Project OOPEN, Opioid Overdose Prevention, Education and Intervention

Study Protocol

1R01 DA030351-01A1, (A Trial to Prevent Opioid Overdose: E.D. Based Intervention & Take-home Naloxone)

Caleb Banta-Green, PhD, MSW, MPH	Principal Investigator	Alcohol and Drug Abuse Institute	206-543-0937
Joseph Merrill, MD, MPH	Acting Assistant Professor	UW School of Medicine	206-744-1834
Dennis Donovan, PhD	Director	UW Alcohol and Drug Abuse Institute	206-543-0937
Phillip Coffin, MD, MIA	Director of Substance Abuse Research	San Francisco Department of Public Health	415-554-8176
Christopher Dunn, PhD	Associate Professor	Psychiatry and Behavioral Sciences	206-251-4890
Norbert Yanez, PhD	Associate Professor	School of Public Health	206-543-8027
Jeanne Sears, PhD, RN	Senior Research Scientist	Health Services	206-543-1360
Lauren Whiteside, MD	Acting Clinical Instructor	Harborview Medical Center	206-744-8464
Anthony Floyd, PhD, CIP	Project Director	Alcohol and Drug Abuse Institute	206-616-7382
Melissa Phares, MSW	Interventionist	Alcohol and Drug Abuse Institute	206-543-0937
Jonnae Tillman	Interventionist	Alcohol and Drug Abuse Institute	206-543-0937
Paul Grekin, MD	Medical Director	Evergreen Treatment Services	206-223-3644
Michelle Peavy, PhD	Assistant Treatment Director	Evergreen Treatment Services	206-223-3644
Esther Ricardo-Bulis, MA	Research Coordinator	Evergreen Treatment Services	206-223-3644

Abstract

Fatal overdoses involving pharmaceutical opioids have increased dramatically over the past decade, surpassing those related to heroin, and are the leading cause of drug overdose in much of the U.S. In Seattle-King County, 75% of drug overdoses involved pharmaceutical opioids and/or heroin in 2009. Opioid overdoses, heroin and pharmaceutical, are preventable and reversible. Research indicates that drug users and their partners can be successfully trained to recognize and reverse overdoses with naloxone (an opioid antagonist medicine or "antidote").

Despite active heroin overdose prevention, education and intervention programs with naloxone (OOPEN) in 15 states with thousands of overdose reversals and no serious adverse events, rigorous studies of these programs on rates of subsequent heroin overdoses have not been conducted. No OOPEN programs or studies have yet been implemented for pharmaceutical opioid users at elevated risk for overdose..

Unique to this setting is the potential to identify high risk pharmaceutical opioid users, a population that is difficult to locate and engage. Interventions using brief behavior change counseling (BBCC) have been shown to significantly improve health behaviors such as alcohol use and injury, to increase entry into drug treatment as well as to reduce costs. Evidence is promising, but limited, regarding the impact of BBCC on opioid related risk behaviors.

This prospective, multi-site, randomized trial will study the effectiveness of an intervention that combines OOPEN with BBCC for both heroin users (n=500) and pharmaceutical opioid users at elevated risk for overdose (n=500). The primary outcome is subsequent opioid overdoses, ascertained by follow up interviews conducted at 3, 6 and 12 months as well as via administrative records for up to 24 months (i.e. medical records, ambulance responses, and death certificates). Hypotheses to be investigated include that the intervention recipients will have: 1) lower rates of opioid overdose, 2) reduced drug use and overdose risk behaviors, 3) more appropriate health care utilization, and 4) lower total health care costs. We will also explore whether the intervention impacts HIV risk behaviors.

Introduction

This research proposes the first prospective, clinical trial to test the effectiveness of an intervention to prevent opioid overdoses among pharmaceutical opioid users and heroin users. Naloxone distribution programs for heroin users are widespread and descriptive studies have been conducted, but prospective, randomized studies necessary to prove effectiveness have not been conducted. To date no research has been published on how to prevent overdoses among pharmaceutical opioid users, now the largest group represented in fatal drug overdoses nationally. The intervention combines two widely used interventions for related health behaviors that have not previously been combined: 1) opioid overdose prevention, education and intervention with naloxone (OOPEN) for heroin users, and 2) brief behavior change counseling (BBCC) which has been shown to prevent future harms for a range of substances.

Opioid overdose is increasingly common, associated with substantial morbidity and mortality and should be responsive to prevention and intervention programs. Brief behavior change counseling is likely to increase the effect of these programs. There is an urgent need for evidence based interventions that can readily access and engage people at elevated risk for overdose, including the under-studied population of pharmaceutical users. Evidence of the impact of interventions on overdose rates, overdose risk behaviors, health care utilization and potential costs savings is needed.

Background and Rationale

Use, misuse and abuse of pharmaceutical opioids and heroin are relatively common and negative health consequences are severe, often fatal, and increasingly frequent. Opioid overdoses involving heroin persist, while overdoses related to pharmaceutical opioids have increased dramatically over the past decade and have surpassed those related to heroin both locally and throughout much of the United States. Health care utilization and costs associated with caring for those with problematic opioid use are substantial and increasing.

Recent, local data indicate the following:

- Of 256 drug caused deaths in Seattle-King County, Washington in 2008, 195 involved pharmaceutical opioids and/or heroin. The opioid caused death rate in Washington State is higher than the national average and the overall drug caused death rate in King County has increased significantly over the past decade, driven by the increase in pharmaceutical opioid involved deaths.

