolling about 59% European-American/non-Hispanic, 25% African-American/non-Hispanic, 15% of Hispanic/Latino, and 1% of Native American.

4.5 Subject Recruitment

The recruitment of participants for this study will be accomplished using a community awareness campaign involving street outreach, targeted social media, and local advertisement. This campaign will begin one month before activation of the rapid induction intervention. During this time, the mobile assessment team will begin to be present in the designated location where we will park the Mobile Clinical Trials Unit (MCTU) – see picture.

The MCTU is a medical vehicle is built on a heavy-duty truck frame that contains an expandable waiting area and two private examination rooms. It has a sink area and a bathroom and is equipped with two locked refrigerators for specimen and medication storage. Dr. Ian Frank serves as the Medical Director for projects and services that take place on the MCTU. The unit is approved for use by the Pennsylvania Department of Health as a site for HIV testing and the exam rooms provide comfortable and private space for counseling, interviews, and data and specimen collections.

The two neighborhoods with the highest concentrations of opioid overdose mortality will serve as our areas for engagement: Kensington and South Philadelphia. The selection of parking l ocations for the MCTU is an important process and will be informed by issues of access to the target population, data regarding recent overdoses, and community support and permissions.

For final site selection in this project, we will build on the work recently completed by the interdisciplinary “CUES Evaluation Working Group” of faculty, fellows, and stakeholders from the city and the drug-using community. The working group was funded by a grant from the Leonard Davis Institute for Health Economics (LDI) to support the development of an objective strategy for assisting the City in identifying potential locations for Comprehensive User Engagement Sites (CUES) where injections would be supervised and access to behavioral health and housing services would be provided.

Using a mixed methods approach that combines geographic analyses and qualitative research methods, the working group asked stakeholders including municipal employees, healthcare providers, PWID, and residents from across Philadelphia for their thoughts about what features would make a location either well suited or not well suited for operating a CUES. That process revealed approximately 20 aspects of the built environment or the social environment that were used to classify each city block according to the presence or absence of each type of asset, barrier, or indicator of demand. Assets for block selection included City Council District support, condom

distribution site, MAT site, HIV testing site, opioid support site, Public Health Center, pharmacy, pharmacy with Naloxone, public transit, social cohesion and syringe exchange site. Barriers to block selection included schools, daycare centers, parks and recreation facilities, police station, fire station, alcohol outlet, gentrification pressures. Factors that indicated blocks with potential demand for the service include overdose deaths, naloxone (Narcan®) administration events, police narcotics arrest, and homeless encampments. Geocoding these location features, assigning a weight to each to represent its relative importance, and summing the values into a score produced a map of Philadelphia that identified 5 specific locations that appear to be most well suited for operating a CUES. As depicted below, among these 5 locations, 1 good site is located in South Philadelphia and 1 best sites in the Kensington neighborhood.
We believe that the factors that were developed for guiding the location of the CUES also apply to locating the MCTU for this research. The circles on the map will be our preliminary target areas for exploration and finalization during the start-up phase of the research.

4.6 Vulnerable Populations

Population protected under HHS regulations 45CFR46 Subparts B, C, & D Study Procedures: Participants who are pregnant at the time of baseline assessments will not be eligible for the study.

Populations vulnerable to undo influence or coercion: Educationally or economically disadvantaged persons are included but not solely targeted for recruitment. Cognitively impaired persons are not included in the current study.
All the participants will be drug-dependent individuals. They are considered a vulnerable population due to the risks, both perceived and real, created through the use of illegal drugs. Care will be taken to ensure that they are treated with respect and consideration throughout the study process.

4.7 Study Procedures

See Table below for a schedule of study procedures.

Day	P.S.	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	180
Pre-screening																																	
Eligibility	X																															
Screening/ Enrolment																																	
Informed consent/ HIPAA		X																														
Locator form		X								X							X							X							X	
Physical exam		X																														
Blood test – liver functions		X																														
Intervention																																
Nurse Practitioner*		X	X	X	X					X							X							X						X		
Case Manager*		X	X		X			X			X			X			X			X			X			X			X		X	
Recovery specialist*		X	X	X	X		X		X			X			X			X			X			X			X			X			
BUP/NX delivery			X							X							X							X						X		
BUP/NX dosing			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Assessment																																	
Demographic		X																														
Specific questionnaire		X																													X	X
PHQ-9 - Depression		X																													X	X
Urine drug screen		X																													X	X
HIV testing		X																														
Outcomes																																
Engagement in MAT																															X	X
Overdose																															X	X
Cost analyses																																
DATCAP																															X	X
NMOS		X																													X	X

Notes:
P.S. = pre-screening day;
* The mobile team (i.e. nurse practitioner, case manager, recovery specialist) will have contact with each participant at least 3 times per week.

4.8 Participant Screening

4.8.1 Subject recruitment

The recruitment of participants for this study will be accomplished using a community awareness campaign involving street outreach, targeted social media, and local advertisement. This campaign will begin one month before activation of the rapid induction intervention. During this time, the mobile assessment team will begin to be present in the designated location where we will park the Mobile Clinical Trials Unit (MCTU).

The MCTU is a medical vehicle is built on a heavy-duty truck frame that contains an expandable waiting area and two private examination rooms. It is approved for use by the Pennsylvania Department of Health as a site for HIV testing and the exam rooms provide comfortable and private space for counseling, interviews, and data and specimen collections. The selection of parking locations for the MCTU is an important process and will be informed

by issues of access to the target population, data regarding recent overdoses, and community support and permission. We will work with the staff of Prevention Point that has an extensive access to the neighborhood to define the best locations within the neighborhood.

4.8.2 Participant Education and the Informed Consent Process

Potential participants who express interest in initiating treatment will be engaged in a structured approach to education about the study and its procedures. The information delivered at this point will be supportive and motivational and describe study participation as an opportunity to consider options for treatment. It will also be explained that their participation can contribute to a better understanding of the most effective ways to assist individuals who want to begin treatment. Staff will make it clear that even if they do not become engaged in treatment, their experiences are important and their contributions to the research will be valuable. We will inform participants that their direct involvement in the project will last for one year and that we will want to contact them at scheduled assessment visits regardless of their treatment status. This discussion will offer potential participants a chance to ask questions and receive prepared materials explaining the study and the requirements for participation.

Those who appear to be eligible and express interest will begin the informed consent process to allow for screening. The informed consent process will give the participant an accurate understanding of the research procedures and make it clear that participation is voluntary. The informed consent document will be read and reviewed with the participant. The consent form includes clear language with special attention to the provision of permissions to contact the participant and individuals they identify as acceptable contacts if we are unable to make direct contact with the participant for the 1- and 6-month assessments. Since we will also need to confirm subsequent treatment engagement, the consent form will include permission to contact treatment providers to determine treatment status as well as permission for the Philadelphia Department of Public Health to look shared information about their subsequent use of health department services (CARES database, http://www.phila.gov/hhs/data/Pages/Cares.aspx). The consent form will also include a statement indicating that research staff will submit their names to the National Death Index for a record search should we be unable to make contact for a 90-day period.

