Increasing Naloxone Access for Persons who use Opioids: An Online Recruitment and Training Approach to Opioid Overdose Education and Naloxone Distribution

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Sponsor: National Institute on Drug Abuse

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to, the protocol will take place without prior documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial subjects. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the local Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from subjects who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Increasing Naloxone Access for Persons who use Opioids: An Online Recruitment and Training Approach to Opioid Overdose Education and Naloxone Distribution
Objectives:	Feasibility and acceptability of completely remote implementation of Opioid Overdose Education and Naloxone Distribution (OEND)
Study Population:	Persons who use opioids at risk for overdose
Description of Study Intervention:	Eligible individuals who agree to participate will complete a questionnaire focused on opioid and other substance use history, overdose experiences, and history of substance use treatment. Interested and eligible individuals will then complete an online training focused on recognizing the signs of an opioid overdose, steps to take in that situation, and how to administer naloxone. Following training, participants will be randomly assigned to either receive a naloxone kit or be given information on how to obtain a kit. Online follow-up assessments will occur at one-, two-, and three-months post-training and focus on whether the participant has obtained or used their naloxone kit, naloxone kit use outcomes, and interest or engagement in substance use treatment.
Study Duration:	24 months
Subject Duration:	3 months

1.2 SCHEDULE OF ACTIVITIES (SOA)

Procedure	Length of Time Required of Participants	Total # of Times the Procedure is Performed
Screening	3 minutes	1
Informational Consent Sheet	3 minutes	1
Opioid Use Questionnaire	10 minutes	1
Decline Survey	5 minutes	1
Consent	20 minutes	1
Demographic Questionnaire	3 minutes	1
Pre-Naloxone Training Knowledge Questionnaire	5 minutes	1
Opioid Overdose & Naloxone Administration Training Video	20 minutes	1
Review of SAVEME Steps	5 minutes	1
Post-Naloxone Training Knowledge Questionnaire	5 minutes	1
Follow-up Assessments	5 minutes	3
Participant Satisfaction Survey	3 minutes	1

2 INTRODUCTION

2.1 STUDY RATIONALE

Deaths relating to opioid overdose have rapidly increased over the past two decades. Due to the serious public health concern of the opioid epidemic, federal agencies recommend employing various harm reduction interventions. The implementation of Opioid Overdose Education and Naloxone Distribution (OEND) programs is effective in reducing opioid overdose mortality, yet these programs do not reach many high-risk individuals. Traditionally, OEND program venues are found in large, urban medical centers, drug treatment facilities, and needle exchange programs. Identifying unreached, high-risk individuals and providing training and naloxone kits through online recruitment could significantly expand access to this life-saving intervention. The primary goal of the current proposed project is to examine the acceptability and feasibility of online recruitment, online opioid overdose and naloxone administration education, and postal distribution of naloxone kits. If the hypotheses of the proposed study are confirmed, this would support the feasibility and acceptability of implementing remote OEND to prevent death among high-risk individuals in areas lacking crucial access to this critical harm reduction strategy.

2.2 BACKGROUND

Drug overdose is the leading cause of accidental death in the United States, with over 65% of drug-related fatalities resulting from the use of opioids. Approximately 130 people die each day in the United States from opioid overdose. This alarmingly high and continually increasing rate of overdose deaths has led to the declaration of an opioid epidemic. Federal agencies such as the Drug Enforcement Agency (DEA) and Centers for Disease Control and Prevention (CDC) have responded to this crisis with recommendations for implementing guidelines for prescribing opioids, increasing funding for substance use treatment, and

enhancing harm reduction approaches such as syringe service programs and naloxone distribution. Naloxone is an opioid antagonist used for decades in an emergency department setting to reverse opioid overdose and effects of excessive opioid use such as sedation, hypotension, and respiratory depression. Naloxone is available in intranasal spray or intramuscular injection forms. A lethal dose of opioids can result in death within 20 minutes to a few hours and emergency services may not be contacted or able to respond within that time frame, especially in rural areas. Recently, laypersons have been successfully trained to recognize signs of opioid overdose and perform timely administration of naloxone in residential and community settings while awaiting medical services, resulting in thousands of lives saved.

