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# 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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# 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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## ABSTRACT

Drug overdose is the primary cause of accidental death in the United States, with a majority of those fatalities involving opioids. Annual rates of fatal opioid overdoses have exponentially increased over the past two decades, leading to the declaration of the current opioid epidemic. The severity of the epidemic has increased due to an upsurge in the use of heroin, synthetic opioids (e.g., fentanyl), and the lacing of other substances with synthetic opioids. As such, federal agencies have made recommendations aimed at combating fatal opioid overdose including the enhancement of naloxone distribution. Administration of naloxone has been expanded from emergency department settings to non-medical first responders and laypersons, allowing for administration of naloxone while waiting for emergency medical services. Opioid Overdose Education and Naloxone Distribution (OEND) programs train laypersons to recognize and respond to opioid overdose and equip them with naloxone. These programs have been shown to effectively reduce overdose mortality. However, implementation has been substandard, and accessibility is limited due to programs typically being located in urban areas at research institutions or drug treatment centers. Individuals who have not presented to treatment or who live in areas without these programs or services lack access to life-saving OEND. Thus, this project aimed to provide preliminary information to ultimately enhance OEND practices by 1) evaluating the feasibility of applying remote methodologies to the OEND

model; 2) identifying characteristics of individuals most interested in receiving OEND; and 3) examining continued criticisms of naloxone possession. Overall, feasibility and acceptability of online opioid overdose and naloxone administration training and postal distribution of naloxone was supported. Differences were identified between individuals who elected to participate in training and those who declined, potentially indicating that OEND programs could benefit from tailoring information and highlighting training benefits for those most likely to decline. Similar to previous research, naloxone possession in this sample did not appear to negatively impact opioid use or interest in treatment, further suggesting that residual unfounded criticisms should not inhibit naloxone distribution. Overall, implementation of remote OEND methodology could greatly expand access to this life-saving intervention and reduce the severity of the opioid epidemic.

Keywords: Opioid overdose education, naloxone distribution, remote methodologies

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# INTRODUCTION

Drug overdose is the primary cause of accidental death in the United States, with over 932,000 related fatalities in the past two decades (*Death Rate Maps & Graphs*, 2022). Annual drug overdose deaths have steadily risen during that time frame with almost 92,000 casualties reported in 2020 (*Death Rate Maps & Graphs*, 2022). Approximately 75% of drug overdose deaths now involve opioids (*Death Rate Maps & Graphs*, 2022). In 1999, only 8,000 opioid overdoses occurred but since then opioid implicated overdoses have multiplied over eight-fold, accounting for nearly 76,000 deaths in 2021 (*CDC WONDER*, 2022; *Data Overview*, 2022). The drastic and persistently increasing rise in opioid overdose mortality throughout the past two decades resulted in the declaration of an opioid epidemic (*Understanding the Epidemic*, 2022).

The opioid epidemic has been broken down into three waves (*Understanding the Epidemic*, 2022). The first wave resulted from the over prescription of opioid medications in the 1990s due to their being marketed to physicians as essentially non-addictive (Van Zee, 2009). After the recognition of opioids' addictive potential, physicians began to restrict prescribing of opioid analgesics. Thus, the second wave started in 2010 with individuals switching from prescription opioids to heroin due to difficulties receiving opioid prescriptions long-term (Cicero & Ellis, 2015; Compton et al., 2016; Unick et al., 2013). Also during this time, opioid-naïve individuals initiating use with heroin, rather than starting with prescription medications, increased dramatically (Harocopos & Allen, 2015). Starting in 2016, the third wave has involved the use of, and lacing of other

substances with, synthetic opioids (e.g., fentanyl), which are now implicated in over 82% of fatal opioid overdoses (*Death Rate Maps & Graphs*, 2022; *Synthetic Opioid Overdose Data*, 2021). Severity of the epidemic has greatly intensified as a result of the upsurge in heroin and synthetic opioid use, in addition to frequent lacing of other substances with more potent synthetic opioids. Thus, federal agencies have recommended several approaches to combat this crisis including evidence-based harm reduction strategies such as enhanced naloxone distribution (Carroll et al., 2018; Kanouse & Compton, 2015; Volkow et al., 2014).