- Non-fatal opioid overdose was reported by 16% of heroin users, with 41% reporting witnessing an overdose, in the prior year according to a 2009 survey conducted at Seattle area syringe exchanges. These rates are likely conservative as evidence suggests that syringe exchange users have lower overdose rates than non-users.

- Heroin related visits to the Harborview Medical Center (HMC) emergency department (ED) in 2008 totaled at least 966 and at least 768 for pharmaceutical opioid users who did not report current heroin use (case types included: drug abuse, overmedication, adverse reaction, and seeking detox). The rate of ED visits for non-medical uses of pharmaceutical opioids was higher in the Seattle area than any other metropolitan area included in the U.S. Drug Abuse Warning Network (DAWN) in 2007 and Seattle ranked fourth nationally for heroin[i].

- Naloxone (opioid antidote) was administered approximately once a day in Seattle by medics attending to opioid overdoses in 2011. Almost all are transported to the HMC ED.

- On August 22, 2012 the Director of the Office of National Drug Control Policy, Gil Kerlikowske, called for increased action to prevent drug overdose deaths, including wider distribution of naloxone.

Objectives

Primary Aims

The primary aims are to test whether those who receive the intervention compared to standard care have:

1) Lower rates of opioid non-fatal and fatal overdose

2) Reduce drug use, in appropriate medication use, and other overdose risk behaviors

Secondary Aims

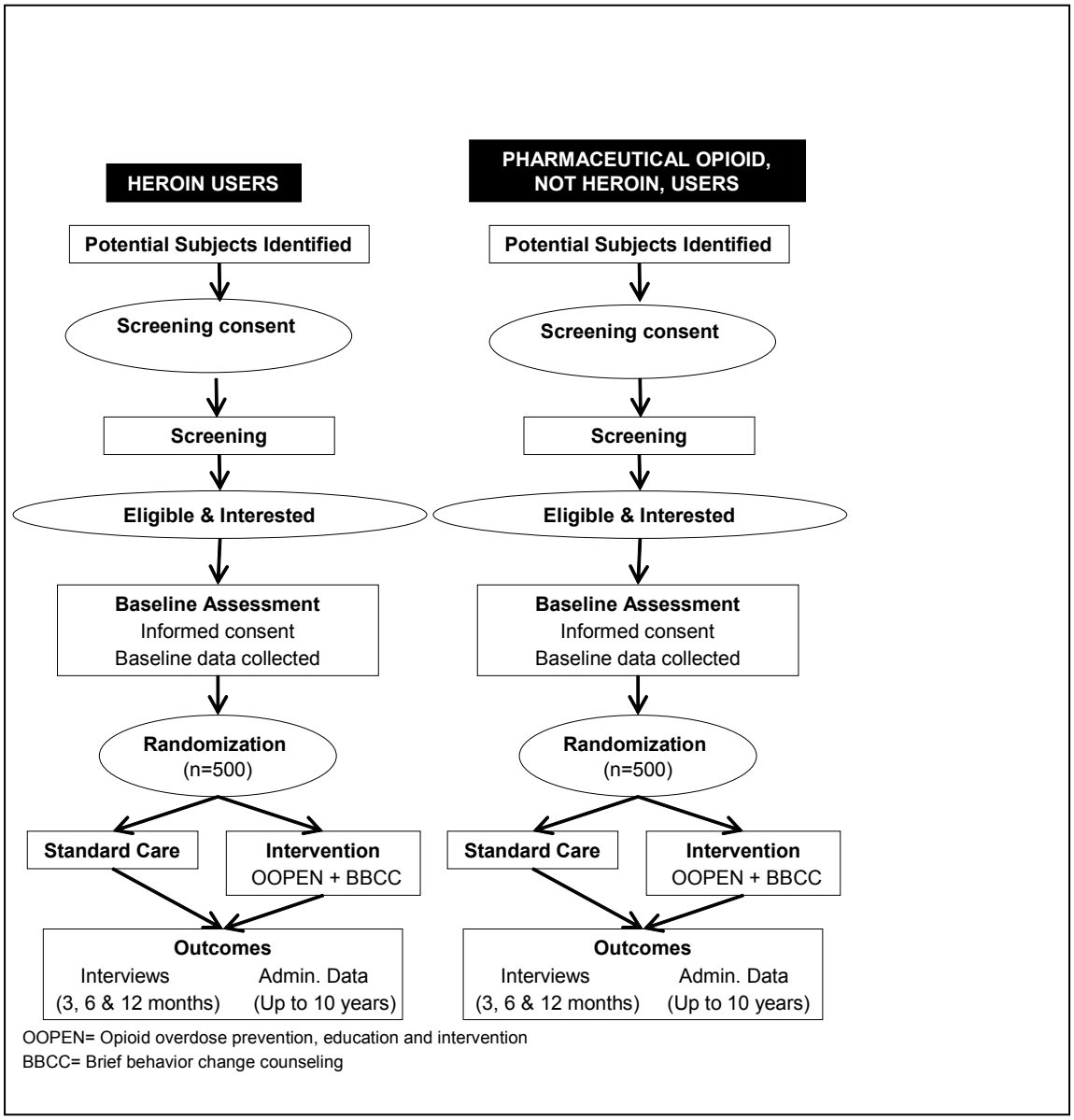
The secondary aims are to test whether those who receive the intervention compared to standard care have:

3) More appropriate health care utilization (e.g. fewer emergency department visits and admissions to inpatient care)

4) Lower total health care costs

5) Determine the prevalence of HIV risk behaviors among heroin and pharmaceutical opioid users at risk for overdose and whether the intervention impacts these behaviors.