4.8.3 Screening assessments

For those who remain interested following discussions about the and appear to meet eligibility criteria, the consent form will be signed and the screening visit will be conducted. This visit will include completion of assessments to confirm inclusion and exclusion criteria. The Nurse Practitioner will complete a medical history, a physical exam, a rapid blood test for HIV, a pregnancy test for women, and collect 10ml of blood for liver function tests. Research staff will complete baseline assessments described in section 3.7 of this protocol. Those who are not eligible will receive a listing of treatment providers and encouraged to make contact for help with their substance use problems. For those who appear eligible following the screening visit, an appointment for initiating the intervention will be scheduled within 1 or 2 days.

4.9 Study Intervention Phase

4.9.1 Overview of Interventions

Rapid Induction Intervention (RI)

The rapid induction intervention will be delivered by the project's mobile team led by a nurse practitioner supported by a certified peer recovery specialist (CPRS), and a case manager (CM). Team members will work closely with each other and coordinate screening and treatment initiation, medication adherence monitoring, and assessment and linkage to ongoing MAT. Two half-time research assistants (RA) will participate as team members but will have intervention responsibilities. The RAs will assist with the community awareness campaign and recruitment and will conduct all assessments for the project. The mobile team will be based at PPP and will receive clinical supervision from the mobile team's buprenorphine physician (David Barclay, MD). As indicated throughout this application, access to the intervention will take place on the MCTU and during home visits following telephone contact.

Induction: Once eligibility has been determined, the NP will begin preparing the participant for induction. We will follow the buprenorphine/naloxone induction protocol used by D'Onofrio et al., 2015. In this protocol, the patient must be exhibiting signs and symptoms of opiate withdrawal, e.g., sweating, lacrimation, goose flesh, rapid pulse, before the first dose is administered. Withdrawal symptoms will be measured by the Clinical Opiate Withdrawal

Scale (COWS; Wesson & Ling, 2003), an 11-item scale designed to be administered by a clinician and that can be used in both inpatient and outpatient settings to reproducibly rate common signs and symptoms of opiate withdrawal and monitor these symptoms over time. The summed score for the complete scale will be used to determine the stage of opiate withdrawal and assess the level of physical dependence on opioids. Under the supervision of the NP, COWS will be used as an objective measure of withdrawal and buprenorphine/naloxone treatment will not initiate until the COWS score falls within the 8 -12 range. If the score is below 8, participants will be asked to the COWS will be re-administered in one hour and patients will receive a careful explanation of why medications cannot be started until clear withdrawal symptoms are present. When withdrawal symptoms are sufficient to initiate medication, patients will be given a 4 mg dose. In this trial, we will use generic buprenorphine/naloxone tablets or film that are easily administered by placing the tablets or film under the tongue and waiting for them to dissolve. The COWS will be repeated in one to three hours to assess the reduction in symptoms. It is expected based upon extensive clinical practice that participants will receive relief from opiate withdrawal symptoms with 4-8 mg doses of buprenorphine/naloxone on day 1 (e.g. a total day 1 dose of 8 mg). However, additional dose(s) may be given to those participants in whom withdrawal symptoms remain after receiving 8 mg of medication. In such cases, the Nurse Practitioner will increase the dosage but no more than 16 mg of buprenorphine/naloxone will be given to a participant on day 1 of induction. As with any pharmacotherapy, the goal of buprenorphine/naloxone treatment is to use the *minimum effective* dose. The immediate goal of buprenorphine/naloxone therapy is to alleviate withdrawal symptoms, with longer-term goals of reducing drug craving, and reducing or eliminating use of opioids. If patients have problems adjusting to buprenorphine/naloxone (e.g., experience persistent withdrawal symptoms or continue to feel compelled to use illicit drugs), the dose may need to be increased. After stabilization, a three-day supply will be provided to the participant with simple instructions for self-administration.

For those who fail to reach threshold for beginning induction while the mobile team is present and the participant in judged by the Nurse Practitioner to be appropriate for self-induction instructions for medication administration will be provided. This “self-induction” procedure has now become quite common (Lee, Vocci, & Fiellin, 2014).

Participants will be asked to maintain contact with the NP on the morning of the following day to assess symptoms of withdrawal. If the participant is not in withdrawal on the morning of day 2, the day 1 dosage will be maintained. If the participant reports feelings of lethargy or sedation, on the next morning the day 2 dosage will be reduced.by 2mgs. If the participant reports feelings of withdrawal on the morning of the second, day the day 2 dosage will be increase by 4mgs.

The final day of dose adjustment will typically be day 3. On the morning of day 3, the participant will be assessed by the NP for signs of sedation or withdrawal and adjust dosages accordingly. Once the stable dose has been determined, the participant will be given a one-week supply of medication and scheduled for an appointment the following week for assessment by the NP and receipt of the second week of medication. This procedure will be continued for the remainder of the treatment month. Participants will meet with the NP weekly, and be invited to have telephone contact as needed.

MAT engagement during the month of intervention will be facilitated by the Peer Recovery Specialist (PRS). The purpose of a PRS is to support the participant in their recovery process. In addition, the project will provide intensive training and ongoing consultation on MAT. The PRS hired for this study will also receive intensive training focused on addiction as a chronic medical condition, motivational enhancement strategies and facilitating short-term behavioral contracts. The PRS will meet with the participant a minimum of 3 times per week and be available for telephone counseling and support throughout the one-month intervention period.

The mobile team’s Case Management (CM) function will be performed by a master’s level social worker. The CM will have primary responsibility for identifying the treatment program that best meets the needs of the participant. The CM effort will be sharply focused on identifying and removing barriers to MAT treatment engagement. This will include completing medication authorization forms and insurance enrollment if necessary, and then making referrals to additional supports, including mental health treatment, housing, medical, legal support, and peer-based recovery supports in the community. The CM will work collaboratively with participants to remove barriers to care and to enhance program outcomes and to provide psychosocial support.

The mobile team will insure that there is a clear plan for rapid engagement with ongoing treatment as soon as possible. Buprenorphine/naloxone will be provided during the time of transition to their long-term provider for up to 1 month. Telephone support will be available should participants have questions or need assistance and the mobile team will also have daily contact with participants until they complete contact with their ongoing provider.