Opioid Overdose Education and Naloxone Distribution (OEND) programs train laypersons, such as high-risk opioid users and their friends or family members, to recognize the signs of opioid overdose, and administer naloxone. Several studies have demonstrated that OEND programs effectively reduce opioid overdose mortality and are both safe and cost-effective. Due to the efficacy of these programs, many states have approved laws to facilitate the implementation of OEND. Unfortunately, even with these laws in place, only 8% of counties in the US have established programs, and barriers to naloxone distribution still exist. Even when OEND is implemented, these programs are typically located in urban areas as part of large medical center research programs, syringe service programs, or drug treatment programs, and individuals unable to access these programs are at heightened risk for overdose death. Recently, states have also implemented standing orders for some national pharmacy chains (e.g., CVS, Walgreens) to provide naloxone without an individual prescription. However, this still requires individuals to seek out the pharmacies and ask a pharmacist for naloxone, which the pharmacy may not have in stock. Overall, these barriers prevent high-risk opioid users from accessing this life-saving treatment.

Considering the many barriers to current methods of naloxone distribution, a novel approach to this crucial harm reduction strategy is greatly needed. Utilizing remote recruitment methodologies and online opioid overdose and naloxone administration training is an untested, yet promising approach to expand OEND to high-risk individuals who are not reached through traditional methods. Remote recruitment through online venues such as Craigslist has been a feasible recruitment strategy in other types of studies. Studies comparing Craigslist to traditional or other internet recruitment approaches (e.g., email invitations or advertisements placed on other online venues) have found that Craigslist is a viable approach for recruiting special populations in rural areas and its use resulted in a more diverse and representative sample. With 90% of U.S. adults accessing the internet in 2014 and over 60 million current monthly Craigslist users, this approach offers the potential for widespread recruitment. Regarding the feasibility of online training, online interventions generally have high session completion and follow-up rates, and overall expand access to treatments.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Physical: Naloxone has been associated with side effects. Some side effects may occur as the result of other drug interactions, such as the use of a stimulant in combination with an opioid, or because of the overdose itself. Most side effects are rare and typically mild. These include:

- Rapid or irregular heart rate
- Increased blood pressure
- Shortness of breath
- Seizures
- Death

Naloxone administration may initiate opioid withdrawal symptoms including:

- Agitation
- Nausea/vomiting
- Teary eyes/dilated pupils
- Fever
- Insomnia
- Spontaneous miscarriage in pregnant women

The specific incidence of naloxone-related side effects is not known at this time. However, they are generally mild in severity and rarely occur. Side effects that most commonly occur with naloxone administration are related to the induction of opioid withdrawal. Opioid withdrawal symptoms are reversible, treatable, and dissipate within days.

Psychological: As with other interventions with a behavioral/psychological component, some participants may be uncomfortable answering personal questions on questionnaires or talking about personal information during an assessment. Furthermore, being presented with information concerning opioid overdose, thinking about personal experiences related to opioid use, or reporting details of a situation in which they administered naloxone may cause some participants to feel upset.

Social, Economic, and/or Legal: Individuals may not seek medical attention after administering naloxone for fear of legal repercussions or belief that the person experiencing overdose does not require additional medical attention.

2.3.2 KNOWN POTENTIAL BENEFITS

If the participant experiences opioid overdose, the use of the provided or acquired naloxone kit could save their life. Similarly, if the participant encounters a person experiencing opioid overdose, the training and possessed naloxone kit could allow them to save another individual's life. If our hypotheses are confirmed, this study will provide strong preliminary data for a large-scale project to evaluate online recruitment, training, and remote naloxone distribution in a fully powered randomized clinical trial. Demonstrating the effectiveness of this approach could expand access to this life-saving medication and reduce the high and increasing morbidity of opioid overdoses in the United States.

3 STUDY DESIGN

3.1 OVERALL DESIGN

The primary purpose of this study is to assess the feasibility and acceptability of remote Opioid Overdose Education and Naloxone Distribution (OEND) in order to expand this life-saving intervention to individuals without access to traditional OEND programs. Secondary outcomes include group comparisons of risky opioid use and treatment seeking between participants who receive a naloxone kit and those who do not, as well as differences in active opioid use, severity of use, and past overdose experience between those individuals who elect to participate in overdose education and those who decline. Current or past six-month opioid users will be recruited via Craigslist, complete online screening questions, and an opioid use

survey. After survey completion, all participants will be asked if they would like online naloxone training. Participants interested in completing training will complete a virtual informed consent process, complete training online, and half will receive a naloxone kit in the mail while the other half will be provided information on where to purchase a naloxone kit. Online follow-ups will occur 1, 2, and 3 months after training.