Naloxone is an opioid antagonist used to rapidly reverse the potentially fatal effects of excessive opioid use such as respiratory depression, hypoxia, hypotension, and sedation. This is achieved through its competitive binding to receptors against opioids, thus blocking opioids from occupying and activating receptors. It is available in a variety of formulations including intramuscular injection and nasal spray, with onset of action occurring within two to five minutes contingent upon route of administration. Naloxone has been utilized in emergency department settings for decades and its use was eventually expanded to non-medical first responders, such as law enforcement officers and firefighters, as well as laypersons (Townsend et al., 2020; Wood et al., 2021). Extension of naloxone use to non-medical persons serves the purpose of reducing time to administration given that overdose death can occur within as quickly as 20 minutes and arrival of emergency medical services may exceed that time frame, especially in rural areas (Darke & Duflou, 2016; Mell et al., 2017; Townsend et al., 2020; Wood et al., 2021). Laypersons can obtain naloxone through various modes including purchase at a

pharmacy with a standing order and Opioid Overdose Education and Naloxone Distribution (OEND) training programs.

OEND programs train laypersons to identify opioid overdose and execute appropriate response strategies, including the administration of naloxone when indicated (Razaghizad et al., 2021). These programs have repeatedly shown an improvement in knowledge of overdose risk factors, signs of overdose, and recommended response procedures following training (Behar et al., 2015; Clark et al., 2014; Giglio et al., 2015; Razaghizad et al., 2021). More importantly, OEND programs effectively increase the use of response protocol, timely administration of naloxone, and considerably reduce opioid overdose mortality (Bird et al., 2016; Clark et al., 2014; Giglio et al., 2015; McAuley et al., 2015; McDonald & Strang, 2016; Razaghizad et al., 2021). Naloxone administration is safe with low potential for adverse effects, even when conducted by non-medical persons, and its distribution is cost-effective (Coffin & Sullivan, 2013; McDonald & Strang, 2016; Razaghizad et al., 2021; Townsend et al., 2020; Wagner et al., 2010). With these demonstrated benefits, OEND programs have become more widespread, and several states have passed legislation aimed at enabling their implementation (Bennett & Elliott, 2021; Lambdin et al., 2018; Smart et al., 2021).

In addition to legislation facilitating OEND, most states have also attempted to increase naloxone access by passing standing order laws (Gertner et al., 2018; Lambdin et al., 2018; Xu et al., 2018). These laws give prescriptive authority to pharmacies such that they can dispense naloxone without an individual prescription being presented by the customer. Standing order laws have resulted in increased naloxone dispensing from retail

pharmacies along with increased Medicaid reimbursement for its purchase (Gertner et al., 2018; Xu et al., 2018).

Despite these efforts to expand OEND and naloxone access, implementation of these programs remains limited and barriers to obtaining naloxone still exist. In general, the OEND model and idea of naloxone possession lack support due to concerns that having naloxone could actually escalate opioid use by acting as a "safety net" (Barocas, 2019; Bazazi et al., 2010; Bennett & Elliott, 2021; Jones et al., 2017; Murphy & Russell, 2020; Sisson et al., 2019; Winograd et al., 2020). Thus far, evidence for this criticism is insufficient, as multiple studies have found no compensatory opioid use, in addition to some studies noting a reduction in use (Jones et al., 2017; McDonald & Strang, 2016; Tse et al., 2022; Wagner et al., 2010; Winograd et al., 2020). Even so, the view that naloxone possession has negative consequences adversely impacts policy enactment, funding, and distribution. Established OEND programs exist in less than 15% of counties with the greatest opioid overdose rates (Lambdin et al., 2017). Furthermore, they are often operated in partnership with syringe exchange programs, which are accessible in only 34 states (Bennett & Elliott, 2021). OEND programs outside of syringe exchange are typically located in urban areas at academic research institutions, treatment programs, or health departments, thereby limiting access for individuals in rural areas or who have not yet presented to treatment (Bennett & Elliott, 2021; Jarlais et al., 2015; Jones et al., 2017; Lambdin et al., 2017, 2018). The increasing price of naloxone potentially threatens the cost-effectiveness of OEND programs and their ability to provide this service free of charge (Gupta et al., 2016; Townsend et al., 2020).