Comparison group – Treatment as usual
During the same period of time, participants will also be recruited at the City of Philadelphia Behavioral Health System Behavioral Assessment Centers (BAC) and Crisis Response Centers (CRC) located at Episcopal Hospital serving Kensington area and Hall Mercer BAC/CRC (a University of Pennsylvania program) serving South Philadelphia area. Two research assistants from the TRI-PHMC will enroll and follow-up 125 participants at BAC/ CRC. The participants will complete the same assessments at baseline, 1- and 6-month follow-up. Authorization for the Philadelphia Department of Public Health to look shared information about their subsequent use of health department services (CARES database, http://www.phila.gov/hhs/data/Pages/Cares.aspx) will also be requested in the consent form. Research staff will only conduct assessments. Treatment engagement services will be provided by the staff of the BAC/CRC as usual.

4.10 Subject Withdrawal

Participants may choose to withdraw from the study at any time. They do this by providing verbal or written communication to this effect. Withdrawal from the study will not impact access to care. The Principal Investigator may withdraw subjects for reasons related to safety or for administrative reasons. It will be documented whether or not each subject completes the study. Subjects who do not complete the intervention will continue to be contacted to complete follow-up visits (Month 1 and 6) to collect final evaluations and assess adverse events.

5 Statistical Plan

5.1 Data Quality

Trained staff will review all forms prior to the completion of the study visit in an effort to minimize problems associated with missing values and incorrect skip patterns. All assessments will be recorded on final version of the electronic Case Reporting Forms (eCRFs). eCRFs will also be developed to capture the results of all biological assessments. All eCRFs will be completed 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 will be responsible for entering all data into the secure web-based developed on REDCap (Research Electronic Data Capture). REDCap is designed to comply with HIPAA regulations. Data will be input with secure web authentication, data logging, and Secure Sockets Layer (SSL) encryption. REDCap allows multisite access. It allows real-time data entry validation (e.g. for data types and range checks), audit trails, and the ability to set up a calendar to schedule and track critical study events such as participant visits.
The data quality control process associated with data processing will consist of the following stages: potential subject pre-screening for eligibility, registration, subject eligibility confirmation, first data entry, second data entry in the form of 100% interactive verification, data validation, and data auditing. A random 5% of the questionnaires in each wave of data collection (i.e., baseline, 1- and 6-month) will be subjected to database auditing throughout the trial. This data quality control process ensures that all stages of the data handling process will be subjected to data quality control.

5.2 Sample Size and Power Determination

Our power analysis has been based on this primary aim. Our primary hypothesis is that participants who received rapid induction will more likely be engaged in ongoing treatment at 1- and 6-month follow-up than participants who sought treatment at BAC/CRC. We will test this hypothesis at a 5% level of significance. Our principal interest is in the comparison of engagement rates between the mobile intervention and BAC/CRC groups, at months 1 and 6. Preliminary data suggest an engagement rate of about 20-30% in the BAC/CRC group. Assuming a steady loss to attrition that yields 80% completers, and a within-subject correlation of 0.3, the methods of Diggle et al. (Diggle, Heagerty et al. 2002) show that our sample size of 125 in each group yields 80% power for differences of about 15% in engagement rates between the two groups (e.g., 80% power for BAC/CRC: 25% vs. Mobile: 40%, corresponding to a RR=1.6 and an OR=2.0)

5.3 Statistical Methods

Propensity score model to account for non-randomized allocation: The participants are not randomly assigned to the mobile rapid induction intervention and BAC/CRC groups, so it is possible that there will be confounding of the group effect with the effects of characteristics of the participants. We will use a propensity score approach (Rosenbaum 2002, Rothman, Greenland et al. 2008) to account for this. We will use a broad range of baseline variables as covariates in a logistic regression model predicting treatment group, including age, race/ethnicity, gender, number of previous overdoses, number of previous treatments for opiate use disorder, type of opioid used, and depression. The model will yield predicted probabilities of BAC/CRC group for all participants (the propensity score), and we will create a five-level ordinal variable based on the quintiles of the propensity score. We will then include this ordinal variable as a stratum variable in our models.

Analyses for the primary aim: i.e. *to evaluate the impact of the mobile, transitional MAT intervention on its ability to engage participants in targeted, existing MAT treatment slots at 1- and 6-month post-enrollment.* For each of the 1- and 6-month time points, we will classify participants as being engaged/not-engaged (where non-engaged will include dropped out or missing). We will compare the groups on engagement rates at the two time points using a repeated measures logistic regression model, incorporating the propensity score as described above (Diggle, Heagerty et al. 2002). The fixed effects will be binary indicators of treatment group and time point; we will test for a group by time interaction to assess whether the group effect differs at month 1 and month 6. As there are only two time points, we will use an unstructured covariance matrix to accommodate within-participant covariance.

Analyses for Aim 2: We will also use a repeated measures model to compare the groups on the ASI drug composite score at months 1 and 6. The model will be similar to that described for the engagement analyses of Aim 1, but with a beta distribution assumed for the response, to accommodate the bounded range (zero to one) of the ASI composite scores. We will compare the groups on the number of overdoses per patient using repeated measures Poisson regression models, if there is sufficient variability in the number of overdoses reported. If a low rate of overdoses causes convergence issues for the Poisson model, we will classify participants as having no overdoses versus at least one, and compare the groups using repeated measures logistic regression models.

Missing data. For the longitudinal analyses described above, premature discontinuation from treatment and occasional missing daily use indicators will lead to incomplete data. The repeated measures models described above can make use of all available data provided by subjects, but the inferences drawn from them will be unaffected by the missing data only if the missing data can be regarded as ignorable, essentially meaning that missingness can be predicted/explained from the baseline data and from responses obtained prior to drop-out. We will assess the sensitivity of our main analyses to the presence of missing data by performing a sensitivity analysis, in which we will obtain estimates of the group effect under various non-ignorability assumptions. We will use selection models to examine the effects of missing data (Robins, Rotnitzky et al. 1995), in which we will explicitly model the probability of premature discontinuation at a time point as a function of baseline characteristics and responses at previous time points, using logistic regression models, and incorporate the predicted probabilities into a weighted analysis of the main hypotheses.

Analyses for Aim 3: We will estimate the total costs and per-participant costs of rapid initiation of MAT for opioid treatment engagement and use a cost-offsets approach to determine the economic value of this novel strategy. A cost-offsets approach requires a comparison of the total cost of the intervention (proposed enhanced procedure or treatment as usual) to the future costs of healthcare utilization avoided (i.e., benefits) due to the intervention. Healthcare utilization and medical costs will be estimated before and after participants receive either rapid initiation of MAT for opioid treatment engagement or treatment as usual. Information on healthcare utilization will be collected from participants at each assessment when study-staff administer the Non-Medical and Other Services Form (NSMOS; detailed description in Instruments section). Medical costs associated with these treatments/services will be estimated using Medicaid data. Costs of the intervention will be collected by Julie Becher, PhD, using the Drug Abuse Treatment Cost Analysis Program (DATCAP; detailed description in instruments section). She will interview staff in order to collect information on economic resource and cost variables such as staff salaries and benefits, study supplies and materials, major equipment, contracted services, building and facilities, and miscellaneous resources and costs. Recognizing that full-time staff members may devote only part of their work time to the proposed study, she will conduct a time-in-motion study with relevant study staff in order to track their time devoted to this study. Adjustments will then be made to salaries and benefits to reflect appropriate compensation attributed to this study. Similar adjustments will be made to reflect the time that some equipment, buildings and facilities, and miscellaneous resources and costs are attributed to the proposed study.