Consent Process: Interested individuals will complete the aforementioned screening questions online through REDCap. Participants who meet the aforementioned inclusion/exclusion criteria will read an informational consent sheet written at a 6th grade reading level. Pressing, "agree to participate" and answering questions on the Opioid Use Questionnaire (described below) will indicate their consent for the anonymous survey. Those participants who complete the online survey and opt in for training will then complete an online informed consent process including a comprehensive overview of the study and encouragement to inquire about any questions or concerns they may have. These participants will receive a secure email link containing the online consent form to read and review. Participants who elect to consent for the study will provide an electronic signature and will receive a PDF of the completed consent form. The investigators will receive a completed consent form, which will be sent electronically.

Opioid Use Questionnaire: Individuals who agree to participate following review of the informational consent sheet will complete an online survey regarding their history of opioid use, prior overdose experiences, and history of substance use treatment. Next, participants will be asked if they would be interested in continuing with the study to receive opioid overdose and naloxone administration education. If they decline participation, we will ask them additional questions to assess the reasons for not receiving training and will thank them for their participation.

Naloxone Training: All participants who elect to continue to the second portion of the study will watch a standardized training video focused on recognizing the signs of opioid overdose, administering naloxone, and seeking medical attention. Following the training video, participants will review a comprehensive outline of the SAVE ME Steps, an acronym of the steps to take in an overdose situation (e.g., Stimulate-Airway-Ventilate-Evaluate-Muscular Injection-Evaluate/Support). The training lasts approximately 20 minutes. Participants' knowledge of opioid overdose and naloxone will be assessed pre- and post-training with a brief survey. Participants randomized to the OEND condition will be mailed a naloxone kit containing a 4mL nasal spray, while those participants randomized to the overdose education (OE) alone condition will be given information on where they can obtain a naloxone kit.

Randomization: Following consent and naloxone training, participants will be randomly assigned to one of two conditions: OEND or OE. Thus, while all participants will receive opioid overdose and naloxone administration training, only individuals randomized to the OEND group will receive a naloxone kit. Participants randomized to the OE group will receive information regarding where they can obtain a naloxone kit. Randomization will be 1:1 allotment with randomization blocks size 4 executed though REDCap.

Naloxone (*Narcan^{TM}*): With a physician's order, participants in the OEND condition will be sent a naloxone kit containing a 4mL nasal spray. Naloxone kits will be packaged in a bubble wrap envelope and sent via U.S. Postal Service. Participants in the OE alone condition will be given information on where they can obtain a naloxone kit (e.g., pharmacies with standing orders for naloxone).

Follow-up Assessments: Follow-up assessments delivered via a secure REDCap link sent to participants' email will occur at one-, two-, and three-months post-training. This assessment takes approximately 5

minutes to complete. Participants will receive compensation for each completed follow-up assessment (Month 1: $30.00; Month 2: $40.00; Month 3: $50.00).

3.2 END OF STUDY DEFINITION

The study will be considered complete when at least 150 participants are recruited for the Opioid Use Questionnaire portion of the study and at least 80 participants are recruited for the training portion of the study. Participants in the training portion who have not completed a follow-up assessment will receive at least three automatic reminder emails generated by REDCap with the goal of at least 80% overall retention.

4 STUDY POPULATION

4.1 INCLUSION CRITERIA

1. 18 years of age or older
2. Current or past six months illicit use of opioids
3. Electronic device access for online survey completion
4. Willing to provide email address to receive survey link and compensation
5. Able to read and speak English
6. Permanent address for mailing of naloxone kit (naloxone training only)
7. Does not currently have a naloxone kit in possession and is unaware of how to obtain a kit or unable to do so

4.2 EXCLUSION CRITERIA

1. Contraindication for naloxone (known severe allergic reaction)
2. Cognitive impairment or unstable psychiatric condition that interferes with the informed consent process

4.3 SCREEN FAILURES

Individuals who are not eligible for the study will be provided with information regarding where they can obtain a naloxone kit and advised to seek immediate medical attention in the event of an overdose. They will also be given the National Opiate Hotline number (1-888-784-6641) and SAMHSA's (Substance Abuse and Mental Health Services Administration) National Helpline (1-800-662-4357). All participants will receive this same information.