Cost of naloxone is also a barrier for laypersons wanting to purchase it from a pharmacy, as prices range from fifty, to hundreds, or even thousands of dollars depending on formulation. Though Medicaid reimbursement for naloxone has increased with standing order laws, many individuals seeking naloxone do not have insurance, or their plan may not include naloxone coverage (Evoy et al., 2021; Xu et al., 2018). Despite standing orders, pharmacies frequently do not have naloxone in stock, especially independent pharmacies in rural areas (Graves et al., 2019; Guadamuz et al., 2019; Guy et al., 2019, 2021; Pollini et al., 2022; Puzantian & Gasper, 2018; Sisson et al., 2019; Stone et al., 2020). Pharmacists holding negative attitudes about naloxone, specifically the view that it allows avoidance of emergent treatment, has been associated with decreased naloxone dissemination from their pharmacy (Sisson et al., 2019).

Overall, OEND programs have demonstrated their utility in combating the current opioid crisis by equipping participators with the knowledge and tools to respond quickly, safely, and effectively in an overdose situation. Uptake and support of naloxone distribution has been substandard, thus limiting the range and impact of this life-saving intervention. Expanding access to these programs and their ability to reach those most likely to witness and mitigate an overdose could substantially lessen overdose mortality. As such, the primary goal of this project was to examine the feasibility of a novel, remote approach to OEND that involved online recruitment, online opioid overdose and naloxone administration education, and postal distribution of naloxone kits. In an effort to further extend the scope and impact of OEND, this study also aimed to initially characterize individuals most interested in receiving training to facilitate future tailoring of these programs. Randomization of participants to either be provided a naloxone kit or

encouraged to obtain one through their local pharmacy allowed for consideration of barriers to pharmacy-based naloxone procurement. Finally, in response to enduring criticisms of naloxone, this project sought to examine the relationship between kit possession and severity of opioid use as well as interest in treatment. Altogether, the objective of this study was to provide preliminary information to ultimately enhance OEND practices as a mechanism to prevent death among high-risk individuals and diminish fatal opioid overdose.

# FEASIBILITY AND ACCEPTABILITY OF ONLINE OPIOID OVERDOSE EDUCATION AND NALOXONE DISTRIBUTION: STUDY PROTOCOL AND PRELIMINARY RESULTS FROM A RANDOMIZED PILOT CLINICAL TRIAL

by

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## Abstract

Drug overdose is the leading cause of accidental death in the United States, with over 70% of drug related fatalities resulting from the use of opioids. The continually increasing rates of opioid overdose deaths in the last two decades have led to the declaration of an opioid epidemic. Federal agencies have responded to this crisis with various recommendations including enhancing harm reduction approaches such as naloxone distribution. Laypersons have recently been successfully trained through Opioid Overdose Education and Naloxone Distribution (OEND) programs to recognize signs of opioid overdose and perform timely administration of naloxone, in homes and community settings while awaiting medical services. Several studies have demonstrated that OEND programs effectively reduce opioid overdose mortality and are both safe and cost-effective. However, OEND programs are typically implemented in urban areas as part of large medical center research programs, needle exchanges, or drug treatment programs. Individuals living in areas without these programs or services lack access to critical and life-saving OEND. The current study examined the acceptability and feasibility of online recruitment, online opioid overdose education, and remote distribution of naloxone kits. Persons who illicitly use opioids and are at risk for overdose were recruited online through online media and completed an opioid use questionnaire. Participants then indicated if they were interested in receiving opioid overdose and naloxone administration training. If interested, they completed pre- and post-intervention knowledge questionnaires, engaged in audiovisual training, and were randomized to either receive a naloxone kit or be given information on where they could obtain one. Remote follow-up assessments were conducted at 1-, 2-, and 3-months post study to

evaluate naloxone kit use and outcomes. Preliminary results indicate feasibility and acceptability as evidenced by strong recruitment and retention, as well as high participant satisfaction ratings. Successful implementation of remote OEND through this project supports future employment of similar remote programs to expand this critical harm reduction strategy to high-risk individuals in areas lacking traditional OEND programs.