Study Design



This prospective, multi-site, randomized clinical trial will compare standard care to a novel intervention that combines OOPEN with BBCC for heroin users (n=500) and pharmaceutical opioid users at elevated risk for overdose (n=500). The study will take place at Harborview Medical Center (HMC) , University of Washington Medical Center (UWMC), and Evergreen Treatment Services. The primary outcomes are subsequent opioid overdoses, ascertained by self-report interviews at 3, 6 and 12 months after recruitment as well as via administrative records for at least 24 months and self-reported drug use and other overdose risk behaviors. Secondary outcomes include: health care utilization, direct health care costs and impact on HIV risk behaviors.

Eligibility Criteria

Inclusion for all subjects:

1) Meets study definition of elevated risk of future opioid overdose

- Reason for visit is opioid overdose (regardless of frequency of use), or
- Use of pharmaceutical opioids not prescribed to the patient 2 or more times in the prior month, or
- Use of other opioids, alcohol, benzodiazepines or stimulants within two hours of using opioids 2 or more times in the prior month, or
- Average daily dose of prescribed opioids consumed is greater than10 mg morphine equivalent analgesic dose or higher for 15 or more days in the last 30.
- Enrolled in opioid substitution program (e.g. methadone or suboxone) and receiving doses.

Inclusion for heroin users:

2) Use of heroin through any route of administration at least 2 times in the last 30 days (or if institutionalized recently, in the most recent month they were not institutionalized) with or without other risks being present.

Inclusion for prescription-type opioid users:

3) Use of pharmaceutical opioids at least 2 times in the last 30 days (or if institutionalized recently, in the most recent month they were not institutionalized) with other risks being present.

Inclusion for opiate registry users:

4) Average daily dose of prescribed opioids consumed is 30 mg morphine equivalent analgesic dose or higher without other risks being present.

In the case of known pregnancy, subjects will not be excluded and will be offered naloxone if randomized to the intervention arm.

Exclusion criteria

1) Unwilling to allow further access to medical or drug treatment records.

2) Inability to communicate in English.

3) Current active suicidal ideation.

4) Significant cognitive or psychiatric impairment (per judgment of clinical staff)

5) Inability to provide adequate contact information to assist with follow-up.

6) Under age 18 or over age 70 at time of recruitment.

7) Not currently living in Washington State or planning to move from Washington State within the following year.

8) Receiving treatment for sexual assault.

9) Have non-expired take-home naloxone at home, on their person, or in their possessions.

Participation in the study is not appropriate for subjects under care for terminal illness, as known reduced life expectancy may skew study results, and the use of high doses of opioid medications may be used during end of life care.

Potential Subjects Identified

Some subject will be identified through prescreening of intake records and medical history for patients admitted to hospital, including those admitted for overdose, or in transit to the ER for overdose. In the emergency departments several large monitors display information related to admission. Some subjects initially seen in the ER will be admitted to the main hospital, but will be listed in ER medical records for the past 3 days. Some subjects may bypass emergency services and be admitted directly into inpatient care. Medical records would again be screened for eligibility. Finally some patients will be recruited through flyers and word of mouth without the use of medical records screening.

We will use this information in combination with information available from prescreening medical records to identify potential subjects. We will communicate with clinical staff pointing out potential subjects identified in prescreening, and reminding clinical staff of potential subjects to be aware of for inclusion. Study staff will regularly attend staff meetings to educate them about the study, enlist their help in identifying potential subjects and obtain feedback on recruitment protocols.

Clinical staff will be asked to look for patients who have experienced overdose, exhibit physical symptoms of drug use (such as abscesses or track marks), present for care with symptoms of pain without apparent injury, or exhibit signs of overmedication (such as pinpoint pupils) for admissions unrelated to drug use or overdose. Clinical staff will also be asked to look for subjects who use opioid medications, have a high number of prescriptions or prescribers for controlled substances (such as opioids or benzodiazepines), or high emergency room utilization or admissions.

If a potential subject is appropriate and medically stable clinical staff may either inform the subject of the availability of the study or confirm that research staff may make the initial approach with subjects. A study flyer will also be made available to clinical staff. If patients express interest, we will approach the potential subject.

Subject Approach and Consent for Screening

If the potential subject is interested in hearing more about the study, research staff will briefly explain the study purpose. To assist with the presentation of the study, a brief video slideshow with audio narration that describes the study and requests permission for eligibility screening will be presented. Subjects will listen to the narration using closed headphones with disposable one-time use covers. After the presentation, we will review the written material, address any questions and concerns the subject may have and confirm their agreement to answer screening questions with a signed consent document.

Eligibility Screening

Subjects will be asked to complete an eligibility screening questionnaire. The items covered are general, such as proximity to the research settings, drug use questions, and medical health questions. Screening questions will be completed by the subject, with assistance from research staff, if required. Research staff will assist subjects with the calculation of their average morphine equivalent dose if the only opioids used are those prescribed to them (not including subjects in opioid substitution treatment).

Subjects who endorse the broader question about having thoughts of being better off dead or of hurting oneself will be asked 5 follow-up questions related to active suicidal ideation using the Modified Scale for Suicidal Ideation (MSSI). Subjects with MSSI values above cut-off levels will be excluded and referred to clinical staff for further care.

We hope to afford as much privacy as possible for subjects who would like to hear more about the study. Screening data will be kept for all subjects whether eligible or not and whether enrolled or not.