4.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment will occur online through advertisements placed on Craigslist (as well as other online venues such as Facebook and Reddit in the case of slow recruitment) that will include a secure link to REDCap for eligibility screening. This trial will also be registered and listed on the NIDA Clinical Trial Locator. In order to circumvent potential bias resulting from recruiting through the use of Craigslist and to ensure that the sample is not skewed toward one demographic, a minimum percentage of participants representing each gender and race will be recruited.

5 STUDY INTERVENTION

5.1 STUDY INTERVENTION(S) ADMINISTRATION

5.1.1 STUDY INTERVENTION DESCRIPTION

Opioid Use Questionnaire. Individuals who agree to participate following review of the informational consent sheet will complete an online survey regarding their history of opioid use, prior overdose experiences, and history of substance use treatment. Next, participants will be asked if they would be interested in continuing with the study to receive opioid overdose and naloxone administration education. If they decline participation, we will ask them additional questions to assess the reasons for not receiving training and will thank them for their participation.

Naloxone Training. All participants who elect to continue to the second portion of the study will watch a standardized training video focused on recognizing the signs of opioid overdose, administering naloxone, and seeking medical attention. Following the training video, participants will review a comprehensive outline of the SAVE ME Steps, an acronym of the steps to take in an overdose situation (e.g., **S**timulate-**A**irway-**V**entilate-**E**valuate-**M**uscular Injection-**E**valuate/Support). The training lasts approximately 20 minutes. Participants' knowledge of opioid overdose and naloxone will be assessed pre- and post-training with a brief survey. Participants randomized to the OEND condition will be mailed a naloxone kit containing a 4mL nasal spray, while those participants randomized to the overdose education (OE) alone condition will be given information on where they can obtain a naloxone kit.

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Naloxone (Narcan™). With a physician's order, participants in the OEND condition will be sent a naloxone kit containing a 4mL nasal spray. Naloxone kits will be packaged in a bubble wrap envelope and sent via U.S. Postal Service. Participants in the OE alone condition will be given information on where they can obtain a naloxone kit (e.g., pharmacies with standing orders for naloxone).

Follow-up Assessments. Follow-up assessments delivered via a secure REDCap link sent to participants' email will occur at one-, two-, and three-months post-training. This assessment takes approximately 5 minutes to complete. This scale includes questions about whether the participant has used their naloxone kit, who received the naloxone, who administered the naloxone, whether CPR was performed, whether a call was placed to 911, whether they have experienced personal or observed overdose, whether they have entered substance use treatment, and whether they are currently using opioids in an illicit manner.

5.1.2 DOSING AND ADMINISTRATION

Participants in the OEND group will receive one 4mL/mg Narcan™ nasal spray.

5.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION

The use of Craigslist as a recruitment tool could introduce potential bias into the sample. In order to circumvent potential bias resulting from recruiting through the use of Craigslist and to ensure that the sample is not skewed toward one demographic, a minimum percentage of participants representing each sex and race will be recruited (40% female, 20% African American). Of note, current OEND recruitment methods localized to hospitals and treatment facilities result in skewed samples primarily representing the Caucasian population. Using Craigslist could allow for more diverse recruitment. Moreover, current OEND programs most often recruit individuals from treatment facilities and hospitals, thus constituting samples of extremely high-risk individuals. Using an online recruitment approach such as Craigslist could expand OEND to individuals across the severity spectrum of opioid use.

6 STUDY INTERVENTION DISCONTINUATION AND SUBJECT DISCONTINUATION/WITHDRAWAL

6.1 DISCONTINUATION OF STUDY INTERVENTION

The Principal Investigator, primary study mentor, and all other mentors will determine if the study needs to be terminated ahead of the planned study conclusion date. Early study termination may be determined necessary as a result of a serious injury or death directly related to study procedures. Given the high-risk nature of this population and the potential for overdose, deaths due to overdose may occur and are not a reason to stop the study.

6.2 SUBJECT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Subjects are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a subject from the study for the following reasons:

- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject

Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

6.3 LOST TO FOLLOW-UP

A subject will be considered lost to follow-up if he or she fails to complete 2 scheduled online assessments and is unable to be contacted by the study site staff.

The following actions must be taken if a subject fails to complete a scheduled online assessment:

- The site will attempt to contact the subject to remind the subject to complete the assessment and counsel the subject on the importance of maintaining the assigned assessment schedule and ascertain if the subject wishes to and/or should continue in the study.

- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or study file.
- Should the subject continue to be unreachable, the subject will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7 STUDY ASSESSMENTS AND PROCEDURES

7.1 STUDY ASSESSMENTS

Table 1: Instrument Description
***Demographics*.** Basic demographic information including age, gender, race/ethnicity, education level, employment status, annual income, marital status, living situation, drug allergies, and history of substance use and psychiatric disorders will be collected.
***Opioid Use Questionnaire*.** A questionnaire assessing history of opioid use, experience of personal and observed overdoses, previous experience with naloxone, and past substance use treatment.
Decline Survey. A survey administered to participants who decline to continue with the study and receive opioid overdose and naloxone administration training to evaluate reasons for refusing training.
***Pre- and Post-Training Assessment*.** This scale will be administered pre- and post-viewing of training materials and will assess opioid overdose and naloxone knowledge.
***Follow-up Assessment*.** This scale includes questions about whether the participant has used their naloxone kit, who received the naloxone, who administered the naloxone, whether CPR was performed, whether a call was placed to 911, whether they have experienced personal or observed overdose, whether they have entered substance use treatment, and whether they are currently using opioids in an illicit manner.
Participant Satisfaction Survey. This assessment queries about participants' satisfaction with the online training program and postal distribution of naloxone kits (or information regarding where to obtain a kit).

7.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

7.2.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

7.2.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event (of note, the term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event, rather than to an event which hypothetically might have caused death if it were more severe)

- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

7.2.3 CLASSIFICATION OF AN ADVERSE EVENT

7.2.3.1 SEVERITY OF EVENT

For adverse events (AEs), the following guidelines will be used to describe severity:

- **Mild** – Events require minimal or no treatment and do not interfere with the subject's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious."

7.2.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the subject based on temporal relationship and their clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

7.2.3.3 EXPECTEDNESS

The Principal Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

7.2.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study subject presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the study subject's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The Study Coordinator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. Events will be followed for outcome information until resolution or stabilization.

7.2.5 ADVERSE AND SERIOUS ADVERSE EVENT REPORTING

All serious adverse events must be reported to the IRB according to regulatory requirements. The Principal Investigator will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or package insert and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the Principal Investigator deems the event to be chronic or the subject is stable. Other supporting documentation of the event may be requested and should be provided as soon as possible.

7.3 UNANTICIPATED PROBLEMS

7.3.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- 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.

7.3.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB within 10 working days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB within 10 working days of the investigator becoming aware of the problem.

8 STATISTICAL CONSIDERATIONS

8.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s):

Hypothesis 1 states that remote OEND will be a feasible approach and will be supported if 80 participants are recruited within the first 13 months of the study, there is an overall significant increase in opioid overdose knowledge post-training, 80% of assessment measures are completed, and 80% of participants endorse high satisfaction scores.

- Secondary Efficacy Endpoint(s):

Hypothesis 2 will be supported if there are group differences between individuals who elect to participate in overdose training and those who decline to do so such that individuals who elect to participate will be

more likely to have active opioid use, have higher severity of use, experience of past overdose, and know someone who has experienced an overdose.

Hypothesis 3 will be supported if there are group differences in kit possession and there are no relevant group differences over time (Months 1-3), as quantified by the point estimates of effect size, in behaviors such as risky opioid use and interest/seeking out treatment between participants who received a kit versus those who did not receive a kit.

8.2 SAMPLE SIZE DETERMINATION

We propose to recruit 80 participants to the training portion of the study over a 12-month period. Sample size was determined by feasibility, since the primary outcomes of the study are feasibility and acceptability of remote OEND. Feasibility and acceptability are operationally defined as 1) recruitment of 80 participants during the first 12 months of the project; 2) increase in opioid knowledge post-training; 3) 80% completion of assessment measures and 4) 80% endorsement of high scores on a participant satisfaction measure. An exploratory aspect of the study involves determining the occurrence of naloxone kit use and outcomes, though the study will not be powered to evaluate this and will serve as a pilot for a larger study. The fundamental purpose of the proposed pilot study is to assess feasibility and acceptability to inform future studies, not to provide sample size estimates. If testing is conducted, assuming recruitment of 80 participants with a dropout rate of 20% (consistent with prior studies), uniformly distributed over the 3-month follow-up period would result in approximately 70 participants on average at each of the three follow-up time points. The sample size provides 80% power to detect a time-averaged mean difference of .55 SD between groups for a continuous outcome, or an odds ratio of 2.69 for a binary outcome, assuming an alpha level of .05 and an intrasubject correlation of .5 (computations in PASS 11 software).