## Background

Drug overdose is the leading cause of accidental death in the United States, with over 70% of drug-related fatalities resulting from the use of opioids (*Understanding the Epidemic*, 2022). Approximately 200 people die each day in the United States from opioid overdose (*Drug Overdose Deaths in the U.S. Top 100,000 Annually*, 2021). This alarmingly high and continually increasing rate of overdose deaths has led to the declaration of an opioid epidemic (Volkow et al., 2014).

Over a brief 15-year period, from 1999-2014, drug overdose-related deaths tripled, and rates have continued to sharply escalate since then (Rudd et al., 2016; Seth et al., 2018). The opioid epidemic began with over prescription of opioid medications in the late 1990s, which was followed by a pendulum constricting of prescribing due to the recognition of these medications' addictive potential (Cicero & Ellis, 2015; Compton et al., 2016; Harocopos & Allen, 2015; Seth et al., 2018; Unick et al., 2013). Difficulty receiving opioid medications long-term resulted in many individuals switching from prescription opioids to heroin (Cicero & Ellis, 2015; Compton et al., 2016; Harocopos & Allen, 2015; Seth et al., 2018; Unick et al., 2013). Concurrently, rates of opioid use initiated with heroin, rather than prescription medications, increased from 8.7% to 31.6% (Cicero & Ellis, 2015). Most recently, the opioid epidemic has been characterized by a large percentage of synthetic opioid-related deaths (e.g., fentanyl), which have accounted for over 73% of opioid-related deaths (*Synthetic Opioid Overdose Data*, 2021).

This upsurge in use of heroin, especially among opioid naïve individuals, and the new danger of synthetic additives, have greatly intensified the severity of the opioid crisis. 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 (Kanouse & Compton, 2015; Rudd et al., 2016; Volkow et al., 2014).

### *Naloxone Distribution*

Naloxone is an opioid antagonist used for decades in an emergency department setting to acutely reverse opioid overdose and effects of excessive opioid use such as sedation, hypotension, and respiratory depression (Johnson et al., 2018). Naloxone is available in intranasal spray or intramuscular injection forms. Onset of action ranges from two to five minutes depending on the route of administration (Adapt Pharma Inc., 2015). 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 (Darke & Duflou, 2016). Recently, laypersons have been successfully trained to recognize signs of opioid overdose and perform timely administration of naloxone in residential and community settings, thus providing care while awaiting medical services. This approach has resulted in thousands of lives saved (Bennett et al., 2018; Clark et al., 2014; Johnson et al., 2018; McAuley et al., 2015; McDonald & Strang, 2016; Razaghizad et al., 2021; Wheeler et al., 2015).

Opioid Overdose Education and Naloxone Distribution (OEND) programs train laypersons, such as high-risk individuals who use opioids 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 (Behar et al., 2015; Coffin & Sullivan, 2013; Lambdin et al., 2017; Walley et al., 2013; Wheeler et al., 2015). Due to the efficacy of these programs, many states have approved laws to facilitate the implementation of OEND (Lambdin et al., 2018). Unfortunately, even with these laws in place, established naloxone programs are limited or exist solely in tandem with syringe exchange programs, which are available in only 34 states across the U.S. (Bennett & Elliott, 2021). Furthermore, several barriers to naloxone distribution still exist (Bennett & Elliott, 2021; Drainoni et al., 2016; Lambdin et al., 2017). For example, the OEND model itself may lack support due to unsubstantiated concerns that possession of naloxone acts as a "safety net" and consequently results in continued or increased opioid use (Bennett & Elliott, 2021; Jones et al., 2017). Multiple studies have demonstrated that this concern is unfounded, as evidenced by reduction in opioid use and increase in substance use treatment enrollment at participant follow-up (Bennett & Elliott, 2021; Jones et al., 2017; Seal et al., 2005; Wagner et al., 2010; Winstanley et al., 2016). 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. Thus, individuals who are unable to access these programs are at heightened risk for overdose death (Bennett & Elliott, 2021; Jarlais et al., 2015; Jones et al., 2017; Lambdin et al., 2017, 2018).