Obtain Informed Consent

Written informed consent will be obtained from all subjects who wish to continue further with the study. Subjects will also be asked to complete HIPAA authorization agreements for medical records information from their ED or inpatient visit along with medical care and drug treatment records from secondary data sources.

Baseline Assessments

Eligible subjects will undergo baseline assessments and provide information on personal information and health:

1) Education, Employment, Income and Housing: This assessment captures other demographic information related to subject's resources and social stability.

2) Overdose Risk Assessment: This assessment is used to determine the potential for future overdose based on prior overdose history, current drug use practices and social context for current drug use. This assessment is not standardized but is compiled from individual items of known risk factors for overdose.

3) World Health Organization Quality of Life (WHOQOL-BREF). This is a short assessment to measure general health and physical, social and emotional functioning.

4) World Health Organization Alcohol, Smoking and Substance Involvement Screening Test (WHO-ASSIST v.3). This is a multi-item tool to determine areas of substance use and misuse. This assessment battery screens for recent and lifetime use of a variety of substances, including illicit drugs, alcohol, pharmaceuticals and tobacco products.

5) Age of First Use: Subjects are asked to provide the ages they first used a variety of substances.

6) HIV Risk Assessment Battery: This assessment is used to determine the potential for contracting HIV, hepatitis and other blood-borne illnesses based on drug use and sexual use behaviors.

7) Overdose History: This assessment will collect information related to any prior overdose that the subject has experienced or witnessed.

8) EQ-5D-3L: This validated quality of life measure asks about problems in mobility, self-care, usual activities, pain and discomfort, anxiety and depression and overall health.

Locator information:

Subjects will be asked to provide a number of sources to ensure they can be contacted for 3, 6 and 12 month follow-up visits. However, because we anticipate a number of high risk subjects to be indigent, subjects may be enrolled if they provide at least one primary source of locator information.

Randomization

Subjects will be randomized to receive either standard of care or the study intervention. We will recruit equal numbers of subjects in the intervention and control arms of the study, meeting eligibility criteria as heroin user or primarily pharmaceutical opioid users.

Follow-up Visits

Follow-up visits will occur at 3, 6 and 12-month after enrollment. All interviews will be by phone. Most assessments given at the baseline interview will be repeated at each follow-up

point. In addition to the assessments subjects will be asked questions about whether they have naloxone and, if not, what happened to any naloxone that was given to them.

Secondary Data Sources

Secondary data on health care and drug treatment utilization will be obtained from Washington State (separate IRB action pending) using the following sources:

- Treatment and Assessment Report Generation Tool (*TARGET*) for drug treatment admissions data
- The Comprehensive Hospital Abstract Reporting System (CHARS) for hospital admissions

Information on any ambulance transports will be obtained from the Seattle Fire Department's Medic 1 unit.

In the event of a subject death during the study will we request information on cause of death from the King County Medical Examiner's Office. If a subject cannot be located we will also check this source to see if they have died and if so to obtain data on the cause of death. If we are unable to locate a subject during the course of the study or at final follow-up we will utilize the King County Jail Inmate Look-up Service. At no time will subjects be contacted or study procedures attempted while the subject is incarcerated.

Intervention Description

Standard care for patients who have used opioids would vary according to individual clinical need and might include referral to drug treatment or detoxification services. Standard care would not include OOPEN and BBCC interventions as specified in this grant. After baseline data are obtained subjects assigned to the intervention undergo the following procedures:

<u>A brief behavior change counseling (BBCC) session</u>

- Conveys subjects' risk for overdose, based on the baseline measures
- Engages them in a reflective discussion of the pros and cons of their current patterns of use
- Has the patients identify behavior change(s) they are interested in making to improve their health
- Encourages them to share opioid overdose prevention and intervention information and materials with their family, friends, housemates, and/or drug using partners.

<u>Education and training on opioid overdose prevention and intervention with naloxone (OOPEN)</u>

- Subjects will view a training video on study laptops that reviews:
    - Information on risk factors for overdose and how to prevent and reduce the risk of overdose

- How to recognize an opioid overdose
- The importance of calling 911
- How to intervene in an overdose
    - Positioning a victim in rescue position
    - Brief overview of rescue breathing
    - Training on how and when to administer naloxone

- Subjects will be given a study brochure that covers the information in the video and reviews the Washington State 911 Good Samaritan overdose law which provides immunity from prosecution for drug possession charges to overdose victims and bystanders who seek aid in an overdose event.

- Prescribing and dispensing overdose rescue kits including 2 doses of intra-nasal naloxone, a disposable rescue breathing mask, and disposable gloves.

- Subjects in the intervention group will be informed that they may have one replacement of the naloxone kit (2 doses) during the 12 month study period.

We expect the intervention to take 30-45 minutes on average based on our experience and that this is feasible and reasonable for subjects and interventionists.

Fidelity assessment for the BBCC will be done with the shortened Motivational Interviewing Treatment Integrity (MITI) instrument.