8.3 STATISTICAL ANALYSES

8.3.1 GENERAL APPROACH

Data will be exported from REDCap to IBM SPSS statistical software, Version 25 and standard data cleaning procedures will be completed. Study variables for the entire sample will be examined using descriptive statistics such as frequencies and percentages (for categorical variables) and means, standard deviations, percentiles, and ranges (for continuous variables) to ensure values are reasonable. Prior to conducting analyses related to the hypotheses of the study, individual distributions of continuous variables will be examined visually with histograms to confirm that all assumptions for the analyses are reasonably met. Methods robust to distributional assumptions will be used as appropriate. The impact of incorrect data entry will be minimized by the implementation of logic checks in the entry forms on REDCap.

Data analysis for between-group comparisons will begin with descriptive statistics for baseline participant characteristics and outcomes by treatment group. Balance between groups will be assessed using measures of effect size such as the standardized mean difference (Cohen's *d*) for continuous variables and d-equivalent for binary or categorical variables. Patterns of missing data will be examined according to baseline covariates. Baseline factors that could be causally related to the outcomes and showing relevant between group imbalances or that are predictive of missing data will be used as adjusting covariates. Mixed-effect modeling techniques and covariate adjustment will reduce the impact of missing data, as

the approach allows for using all collected data, and the missing data are considered missing conditionally (on the covariates) at random, a milder assumption than missing completely at random.

8.3.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Measures of effect size and tests of between group differences (e.g., t-tests, chi-squared tests) will be conducted to compare groups. An FDR approach will be used to adjust for multiple exploratory inferences.

8.3.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Generalized linear mixed-effects models with random effects for subject (and logit links for binary outcomes) will be fitted to the repeated measures data. Linear contrasts will be used to estimate between-group differences. Inverse-link estimates will be computed to facilitate interpretation. A false discovery rate (FDR) approach will be considered to adjust for multiple inferences if necessary. Confidence intervals (possibly adjusted for multiple inferences) will be computed to quantify uncertainty about estimates.

9 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

9.1.1 INFORMED CONSENT PROCESS

9.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO SUBJECTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to conducting study screening procedures. A separate screening consent form will not be used.

9.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the subject will be asked to read and review the document. The investigator will explain the research study to the subject and answer any questions that may arise. A verbal explanation will be provided in terms suited to the subject's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research subjects. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing. The subjects should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The subject will sign the informed consent document prior to any procedures being done specifically for the study. Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the subjects for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the subject undergoes any study-specific procedures. The rights and welfare of the subjects will be protected by

emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

9.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study subjects and the Institutional Review Board (IRB), will provide the reason(s) for the termination or suspension. Study subjects will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB.

9.1.3 CONFIDENTIALITY AND PRIVACY

Subject confidentiality and privacy is strictly held in trust by the participating investigators and their staff. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Principal Investigator.

All research activities will be conducted in as private a setting as possible.

Representatives of the Institutional Review Board (IRB) may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB and/or Institutional policies.

Study subject research data, which is for purposes of statistical analysis and scientific reporting, will be stored at the UAB Department of Otolaryngology research office. This will not include the subject's contact or identifying information. Rather, individual subjects and their research data will be identified by a unique study identification number. The study data entry and study management systems used by research staff will be secured and password protected.

9.1.4 QUALITY ASSURANCE AND QUALITY CONTROL

The site will perform internal quality management of study conduct, data collection, documentation and completion. Quality control (QC) procedures will be completed by the Data Manager during data entry into the appropriate CRF. Any missing data or data anomalies will be communicated to the Study Coordinator for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted, and data are generated are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements.

The site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and inspection by local and regulatory authorities.

9.1.5 DATA HANDLING AND RECORD KEEPING

9.1.5.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the Principal Investigator. The Principal Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

9.1.5.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 3 years after the completion of the study. These documents should be retained for a longer period, however, if required by local regulations.

9.1.6 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the Principal Investigator to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The Principal Investigator is responsible for knowing and adhering to the reviewing IRB requirements.

9.1.7 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

9.2 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DHHS	Department of Health and Human Services
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
LSMEANS	Least-squares Means
NCT	National Clinical Trial
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOA	Schedule of Activities
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

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