Differences in pre-post medical costs will be used as an estimate of the value of downstream costs avoided due to the intervention. We will compare these differences across groups for statistical significance. We hypothesize that the medical costs after the intervention will be significantly lower for the participants that receive rapid initiation of MAT for opioid treatment than for the participants that receive treatment as usual. The economic value of this novel intervention will be positive if the costs of this novel intervention are outweighed by the medical cost savings that result from participants obtaining long-term and consistent opioid treatment. The proposed intervention is expected to aid with this process. Therefore, we hypothesize that the cost of rapid initiation of MAT for opioid treatment will be outweighed by the resulting avoidance of healthcare utilization costs.

We conduct our cost analyses from the perspective of the City of Philadelphia Department of Public Health since they may decide to scale-up the proposed services for other Philadelphia residents at risk of substance use overdose. Thus, we focus on healthcare utilization costs avoided as benefits of the proposed services. We may extend our analysis later to use a societal perspective that would consider other economic costs, such as criminal justice costs, unemployment costs, and participant costs (e.g., travel, work time missed, childcare expenses, etc.). Inclusion of the economic costs avoided due to opioid use disorder treatment will make the economic value of the proposed intervention even more positive than it is hypothesized to be when considering only healthcare utilization costs avoided due to opioid use disorder treatment.

6 Safety and Adverse Events

6.1 Data Safety Monitoring Plan (DSMP)

For this study, we will use established University of Pennsylvania procedures and infrastructure for data and safety monitoring. During the course of the study, safety and data quality monitoring will be performed on an ongoing basis by the Principal Investigators and the study staff. Study staff members are responsible for collecting and recording all clinical data using the established MOP. This includes ensuring that all source documents exist for the data on the Case Report Forms, ensuring all fields are completed appropriately, and ensuring that all corrections are done according to Good Clinical Practice (GCP). Any inconsistencies/deviations will be documented. The study Key Personnel will review data on an ongoing basis and will document reviews by initialing and dating reports. Study staff members conduct 100% quality assurance on data.
Staff training will consist of an explanation of the protocol and review of the e-Case Report Forms. In addition, the duties of each staff person will be outlined and all applicable regulations will be reviewed. Senior personnel will supervise junior staff and provide re-training in the study protocol as needed.

The Independent Monitor for this study is the University of Pennsylvania Center for Studies on Addiction DSMB. The DSMB will review the study every 6 months for all the duration of the study. The DSMB form could be find in Appendix at the end of this document. The PI will provide a summary of the status of the project that occurs during the reporting period. These data will also be reported to CDC on an annual basis as part of the progress report. The DSMB report will include the participants' socio-demographic characteristics, expected versus actual recruitment rates, treatment retention rates, any quality assurance or regulatory issues that occurred during the past year, summary of SAEs, and any actions or changes with respect to the protocol.

6.2 Adverse Events

Adverse events that occur at any point in the trial will be identified, managed, and documented in accordance with reporting requirements of the the City IRB (the IRB of record) and the sponsor (the CDC). Adverse events are defined as negative biologic events and/or social harms that occur during the course of the trial. When needed, referrals to medical treatment or specialists will be made. All patients will have comprehensive psychiatric and medical screening prior to randomization and at each counseling and assessment where evaluations for AEs will be routine. A member of the research team will be available at all times to answer questions and assess possible AEs. Participants will be withdrawn from the study if they show severe deterioration or if determined clinically necessary for other reasons.

<u>Documenting Adverse and Other Negative Events</u>
We will document adverse events. The study will use an ANEF (Adverse and Negative Events Form), so that the distinction between an "adverse event" a "serious adverse event" (such as hospitalization or death), and a "negative event" (i.e., not meeting the criteria for adverse event) will be recorded. All adverse events will be documented on this form (along with a description of measures taken in response to the event). Each time an adverse or serious negative event is identified, the project staff member who identified the event will complete an ANEF. The report form will include date, description of the event, duration, severity, measures used to ameliorate effects of the event,

and type of referral. Dr. Metzger will be notified immediately. The report form will be reviewed and signed by him and he will be responsible for ensuring that appropriate actions have been taken.

In the event of a serious adverse event or a serious negative event, the Principal Investigator, Dr. Metzger will be notified via telephone or email within 8 hours of the event. The Principal Investigator will report the event to University of Pennsylvania IRB within 48 hours. If a serious adverse event occurs, the PIs will inform and consult with the Institutional Review Board within 24 hours of that event.

Responding to Participant Needs Due to Adverse or Other Negative Events
In all reports of adverse events, the research team's first priority will be to ensure that appropriate responses to address the stated problem have been made. The project team has the ability to ensure access to available medical and social services. Staff will maintain contact with the participant until the problem is resolved or properly managed.

6.3 Internal Monitoring and Auditing

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. Ongoing assessments of the data quality and timeliness will be undertaken. Participant recruitment and retention will be reviewed formally on a monthly basis. Scientific or therapeutic developments that may have an impact on the safety of the participants or ethics of the trial will also be considered on an ongoing basis. Weekly meetings will be held to monitor the progress of the trial. These meetings will involve the Principal Investigators, Co-Investigators, Project Director, Site coordinator and other study staff. 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 in order to maintain a consistently high quality of study conduct. Concerns identified will be addressed through training and retraining of personnel.

The study will be monitored by the PIs and co-investigators, and regulatory committees at Philadelphia Department of Public Health Institutional Review Board and University of Pennsylvania (i.e., IRBs, OHR). The following monitoring activities will be conducted according to standard operating procedures. These activities will be performed in association with database auditing and facilities monitoring by the PENN OHR and/or study staff.

Database Auditing: Project director and RAs will review data entered into the database versus that recorded on the CRFs. All accrued cases will be subjected to database auditing throughout the duration of the trial. Depending on the data management findings, re-training will be provided, should problems such as increased errors be detected.

Data Auditing: Project director and staff RAs will review safety data recorded on the CRF versus that contained on the actual source document (client chart, EHR). All accrued cases will be subjected to auditing throughout the duration of the trial. A Regulatory Binder Review by OHR will include the following essential documents: IRB Protocol, Consent Form and Amendment Approvals, IRB Closure Letter, List of Authorized Signatures, Laboratory Certifications, Protocol and Amendment Signature Pages, Financial Disclosure Questionnaires, and Monitoring Log. Additional monitoring by OHR may include: source documentation verification; adverse event documentation; and facility assessment.