Schedule of and Sources Data Obtainment

	DATA SOURCES AND TIMING				
	Interview Case Report Form			**Administrative**	
MEASURES	**Base-line**	**3 & 6 mos.**	**12 mo.**	**Up to 10 yrs.**	**Up to 10 yrs.**
PRIMARY AIMS					
Aim 1: Overdose					
Subject overdosed prior 3/6* months Y/N	x	x	x		
Subject overdosed Y/N & Date					x
Aim 2: Drug use and other overdose risk behaviors					
Alcohol/Drugs 3/6 month use frequency	x	x	x		
Opioid use following interruption past 3/6 months	x	x	x		
Using opioids without others present	x	x	x		
Avg. daily opioid dose- Prescribed Opioid Users	x	x	x		
Opioid substitution drug treatment prior 3/6	x	x	x		x
Other drug treatment sought or used prior 3/6	x	x	x		x
SECONDARY AIMS					
Aim 3: Health care utilization					

ED, Outpatient, Inpatient and Ambulance- # &				x	x
Aim 4: Health care costs					
Hospital-based total direct health care costs				x	x
Aim 5: HIV Risk Behaviors	x	x	x		
CO-VARIATES & POTENTIAL EFFECT MODIFIERS					
Demographics	x				
Employment, health insurance, income, housing	x	x	x		
Alcohol/Drugs ages of first use	x				
Medical status and satisfaction (WHO QOL BREF, EQ-5D- 3L)	x	x	x		
Behavior change plans and readiness	x				
Overdose lifetime history	x				
Possessed, "carried" naloxone, # of days past 3/6	x	x	x		
Overdose # witnessed events past 3/6 months	x	x	x		
Source of naloxone- Study, other	x	x	x		
Subject had naloxone administered to them, #, by	x	x	x		x
Disposition of naloxone	x	x	x		
Subject had negative/allergic reaction to naloxone	x	x	x		
FIDELITY ASSESSMENT OF BASELINE					
Overdose prevention & intervention training. Item	x				
Motivational Interviewing Treatment Integrity 3.1.1	x				

*Past 3 months timeline for 3 and 6 month follow ups, past 6 months used at 12 month follow up.

Brief Behavioral Change Counseling (BBCC)

The BBCC will be conducted according to the demeanor and guidelines of Motivational Interviewing (MI), a style for counseling patients about sensitive behaviors and for giving them information to enhance their health and safety in a non-judgmental manner. MI has been widely implemented in brief intervention studies for drug use and other behavior change. MI is non-confrontational and respectful of subjects' autonomy to discuss or not discuss sensitive topics The BBCC will consist of 4 elements:

1) The interventionist will show to the patient an approximately 8-minute video on overdose prevention, recognition and intervention, which subjects will view on a laptop while they are using headphones. The interventionist will debrief the video with subjects and answer questions.

2) Next, the interventionist will review with subjects their overdose risk. This task involves informing subjects of the "good news" about overdose risks they are NOT incurring in their current behaviors for the purpose of reinforcing and hopefully continuing more positive health behaviors (e.g., not inappropriately mixing other drugs or alcohol with

opiates). Next, the interventionist will respectfully and in a neutral tone review with subjects the behaviors that currently place them at risk for opiate overdose (e.g., using opiates when alone or after a long period of abstinence).

3) From the video and risk feedback, the interventionist will segue into an open discussion of any changes subjects are thinking of making to increase their safety from overdosing. If at any time during the interview, subjects indicate that they would prefer to quit opiates or to seek opiate detox or treatment, the interventionist will help with these referrals. The discussion will culminate in a summary of healthy changes, if any, that subjects intend to make. Subjects will take with them a handout that has been customized to summarize any changes subjects indicate that they want to make.

4) Finally, the Overdose Prevention Kit will be shown to the patient. This involves a hands on demonstration of how to set up and administer the naloxone nasally, with the goal of subjects' learning this well enough to be able to use or teach significant others to administer naloxone to the subjects, if ever needed. The entire intervention is conducted in a Motivational Interviewing style of counseling. The interventionist will then summarize the conversation.

All interventions will be audio recorded if subjects permit, allowing the trainer/supervisor of the interventionists to monitor MI and overdose education fidelity throughout the course of the study.

Study Medication

The medication, naloxone, is being used for an indicated condition, opioid overdose. The specific formulation of Naloxone we plan to use is a 2mg/ml-2ml syringe that is made by International Medication Systems in El Monte, California (NDC # 00548336900).

The device used to deliver the medication nasally is a mucosal atomizer device (MAD300). The mucosal atomization device is licensed for intranasal atomization of prescription medications.

At usual doses, naloxone is relatively free of adverse effects. Because the duration of action of naloxone may be shorter than that of the narcotic being reversed, patients being treated for opioid intoxication with symptoms of respiratory depression should be closely monitored as additional doses of naloxone may be required. Administration of naloxone to opioid-dependent patients may provoke an acute withdrawal syndrome (including body aches, diarrhea, tachycardia, fever, runny nose, sneezing, piloerection, sweating, yawning, nausea or vomiting, nervousness, restlessness or irritability, shivering or trembling, abdominal cramps, weakness, and increased blood pressure). Withdrawal reaction are not life threatening. Agitation and paresthesia have been infrequently reported with the postoperative use of naloxone hydrochloride injection.

Hypersensitivity reactions, such as allergic reactions, are theoretically possible, but have never been documented with naloxone. We will ask about allergic reactions to naloxone during the baseline interview and at each of the three follow up interviews. Any allergic reactions will be reported to the University of Washington's human subjects division and the sponsor the National Institute on Drug Abuse.

Several articles have been published showing the effectiveness of nasally administered naloxone in overdose situations and the comparability of effect between intranasal administration with other routes of administration for naloxone. The intra-nasal route of delivery of naloxone with a mucosal atomization device has been used in 1,000's of reversals safely and effectively by both medical professionals and lay persons.

According to the naloxone package insert "When administered in usual doses and in the absence of opioids or agonistic effects of other opioid antagonists, it exhibits essentially no pharmacologic activity." Its use on an unconscious person who did not use opioids is very likely to be benign.