Standing order laws have been implemented that allow for pharmacies to dispense naloxone without an individual prescription being presented (Gertner et al., 2018; Lambdin et al., 2018; Xu et al., 2018). However, barriers such as inadequate common

knowledge about this option, lack of insurance coverage, and even pharmacists' negative perceptions about naloxone hamper the potential benefits of this legislation (Sisson et al., 2019). Overall, inadequate implementation of OEND programs and standing orders prevents high-risk opioid users from accessing this life-saving treatment.

### *Remote Recruitment and Online Training*

Considering the limitations of 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 a largely untested, yet promising approach to expand OEND to high-risk individuals who are not reached through traditional methods. Remote recruitment through online venues (e.g., Craigslist) has been a feasible recruitment strategy in other clinical trials, such as those involving smoking cessation treatment (Carpenter et al., 2010, 2011). Computer-assisted therapies have been used successfully with a wide range of interventions in order to expand the availability and reach of treatment, suggesting that online training for naloxone distribution is feasible (Carroll et al., 2014; Wright et al., 2019). Online interventions generally have high session completion and follow-up rates, and overall expand access to treatments (Carroll et al., 2014).

### *Summary and Aims of the Current Project*

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 OEND 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. To further extend the benefits of OEND, there is compelling need to identify unreached, high-risk individuals and provide training and naloxone kits through online methods. The primary goal of the current project was to examine the acceptability and feasibility of online recruitment, online opioid overdose and naloxone administration education, and postal distribution of naloxone kits.

## Methods

### *Participants*

Since this was a pilot study, sample size was determined on the basis of examining feasibility and not for testing of outcomes (*Pilot Studies*, 2022). Participants included 304 individuals who had illicitly used opioids (e.g., illicit prescription opioids, heroin, fentanyl) within the past six months. Recruitment occurred online through advertisements placed on Craigslist that included a secure link to an online REDCap survey for eligibility screening. Advertisements were posted for two rural and two urban cities within four southeastern states (16 cities total) in which naloxone is legal to obtain without a prescription. Inclusion criteria consisted of age (18 years or older), illicit opioid use within the past six months, access to an electronic device for online survey completion, and willingness to provide a permanent mailing address for receipt of naloxone kit and payment. Individuals were excluded from the study if they had a known contraindication for naloxone, already possessed a naloxone kit, or had a reported cognitive impairment that would interfere with the consent process. More information on

these criteria can be found on ClinicalTrials.gov, where the study is registered (NCT04303000).

*Consent Process*

Participants who met the aforementioned inclusion/exclusion criteria were automatically advanced to an online informational consent detailing the first portion of the study and baseline assessment: the Opioid Use Questionnaire (described below). Those that agreed to participate were directed to the survey. Participants who completed the online survey and opted to continue to the naloxone training portion of the study reviewed a comprehensive consent document in REDCap, provided an electronic signature, and received a PDF copy of the document via email. Participants were given study personnel contact information and encouraged to reach out with any questions or concerns prior to signing the consent form. This consent process, and the entirety of the study protocol, was reviewed and approved by the Institutional Review Board at the University of Alabama at Birmingham.

*Opioid Use Questionnaire*

Individuals who agreed to participate following review of the informational consent sheet completed an online baseline survey regarding their history of opioid and other substance use, prior overdose experiences, and history of substance use treatment. At survey completion, participants were asked if they would be interested in continuing with the study to receive opioid overdose and naloxone administration education.

*Opioid Overdose and Naloxone Administration Training*

All participants who elected to continue to the second portion of the study watched a one-time standardized training video (~10 minutes) focused on recognizing the signs of opioid overdose, administering naloxone, and seeking medical attention (*Prevent an Overdose, Save a Life*, 2013). Following the training video, participants reviewed 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/Nasal Spray-**E**valuate/Support; *SAVEME Steps: What to Do for a Suspected Overdose*, 2022). The training lasted approximately 20 minutes. Participants' knowledge of opioid overdose and naloxone was assessed pre- and post-training with a 9-item survey adapted from a previously validated scale (Williams et al., 2013). They also answered questions regarding the acceptability of the remote study format.