Data Security: Using network firewall technologies, the database will prevent the three major sources of data security problems: unauthorized internal access to data, external access to data, and malicious intent to destroy data and systems. Controlled user access will ensure that only appropriate and authorized personnel are able to view, access, and modify trial data. All modifications to data will document user access and data associated with the modification, as well as values prior to modification.

Evidence of Training in Human Subject Research: All personnel working on this project will be required to review the protocol, complete training in the protection of human subjects and undergo training.

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.). Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

7 Study Administration, Data Handling and Record Keeping

7.1 Confidentiality

Since self-report and medical data will be collected and stored as part of this study, it is possible that subject privacy or confidentiality can be threatened. To address this concern, the Data Management System has set up several safeguards to prevent unauthorized access to study data. An automatically generated index number is assigned to a subject's study identification number (unique for personnel and clients). A linked subject identification table is created for the storing of subject name, address and telephone contact information. This table uses the automatically generated index number rather than the study identification number. The master subject map and subject identification information tables are maintained in a separate database. Using this method, no identifying subject information is directly linked to medical information or other study data. For our multi-site trials, we have long-established protocols to guard against improper use of hard copies of data (e.g., locked files, numeric coding procedures). The present research team has not experienced the unauthorized use of study data. A web-based data collection procedure will minimize the possibility of loss of privacy or confidentiality. The risk of a potential breach of confidentiality is addressed in the informed consent documents.

7.2 Sources of Research Material

All information will be derived from biological tests, standard clinical procedures, standardized interviews, and self-report questionnaires. All subjects will receive a unique participant number that will be kept separate from any personal information that includes identifying variables such as name, address, relatives, place of work, etc. It is necessary for subject retention that personally identifying material be kept.

7.3 Computers and Databases

Trained staff will review all forms prior to the completion of the study visit in an effort to minimize problems associated with missing values and incorrect skip patterns. All assessments will be recorded on final version of the electronic Case Reporting Forms (eCRFs). eCRFs will also be developed to capture the results of all biological assessments. All eCRFs will be completed 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 will be responsible for entering all data into the secure web-based developed on REDCap (Research Electronic Data Capture). REDCap is designed to comply with HIPAA regulations. Data will be input with secure web authentication, data logging, and Secure Sockets Layer (SSL) encryption. REDCap allows multisite access. It allows real-time data entry validation (e.g. for data types and range checks), audit trails, and the ability to set up a calendar to schedule and track critical study events such as participant visits.

8 Ethical Considerations

8.1 Risks

The risks to participants in this study are related to: 1) side effects of buprenorphine/naloxone, 2) negative reactions to the questions asked, and, 3) violations of confidentiality and unwanted disclosures.

- Risks associated with taking buprenorphine/naloxone: Because the medicine must be dissolved under your tongue, it may cause some mild irritation or leave a bad taste in your mouth. The most common side effects of this FDA approved medication are headaches, pain, sweating, nausea, sleeping problems, stomach pains and constipation. Buprenorphine/naloxone may impair mental and physical abilities involved in activities such as driving or operating machinery. Buprenorphine/naloxone can cause breathing difficulties especially when mixed with other drugs like alcohol or benzodiazepines. The combination of buprenorphine/naloxone and alcohol is dangerous and combined use with benzodiazepines has been known to cause death. In rare cases, individuals have had allergic reactions to buprenorphine such as itching or rashes.

- Unpleasant reactions to the assessment: The questions about sexual activity and drug use might make some participants feel uncomfortable or embarrassed.

- Unwanted disclosure: It is possible that others might determine that an individual is in a study about treatment of opioid use disorder and assume that they are a drug user. Some may react negatively and treat the participant unfairly, including family members and people in the community.

8.2 Risk Minimization

The following methods will be employed to minimize participant risk.

Oversight and Monitoring: The PENN IRB will monitor the protection of human subjects and the safe and secure collection and storage of data. This committee assesses all studies before study initiation and then reviews protocols annually. The committee ensures the scientific, technical, and statistical soundness of the research and guarantees that methods for the ethical and safe treatment of human subjects are in place. The committee scrutinizes the scientific and ethical aspects of protocols and provides for an objective and ongoing assessment of the study's scientific and ethical integrity. We will comply with all of the data and safety procedures outlined in the Data Safety Monitoring Plan and will seek regular recruitment advice from our Community Advisory Council.

Quality Assurance Procedures and Participant Confidentiality: All subjects will be screened for eligibility using formal study forms and the Principal Investigator will regularly audit accrual to ensure that participants meet eligibility criteria. In addition, the Study Coordinator will audit all study files to ensure that questionnaires completed by subjects contain all items. Lastly, to protect confidentiality, all data will be numerically coded and information linking the numeric code to the subject's name will be kept in a secured file cabinet and office. In addition, computer data files will be stored on password-protected computers and communication among the staff will use participant code numbers, not names. No information concerning data will be presented with participant names. Data will be collected in a private room or via telephone.

Undue Influence/Coercion and Enrollment Status: In order to protect personnel participants from possible undue influence and coercion regarding enrollment in our study, the voluntary nature of the study is stressed throughout the informed consent documents.

Adverse Event Reporting: In accordance with IRB guidelines, this protocol will employ the following mechanisms for adverse event reporting: 1) alert the IRB of any and all reports of serious adverse events; 2) informing all members of the study team of any and all reports of serious adverse events; and 3) notification to NIH of any actions taken by the IRB with regard to data safety monitoring.

8.3 Benefits

The potential benefits of this study outweigh the potential risks. The study provides one-month of comprehensive treatment for opiate use disorder free of charge and link them to ongoing treatment.

8.4 Informed Consent Process / HIPAA Authorization

Subjects will hear a study description where all study procedures, risks, and information about the study medication will be reviewed. Subject questions will be answered. Following this presentation, the combined informed consent and HIPAA form will be completed by participants.

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

The following personal health information will be collected as part of this study:

1. Name
2. Address
3. Date of Birth
4. Phone number(s)
5. Electronic mail address

6. Dates of procedures and events (such as hospital admissions and discharges) relevant to side effect and adverse event reporting

The following individuals and organizations may use or disclose personal health information:

- The Principal Investigator (PI) and research staff
- The Philadelphia Department of Public Health Institutional Review Board
- The University of Pennsylvania Office of Regulatory Affairs
- The University of Pennsylvania Office of Human Research (the office that monitors research studies)

The Principal Investigators or research staff will inform participants if there are any changes to the list above during their active participation in the trial.