There is no known mechanism by which naloxone could potentially be converted into an opioid agonist that could be abused. Nothing has ever been published that suggests such a conversion of naloxone has been accomplished and discussions with professors in schools of medicine (Dr. Andy Saxon) and pharmacology (Dr. Charles Chavkin) at the University of Washington indicated no evidence that naloxone has ever been modified in such a way as to facilitate its being abused. According to the naloxone package insert: "NARCAN is an essentially pure opioid antagonist, i.e., it does not possess the "agonistic" or morphine-like properties characteristic of other opioid antagonists. "

Subjects will be educated about withdrawal reactions. The overdose intervention training and all education materials will clearly and strongly encourage calling 911 during any suspected overdoses. Emergency medical services are well equipped to handle any withdrawal reactions. Intra-nasal administration of naloxone generally results in more mild withdrawal symptoms than other routes of administration.

Regulatory Compliance and Safety

Regulatory binder

The regulatory files should contain all required documents, study-specific documents, and all important communications. Regulatory files will be checked for compliance prior to study initiation, throughout the study, as well as at study closure.

Study documentation includes all case report forms, data collection forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence, and signed protocol and amendments, or Institutional Review Board correspondence and approved current and previous consent forms and signed participant consent forms.

Source documents include all reports and records necessary for the evaluation and reconstruction of the clinical research study. The original recording of an observation should be retained as the source document. Because direct data entry through the REDCap electronic data capture system will be employed relatively few source documents are anticipated for the collection of primary data.

Data Safety Monitoring Oversight Committee

The Data Safety Monitoring Oversight Committee will have three representatives who have clinical and research expertise relevant to the study. They are not directly involved in the study. They will meet during the period of study planning, one month after the study is initiated and quarterly from then on. The committee will receive regular reports on the progress of the study, including the number and characteristics of subjects and those who declined to participate. Any serious adverse events (SAE) will be discussed with the committee to determine if the risks of SAE could be modified by any changes in study procedures. Other reports will be provided as the committee requests.

The committee will include two physicians: Andy Saxon, MD a psychiatrist at the Veterans Affairs Puget Sound Health Care Network, where he is the medical director of addiction treatment services, he is also a Co-Investigator for medication studies for the Pacific Northwest Node of NIDA's Clinical Trials Network and conducts clinical trials and medical trainings on Suboxone- a medication which contains naloxone. The other physician member is Matthew Golden, MD the director of HIV/STD programs for Public Health- Seattle & King County and Associate Professor of Medicine at the University of Washington. An additional committee member will have expertise in community based substance abuse treatment and the epidemiology of opioid abuse: T. Ron Jackson, MSW is the director of Evergreen Treatment Services a methadone maintenance clinic serving more than 1,000 patients in the Seattle area, he is also the co-investigator for community treatment programs for the Pacific Northwest Node of NIDA's Clinical Trials Network.

Drug accountability

Study medication will be ordered, stored, maintained and dispensed by the Investigational Drug Service Pharmacies at Harborview Medical Center and UW Medical Center and the clinical dispensary at Evergreen Treatment Services. Upon receipt, the investigator, pharmacist, or authorized designee is responsible for taking inventory of the investigational agent. A record of this inventory will be kept and usage will be documented. Any unused or expired investigational agent shall be accounted for.

Adverse event reporting

The risks expected from trials employing behavioral interventions are presumed minimal and the medication being prescribed for possible future use is designed to be used to prevent a fatal overdose with side effects being rare. However, given the nature of ongoing drug and/or medication use the population studied in this trial is possibly at risk for an overdose. Adverse events (AEs) will be categorized as serious or non-serious, as related or not related to the study, and as expected or unexpected. An AE is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial. Stable chronic conditions, such as substance abuse, which are present prior to clinical trial entry and do not worsen, are not considered AEs. Common, minor ailments and complaints will be excluded from any type of documentation. These may include: colds, flu's, cuts, scrapes, coughs, headaches, stomach complaints, and general fatigue.

Serious adverse events (SAEs) are defined as any fatal event, any immediately life threatening event, any permanent or substantially disabling event, any event that requires or prolongs inpatient hospitalization, congenital anomaly or birth defect, or any event requiring intervention to prevent any of the previously listed serious events. Hospital visits that do not result in admittance are not considered SAE's (e.g. emergency room visit for a non- study-related injury that does not result in admittance). Normal childbirth and pre-planned elective procedures are not considered SAEs. AE/SAE's will be elicited by interventionists/research interviewers at each assessment visit by asking the participants if they have noticed any new problems or existing problems that have gotten worse (using the Adverse Events Worksheet).

Disclosure of an AE/SAE may also occur in an unsolicited manner to a research or clinical staff member. The interviewers should be focused on gathering data to aid in determining study relatedness. Study-relatedness will be determined by the interviewers in consultation with one of the investigators. All AEs and SAEs will be recorded in the AE/SAE log and entered into the secured project database. AEs that are not study related do not require any further paperwork documentation besides the AE Log. In this study, potential AEs that may be related to the study would be an increase in emotional distress in relation to discussion of past or current drug use behaviors *or side effects of naloxone.*

University of Washington Adverse Events reporting requirements

The term adverse event is generally used to refer to any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Adverse events encompass both physical and psychological harms. They occur

most commonly in the context of biomedical research although, on occasion, they can occur in the context of social and behavioral research.

Unanticipated problems, in general, include any incident, experience, or outcome that meets all of the following criteria:

1. unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. related or there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research; and
3. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

The adverse event report form is to be used to report an adverse event where there is a reasonable probability that the event was attributable to a study procedure. The UW IRB defines reasonable probability as "more likely than not" - that is, there is a greater than 50% likelihood of the event having been caused or partially caused by the research or arising from the circumstances of the research.

Per HSD policy the form is required to be submitted as soon as possible but no later than 10 business days after becoming aware of the event.

Data security

Data will be uploaded to ADAI servers weekly. Only authorized individuals are permitted access to the project database. Data are backed up nightly so there is minimal risk of data loss. Any edits to previously saved data are fully tracked in an electronic audit table and include the date/time stamp and user ID of the person making the edit. Ongoing data monitoring will be the responsibility of the research coordinator.

Confidentiality

We will obtain a federal Certificate of Confidentiality (CoC), protecting participants against disclosure of sensitive information (e.g., drug use). The Department of Health and Human Services (HHS) office that issues the CoC will be advised of any changes in the CoC application information.

Participant records will be kept confidential by the use of study codes for identifying participants on data collection forms, secure separate storage of any documents that have

participant identifiers, and secure computing procedures for entering and transferring electronic data.

Study monitoring

The monitoring of study records will be conducted on a regular basis by the research coordinator. The purpose of these visits is to encourage and assess regulatory compliance and to document the integrity of the trial progress. Monitoring activity will assure that submitted data are accurate and in agreement with source documentation and will also review regulatory/essential documents such as correspondence with the IRB. Areas of particular concern will be participant informed consent, protocol adherence, safety monitoring, IRB reviews and approvals, regulatory documents, participant records, study drug accountability, and principal investigator supervision and involvement in the trial. The research coordinator will ensure that staff are trained and able to conduct the protocol appropriately and that study procedures are properly followed. If additional training of study personnel is needed, project staff will undertake or arrange for that training.

Data monitoring

Study data will be entered by interventionists directly into password protected, study specific laptop computers. Data will be captured using the REDCap electronic data capture system which uses a secure connection to local REDCap servers located at ITHS. Only authorized users will be allowed access to the data entry system and no identifiable data will be entered into REDCap. Research staff will use password protected UW works for data entry.

Data completion will be verified when study interviews are completed. Baseline data and study arm assignment will be captured by secure data servers at ITHS as data are collected in REDCap. Data will be managed by the principal investigator and research coordinator, who will access study data from desktop computers connected via local area network to computer servers that are in a locked room in a locked office suite at the Alcohol and Drug Abuse Institute (ADAI). Similarly, follow-up interview data will be entered directly into password protected, study specific laptop computers using REDCap, with data uploaded to servers at ADAI weekly.

Health services and cost data will be obtained, cleaned and made into analytic data sets by Dr. Sears. Data will be transferred securely and stored on ADAI servers which are backed up nightly. The research coordinator will be responsible for the integrity of all study data and will prepare regular reports for the 3-person data and safety monitoring oversight committee which will review any adverse events as well as monitor study progress to ensure that study results are scientifically valid.

The research coordinator for the study will conduct software programming and data management activities. Data will be stored on computer servers at ADAI that are fully HIPAA-

compliant in accordance with the University of Washington School of Medicine. The senior computer specialist at ADAI maintains nightly tape backups and active disaster recovery protection and procedures. The research coordinator will develop data collection forms used by research staff. These forms will also have a companion data dictionary which comprehensively defines each data element. The data dictionary specifies missing, illogical, out of range, and inconsistent value checks for each data element, in addition to logic checks and assists the project data analysis.

Intervention fidelity monitoring

The primary threat to the integrity of the intervention is that the intervention may not be delivered as intended. This potential problem is minimized because the intervention is highly structured and intervention fidelity will be regularly monitored by co-investigators who will monitor audio recordings of intervention sessions after the interventionist has initially been approved to conduct interventions without supervision.

Data Analysis

Sample Size Calculation

The study was powered to address aim 1, the impact of the intervention on non-fatal overdose. For the study of each opioid user type (heroin and pharmaceutical opioids) the number of subjects needed in each arm of the study (intervention and comparison) to achieve power of 0.80 to detect a decline in the overdose rate from 20% to 10% at a confidence level of 0.05, is 219 subjects. To increase power somewhat and account for potential loss to follow up, we plan to enroll more subjects, 250 in each arm of each study, for a total of 500 heroin using subjects and 500 pharmaceutical opioid, non-heroin using subjects. Other outcomes to be analyzed include drug use and services utilization. Data on brief interventions in ED's shows declines in drug use and ED utilization of at least 40%. Specifically in Washington State, the Screening and Brief Intervention Referral and Treatment (SBIRT) found a 45% reduction in average days of drug use among high risk heroin users who received a brief intervention in an ED (from 15.8 days to 8.7 days in the prior month) and 41% reduction among high risk pharmaceutical opioid users (12.8 to 7.5 days).