Authorization for use of personal health information for this specific study does not expire while the study is no longer active (about 3 years). Paper research records are saved in an archive for 3 more years and are then destroyed. Study participant contact information may be held in a research database. However, the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- The participant has given written authorization
- The University of Pennsylvania or the Philadelphia Department of Public Health Institutional Review Boards grant permission
- As permitted by law

9 Resources Necessary for Human Research Protection

9.1 Qualifications of principal investigator

David S. Metzger Ph.D. (Principal Investigator): Dr. David Metzger, Ph.D. is Research Professor and Director of the HIV Prevention Research Division in the Department of Psychiatry of the Perelman School of Medicine at the University of Pennsylvania. Dr. Metzger is currently the Co-Director of the Penn Mental Health AIDS Research Center and Director of its Developmental Core. He is Director of the Prevention Science and Community Engagement Core of the Penn Center for AIDS Research and the Co-Director of the Prevention Clinical Research Site of the Penn Clinical Trials Unit funded by NIAID. He began conducting research on the efficacy of substance abuse treatment in 1978. Since 1989, he and colleagues from the HIV Prevention Research Division have been conducting AIDS related longitudinal trials among individuals at high risk of infection as well as those living with HIV. Dr. Metzger's research division has developed innovative community-based strategies for recruiting and retaining individuals into prospective research and clinical trials of biomedical and behavioral prevention interventions. He has led HIV prevention and treatment studies on agonist treatments and counseling strategies for opioid injectors in Philadelphia, China, Thailand, Vietnam and Indonesia. An overarching objective of his work has been to provide valid and reliable data that can increase understanding of the public health impact of participation in substance abuse treatment. Currently, his work involves studies focused on understand the intersecting opioid and HIV epidemics in the US and testing strategies for the integration of the treatments for substance use disorders within HIV treatment and primary care settings.

9.2 Research Staff

The following research staff will be directly involved with the implementation and execution of the current study

Name	Study Role
David Metzger, PhD	Principal Investigator, University of Pennsylvania
David Barclay, MD	Study physician, Prevention Point Philadelphia
Jose Benitez, MSW	Site supervisor, Prevention Point Philadelphia
Travis Cos, PhD	Co-investigator, Public Health Management Corporation
Karen Dugosh, PhD	Co-investigator, Site supervisor, Public Health Management Corporation
David Festinger, PhD	Co-investigator, Public Health Management Corporation
Kyle Kampman, MD	Co-investigator and study expert physician, University of Pennsylvania
Julie Kraut-Becher, PhD	Co-investigator and health economist, University of Pennsylvania
Kevin Lynch, PhD	Co-investigator and Statistician, University of Pennsylvania
Kendra Viner, PhD, MPH	Co-investigator, Philadelphia Department of Public Health
Brook Burkley, MSW	Research coordinator, Public Health Management Corporation
Cecile Denis, PhD	Research Project Director, University of Pennsylvania
Deb Dunbar, NP	Nurse Practitioner, University of Pennsylvania
Tiffany Dominique, BA	Research Assistant, University of Pennsylvania
Danielle Fiore, BS	Database Manager, University of Pennsylvania
Lia Pizzicato, MPH	Database analyst, Philadelphia Department of Public Health
TBN	Research assistant, University of Pennsylvania
TBN	Nurse Practitioner, Prevention Point Philadelphia
TBN	Certified Recovery Specialist, Prevention Point Philadelphia
TBN	Case Manager, Prevention Point Philadelphia
TBN	Research Assistant, Public Health Management Corporation

10 Study Finances

10.1 Funding Source

This study is funded through a grant from the Center for Disease Control and Prevention to the University of Pennsylvania. This study has a sub-contract with Prevention Point Philadelphia and another sub-contract with Public Health Management Corporation. Dr. Metzger will oversee all the finances.

10.2 Conflict of Interest

All investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research. All Public Health Management Corporation and Prevention Point investigators will sign an agreement to follow the University of Pennsylvania rules.

10.3 Subject Compensation

All participants will be compensated for participation (see Participant Compensation Schedules below). Compensation will be provided via debit card activated following completion of assessment visit.

Participant Compensation Schedule Compensation Schedule			
Session	**Time Point**	**Time and Effort Reimbursement**	**Travel reimbursement**
1	Baseline	$30	$5
3	Week 4	$30	$5
8	Week 24	$30	$5
Total		**$90**	**$15**

11 Publication Plan

We will follow standard methods for publishing the results of this study and in accordance with any publication policies of the University, Department, Division or Research Center. Generally, University of Pennsylvania recommends that its researchers share data through communication channels such as speaking engagements and publications, postings on laboratory or institutional webpages, or data archives or enclaves, as appropriate. Because of the breadth and diversity of research supported by the NIH, the agency does not prescribe the formatting, presentation or mode of communication for research findings. However, it expects that data will be shared in a timely manner, typically no later than the acceptance for publication of the main findings from the final dataset.

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer reviewed scientific or medical journal. Dr. David Metzger will be the last author on abstracts and publications of the clinical data generated from this study. The investigators involved in the proposed protocol will fully adhere to the timeline stipulated in the NIH policy of dissemination of clinical trial information and publicly disseminate the research observations within 30 months from completion of the study. In addition, the investigators will ensure that the clinical trial as funded by the proposed award is registered and results information is submitted to ClinicalTrials.gov.

12 References

1. American Society of Addiction Medicine. (2014). "Treating opioid addiction as a chronic disease." from https://www.asam.org/docs/default-source/advocacy/cmm-fact-sheet---11-07-14.pdf.
2. Auriacombe, M., M. Fatseas, J. Dubernet, J. P. Daulouede and J. Tignol (2004). "French field experience with buprenorphine." Am J Addict **13 Suppl 1**: S17-28.
3. Auriacombe, M., P. Franques and J. Tignol (2001). "Deaths attributable to methadone vs buprenorphine in France." JAMA **285**(1): 45.
4. Auriacombe, M., F. Serre, C. Denis and M. Fatseas (2018). Diagnosis of Addictions. The Routledge Handbook of the Philosophy and Science of Addiction. H. Pickard and S. Ahmed, Routlege**:** 132-144.
5. Bachhuber, M. A., C. Thompson, A. Prybylowski, J. Benitez, S. Mazzella and D. Barclay (2018). "Description and outcomes of a buprenorphine maintenance treatment program integrated within Prevention Point Philadelphia, an urban syringe exchange program." Subst Abus: 1-22.
6. Baser, O., M. Chalk, D. A. Fiellin and D. R. Gastfriend (2011). "Cost and utilization outcomes of opioid-dependence treatments." Am J Manag Care **17 Suppl 8**: S235-248.
7. Belenko, S., M. Hiller and L. Hamilton (2013). "Treating substance use disorders in the criminal justice system." Curr Psychiatry Rep **15**(11): 414.
8. Blum, K., M. Gold, H. W. Clark, K. Dushaj and R. D. Badgaiyan (2016). "Should the United States Government Repeal Restrictions on Buprenorphine/Naloxone Treatment?" Subst Use Misuse **51**(12): 1674-1679.
9. Bretteville-Jensen, A. L., M. Lillehagen, L. Gjersing and J. B. Andreas (2015). "Illicit use of opioid substitution drugs: prevalence, user characteristics, and the association with non-fatal overdoses." Drug Alcohol Depend **147**: 89-96.
10. Caudarella, A., H. Dong, M. J. Milloy, T. Kerr, E. Wood and K. Hayashi (2016). "Non-fatal overdose as a risk factor for subsequent fatal overdose among people who inject drugs." Drug Alcohol Depend **162**: 51-55.
11. Centers for Disease Control and Prevention. (2018). "Drug overdose death data." from https://www.cdc.gov/drugoverdose/data/statedeaths.html.
12. Cunningham, C. O., R. J. Roose, J. L. Starrels, A. Giovanniello and N. L. Sohler (2013). "Prior buprenorphine experience is associated with office-based buprenorphine treatment outcomes." J Addict Med **7**(4): 287-293.
13. D'Onofrio, G., M. C. Chawarski, P. G. O'Connor, M. V. Pantalon, S. H. Busch, P. H. Owens, K. Hawk, S. L. Bernstein and D. A. Fiellin (2017). "Emergency Department-Initiated Buprenorphine for Opioid Dependence with Continuation in Primary Care: Outcomes During and After Intervention." J Gen Intern Med **32**(6): 660-666.
14. D'Onofrio, G., P. G. O'Connor, M. V. Pantalon, M. C. Chawarski, S. H. Busch, P. H. Owens, S. L. Bernstein and D. A. Fiellin (2015). "Emergency department-initiated buprenorphine/naloxone treatment for opioid dependence: a randomized clinical trial." JAMA **313**(16): 1636-1644.
15. Daniels, A. M., E. Salisbury-Afshar, A. Hoffberg, D. Agus and M. I. Fingerhood (2014). "A novel community-based buprenorphine program: client description and initial outcomes." J Addict Med **8**(1): 40-46.
16. Dennis, B. B., L. Naji, M. Bawor, A. Bonner, M. Varenbut, J. Daiter, C. Plater, G. Pare, D. C. Marsh, A. Worster, D. Desai, Z. Samaan and L. Thabane (2014). "The effectiveness of opioid substitution treatments for patients with opioid dependence: a systematic review and multiple treatment comparison protocol." Syst Rev **3**: 105.
17. Department of Drug and Alcohol Programs. (2018). "The Department's focus on addressing overdose." from http://www.ddap.pa.gov/overdose/Pages/Department%20Focus%20on%20Addressing%20Overdose.aspx.
18. Diggle, P. J., P. Heagerty, K.-Y. Liang and S. L. Zeger (2002). Analysis of Longitudinal Data (2nd edition), Oxford.
19. Dupouy, J., A. Palmaro, M. Fatseas, M. Auriacombe, J. Micallef, S. Oustric and M. Lapeyre-Mestre (2017). "Mortality Associated With Time in and Out of Buprenorphine Treatment in French Office-Based General Practice: A 7-Year Cohort Study." Ann Fam Med **15**(4): 355-358.
20. Fairbairn, N., P. O. Coffin and A. Y. Walley (2017). "Naloxone for heroin, prescription opioid, and illicitly made fentanyl overdoses: Challenges and innovations responding to a dynamic epidemic." Int J Drug Policy **46**: 172-179.
21. Fatseas, M. and M. Auriacombe (2007). "Why buprenorphine is so successful in treating opiate addiction in France." Curr Psychiatry Rep **9**(5): 358-364.

22. Faulkner-Gurstein, R. (2017). "The social logic of naloxone: Peer administration, harm reduction, and the transformation of social policy." Soc Sci Med **180**: 20-27.
23. Fox, A. D., A. Chamberlain, T. Frost and C. O. Cunningham (2015). "Harm Reduction Agencies as a Potential Site for Buprenorphine Treatment." Subst Abus **36**(2): 155-160.
24. Fox, A. D., A. Chamberlain, N. L. Sohler, T. Frost and C. O. Cunningham (2015). "Illicit buprenorphine use, interest in and access to buprenorphine treatment among syringe exchange participants." J Subst Abuse Treat **48**(1): 112-116.
25. Fox, A. D., N. L. Sohler, T. Frost, C. Lopez and C. O. Cunningham (2017). "Development and evaluation of a community-based buprenorphine treatment intervention." Harm Reduct J **14**(1): 23.
26. Hartung, D. M., D. McCarty, R. Fu, K. Wiest, M. Chalk and D. R. Gastfriend (2014). "Extended-release naltrexone for alcohol and opioid dependence: a meta-analysis of healthcare utilization studies." J Subst Abuse Treat **47**(2): 113-121.
27. Holder, H. D. (1998). "Cost benefits of substance abuse treatment: an overview of results from alcohol and drug abuse." J Ment Health Policy Econ **1**(1): 23-29.
28. Holder, H. D. and J. O. Blose (1992). "The reduction of health care costs associated with alcoholism treatment: a 14-year longitudinal study." J Stud Alcohol **53**(4): 293-302.
29. Hser, Y. I., E. Evans, D. Huang, R. Weiss, A. Saxon, K. M. Carroll, G. Woody, D. Liu, P. Wakim, A. G. Matthews, M. Hatch-Maillette, E. Jelstrom, K. Wiest, P. McLaughlin and W. Ling (2016). "Long-term outcomes after randomization to buprenorphine/naloxone versus methadone in a multi-site trial." Addiction **111**(4): 695-705.
30. Huhn, A. S., D. A. Tompkins and K. E. Dunn (2017). "The relationship between treatment accessibility and preference amongst out-of-treatment individuals who engage in non-medical prescription opioid use." Drug Alcohol Depend **180**: 279-285.
31. Johnson, R. E., E. C. Strain and L. Amass (2003). "Buprenorphine: how to use it right." Drug Alcohol Depend **70**(2 Suppl): S59-77.
32. Kelty, E. and G. Hulse (2017). "Fatal and non-fatal opioid overdose in opioid dependent patients treated with methadone, buprenorphine or implant naltrexone." Int J Drug Policy **46**: 54-60.
33. Kimber, J., S. Larney, M. Hickman, D. Randall and L. Degenhardt (2015). "Mortality risk of opioid substitution therapy with methadone versus buprenorphine: a retrospective cohort study." Lancet Psychiatry **2**(10): 901-908.
34. Kirane, H., M. Ketteringham, S. Bereket, R. Dima, A. Basta, S. Mendoza and H. Hansen (2016). "Awareness and Attitudes Toward Intranasal Naloxone Rescue for Opioid Overdose Prevention." J Subst Abuse Treat **69**: 44-49.
35. Knudsen, H. K. (2015). "The Supply of Physicians Waivered to Prescribe Buprenorphine for Opioid Use Disorders in the United States: A State-Level Analysis." J Stud Alcohol Drugs **76**(4): 644-654.
36. Knudsen, H. K., J. R. Havens, M. R. Lofwall, J. L. Studts and S. L. Walsh (2017). "Buprenorphine physician supply: Relationship with state-level prescription opioid mortality." Drug Alcohol Depend **173 Suppl 1**: S55-s64.
37. Lee, J. D., F. Vocci and D. A. Fiellin (2014). "Unobserved "home" induction onto buprenorphine." J Addict Med **8**(5): 299-308.
38. Mammen, K. and J. Bell (2009). "The clinical efficacy and abuse potential of combination buprenorphine-naloxone in the treatment of opioid dependence." Expert Opin Pharmacother **10**(15): 2537-2544.
39. Mattick, R. P., C. Breen, J. Kimber and M. Davoli (2014). "Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence." Cochrane Database Syst Rev(2): CD002207.
40. McLellan, A. T., D. C. Lewis, C. P. O'Brien and H. D. Kleber (2000). "Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation." JAMA **284**(13): 1689-1695.
41. Morgan, J. R., B. R. Schackman, J. A. Leff, B. P. Linas and A. Y. Walley (2018). "Injectable naltrexone, oral naltrexone, and buprenorphine utilization and discontinuation among individuals treated for opioid use disorder in a United States commercially insured population." J Subst Abuse Treat **85**: 90-96.
42. Nielsen, S., B. Larance, L. Degenhardt, L. Gowing, C. Kehler and N. Lintzeris (2016). "Opioid agonist treatment for pharmaceutical opioid dependent people." Cochrane Database Syst Rev(5): CD011117.
43. Orman, J. S. and G. M. Keating (2009). "Buprenorphine/naloxone: a review of its use in the treatment of opioid dependence." Drugs **69**(5): 577-607.
44. Parthasarathy, S., C. Weisner, T. W. Hu and C. Moore (2001). "Association of outpatient alcohol and drug treatment with health care utilization and cost: revisiting the offset hypothesis." J Stud Alcohol **62**(1): 89-97.
45. Peters, R. H., M. S. Young, E. C. Rojas and C. M. Gorey (2017). "Evidence-based treatment and supervision practices for co-occurring mental and substance use disorders in the criminal justice system." Am J Drug Alcohol Abuse **43**(4): 475-488.