Assumptions behind the power estimate are based upon an annual rate of non-fatal heroin overdose estimated to be a median of 25% across studies and for fatal overdoses approximately 1%. For the purposes of this sample size estimate we are conservatively assuming a total annual overdose rate for heroin users of 20%. We believe that a reduction of the OD rate by 50% may be possible based on the potential for additive effects of the OOPEN and the BBCC interventions. Preliminary data on overdose rates for pharmaceutical opioid

abusers (no regular heroin use) indicates a rate approximately half that of heroin users based upon analyses conducted by Dr. Banta-Green of interviews from 1,661 clients entering methadone maintenance treatment which indicate a *lifetime* overdose rate for pharmaceutical opioid abusers (25%) that is half the rate of heroin abusers (49%). These findings were extrapolated to a 50% lower rate of *annual* overdose, the validity of which cannot currently be determined, but will be ascertained at the conclusion of this proposed study. We are assuming an annual overdose rate of 10% for pharmaceutical opioid users, or 20% over two years which is the amount of time over which follow up via administrative data will be collected. The power estimates above therefore address one year overdose rates for heroin and 2 years for pharmaceutical opioid users.

Planned methodology

Intent to treat analyses will be the primary analytic approach used to analyze the data resulting from this randomized controlled study. Intent to treat analyses compare those assigned to the intervention group to those in the standard care group, regardless of whether those in the standard care group receive some amount of the intervention.

Planned analyses

Aim 1 Test whether the intervention group has lower rates of opioid overdose and longer time to occurrence of overdose. Overdose will be ascertained at 12 months via self-report and across at least 24 months via administrative data. Because randomized controlled studies are designed to account for potential confounding factors by distributing confounders, measured and unmeasured, equally across comparison and intervention groups, the initial unadjusted analysis will be a logistic regression analysis comparing the probability of opioid overdose in the two study arms. To examine differences in the time to overdose and to account for time varying covariates, such as overdose risk factors, survival analyses will be conducted with the outcome time to overdose(s). A Cox proportional hazards model will be used to investigate the possible association between these factors and event time. We will use sandwich standard error estimates in all statistical tests. Multivariable logistic regression analyses will be conducted to examine the association between predictors and moderators and of the odds of overdose occurrence. Predictors will include treatment assignment and overdose risk factors such as concomitant drug use, interruption in tolerance and homelessness. Potential effect modification will be assessed by including interaction terms for the treatment assignment by severity of opioid and other substance use as measured by the ASSIST. For the pharmaceutical opioid only group, effect modification by opioid user type will be assessed; opioid user typologies will be based upon which inclusion criteria subjects met.

Aim 2 Test whether the intervention group has fewer overdose risk behaviors. These are measured as both binary and continuous data. Binary data will be examined with logistic

regression and continuous data analyzed with ordinary least-squares regression. Analyses will adjust for the overdose risk behavior level or frequency reported at baseline as a concomitant variable, the outcome is the overdose risk behavior at 12 months, and the primary predictor is the treatment group assignment. We will compute robust standard error estimates for each model and use them in all hypothesis tests and confidence intervals.

*Aims 3 and 4 Test whether the intervention group has more appropriate health care utilization and lower total health care costs***.** We will analyze utilization for three separate outcomes: ED visits, outpatient visits, and inpatient hospital admissions as we would expect the intervention to result in declines in ED and inpatient care with concomitant increases in outpatient care over time as patients stabilize their health status. For these analyses we will use a rate modeling approach (negative binomial or Poisson regression, with an exposure adjustment should there be a need to account for differing amounts of follow-up time). We will examine health care costs (combined hospital and ambulance costs) from the health care system perspective.

Mean-per-month health care costs will be calculated for both pre- and post-randomization periods for each individual. We will assess the difference in health care costs across the two study arms by regressing post-randomization mean health care costs on study arm, and controlling for pre-randomization mean health care costs (which should reduce variance and increase power) along with other important covariates. We expect that 500 per arm will be an adequate number to support the use of Ordinary Least-Squares (OLS) regression to model mean cost differences, but will use Generalized Linear Models (GLM) models *to* examine the sensitivity of OLS results. In addition, we will calculate unadjusted and adjusted cost offsets by adding the cost of the intervention to health care costs and comparing average monthly total costs of services for the intervention group to the average for the standard care group.

Aim 5 Test whether the intervention group has fewer HIV risk behaviors. These are measured as both binary and continuous data. Binary data will be examined with logistic regression and continuous data analyzed with ordinary least-squares regression.

Other analyses

In order to determine whether there is recruitment reactivity, whether those enrolled in either arm of the study have a change in behaviors compared to those not enrolled, we will examine ED re-visit rates at two years for those receiving standard care compared to those with similar demographic characteristics, CPT codes and ED visit dates, but were not enrolled. While this will not directly measure the impact of recruitment on overdose, it will provide some information about recruitment reactivity. Subsequent to intent to treat analyses we will examine whether any subjects in the standard care group received take-home naloxone and overdose prevention and intervention training i.e. “crossed over”. If so, it is possible that this intermediate group might be more similar to the intervention than the standard care group. *Crossovers* will be identified by as interview question, such as “Did you possess or have ready access to naloxone during the past 3/6 months?” If there is a group that crossed over, post-hoc analyses will compare overdose rates at two years for the cross over group compared to each of the other two study arms. Completion level of administrative data will be assessed by the interview questions at each follow up that document what types of services, in broad categories, were

obtained at non-HMC or non-UWMC facilities or ambulance services not in Seattle-King County. This will allow for an evaluation of *ascertainment bias*, that is, how complete data based on HMC/UWMC and King County ambulance data are and whether there are differential levels of data completion by study arm assignment.

Missing data and dropouts

Missing data will be minimized by the study procedures described above. However, missing data are inevitable and could lead to biased results. Baseline data values and study arm assignment will be examined to determine the relationship with missingness. Sensitivity analyses will be conducted that assume any person lost to follow up had constant levels of drug use based upon their most recent measurement point. This will provide some guidance as to the amount of bias possibly introduced by missing data.