46. Robins, J. M., A. Rotnitzky and L. P. Zhao (1995). "Analysis of Semiparametric Regression Models for Repeated Outcomes in the Presence of Missing Data." Journal of the American Statistical Association, **90**(429): 106-121.
47. Rosenbaum, P. R. (2002). "Covariance Adjustment in Randomized Experiments and Observational Studies." Statistical Science **17**(3): 286-327.
48. Rothman, K., S. Greenland and T. L. Lash (2008). Modern Epidemiology, 3rd Edition. Philadelphia, PA, Lippincott Williams & Wilkins.
49. Rowe, C., G. M. Santos, E. Vittinghoff, E. Wheeler, P. Davidson and P. O. Coffin (2015). "Predictors of participant engagement and naloxone utilization in a community-based naloxone distribution program." Addiction **110**(8): 1301-1310.
50. Saulle, R., S. Vecchi and L. Gowing (2017). "Supervised dosing with a long-acting opioid medication in the management of opioid dependence." Cochrane Database Syst Rev **4**: CD011983.
51. Scott, C. K., C. E. Grella, L. Nicholson and M. L. Dennis (2018). "Opioid recovery initiation: Pilot test of a peer outreach and modified Recovery Management Checkup intervention for out-of-treatment opioid users." J Subst Abuse Treat **86**: 30-35.
52. Seth, P., L. Scholl, R. A. Rudd and S. Bacon (2018). "Overdose Deaths Involving Opioids, Cocaine, and Psychostimulants — United States, 2015–2016." CDC Morbidity and Mortality Weekly Report **67**(12): 349-358.
53. Sharma, A., S. M. Kelly, S. G. Mitchell, J. Gryczynski, K. E. O'Grady and R. P. Schwartz (2017). "Update on Barriers to Pharmacotherapy for Opioid Use Disorders." Curr Psychiatry Rep **19**(6): 35.
54. Sittambalam, C. D., R. Vij and R. P. Ferguson (2014). "Buprenorphine Outpatient Outcomes Project: can Suboxone be a viable outpatient option for heroin addiction?" J Community Hosp Intern Med Perspect **4**.
55. Sordo, L., G. Barrio, M. J. Bravo, B. I. Indave, L. Degenhardt, L. Wiessing, M. Ferri and R. Pastor-Barriuso (2017). "Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies." BMJ **357**: j1550.
56. Soyka, M. (2015). "New developments in the management of opioid dependence: focus on sublingual buprenorphine-naloxone." Subst Abuse Rehabil **6**: 1-14.
57. Stancliff, S., H. Joseph, C. Fong, T. Furst, S. D. Comer and P. Roux (2012). "Opioid maintenance treatment as a harm reduction tool for opioid-dependent individuals in New York City: the need to expand access to buprenorphine/naloxone in marginalized populations." J Addict Dis **31**(3): 278-287.
58. Substance Abuse and Mental Health Service (2016). "Medication assisted treatment for opioids use disorders reporting requirements. Final rule." Federal Register **81**(187): 66191.
59. Thomas, C. P., C. A. Fullerton, M. Kim, L. Montejano, D. R. Lyman, R. H. Dougherty, A. S. Daniels, S. S. Ghose and M. E. Delphin-Rittmon (2014). "Medication-assisted treatment with buprenorphine: assessing the evidence." Psychiatr Serv **65**(2): 158-170.
60. US Department of Health and Human Services. (2018). "Understanding the opioid crisis." from https://www.hhs.gov/opioids/about-the-epidemic/.
61. Volkow, N. D., T. R. Frieden, P. S. Hyde and S. S. Cha (2014). "Medication-assisted therapies--tackling the opioid-overdose epidemic." N Engl J Med **370**(22): 2063-2066.
62. Wagner, K. D., L. J. Bovet, B. Haynes, A. Joshua and P. J. Davidson (2016). "Training law enforcement to respond to opioid overdose with naloxone: Impact on knowledge, attitudes, and interactions with community members." Drug Alcohol Depend **165**: 22-28.
63. Wu, L. T., H. Zhu and M. S. Swartz (2016). "Treatment utilization among persons with opioid use disorder in the United States." Drug Alcohol Depend **169**: 117-127.
64. Zywiak, W. H., N. G. Hoffmann, R. L. Stout, S. Hagberg, A. S. Floyd and S. S. DeHart (1999). "Substance abuse treatment cost offsets vary with gender, age, and abstinence likelihood." J Health Care Finance **26**(1): 33-39.