*Randomization*

Following consent and naloxone training, participants were randomly assigned to one of two conditions: 1) receipt of 4mL nasal spray naloxone kit, or 2) a control condition in which participants were given specific information detailing the name, address, and phone number of pharmacies in their area where they could obtain a naloxone kit. Randomization was a 1:1 allotment with randomization blocks size 4 executed though REDCap software.

*Follow-up Assessments*

Follow-up assessments were delivered via a secure REDCap link sent to participants' email at one, two, and three-months post-training. This assessment inquired about whether the participant had used their naloxone kit (or obtained and used a kit for those in the control condition), circumstances during the overdose situation, and kit use outcomes. Participants were also asked whether they were currently using opioids in an illicit manner and if they were considering or had entered substance use treatment.

*Data Analytic Approach*

Average recruitment rate per week was calculated by dividing the number of enrolled participants by the number of active recruitment weeks. Percentages of participants who completed assessment measures and retention over the course of the study were also calculated. Data analysis for between-group comparisons involved descriptive statistics for baseline participant characteristics. Balance between groups was assessed using measures of effect size including the standardized mean difference (Cohen's *d*) for continuous variables and Cramer's *V* for binary or categorical variables (Rosenthal & Rubin, 2003). The overall percentage of participants who endorsed high satisfaction scores was calculated. High satisfaction was classified as a score of 90% or higher.

# Results

## *Participant Demographic Characteristics*

Demographic characteristics of the sample (N = 304) included the following: 53% female (47% male), 11.8% Black/African American, 82.9% White/Caucasian, 4.9% Hispanic ethnicity, and 61.8% attainment of high school education. A majority (79.3%) of the sample reported an annual household income between $10,000 and $49,999. On average, participants were 37.5 years old (*SD* = 9.55). All participants reported illicit opioid use within the past six months.

Participants who completed the naloxone training portion of the study did not substantively differ from those who declined in terms of age, race, income, or education level. However, female participants were more likely to complete the training, though the effect size was small ($X^2$ = 3.28, $p$ = .015, Cramer's $V$ = 0.14). See Table 1 for detailed demographic characteristics.

## *Recruitment and Retention*

Recruitment occurred over an 11-week period with a combined total of 304 participants enrolled for both portions of the study. For the first portion of the study that involved completion of the Opioid Use Questionnaire, 447 individuals were screened. Of those who were eligible and initiated the Opioid Use Questionnaire, only two individuals did not complete the survey. The average recruitment rate for this portion of the study was 13 individuals per week. Of the total, 193 individuals discontinued after completing the survey or were not eligible to complete the second portion of the study. For the second portion of the study that included opioid overdose and naloxone administration

training, 219 individuals were screened and 111 were enrolled. The average recruitment rate for this portion of the study was 9 individuals per week.

Overall, the study demonstrated strong retention rates. For the first portion of the study, 304 out of 306 (99.3%) participants finished the survey. For the second portion of the study, 98 out of 111 (88%) enrolled individuals completed the training and the one-month follow-up assessment. The two and three-month follow-up assessments had 86% (n = 95) and 83% (n = 92) completion, respectively. There was no statistical difference in completion rates between the randomized groups. See Figure 1 for a consort diagram detailing enrollment, allocation, and completion.

### *Participant Satisfaction*

Participants who completed the training portion of the study ($n$ = 98), had a mean satisfaction score of 94.63%. When "high satisfaction" was classified as 90% or greater, 87.8% of participants endorsed high satisfaction with the study format. A large percentage (85.4%) of participants in the OEND group reported being "*Very satisfied*" with receiving a naloxone kit while only 60% in the OE group were as satisfied with receiving information on where to obtain a naloxone kit ($X^2$ = 9.81, $p$ = .044, Cramer's $V$ = 0.32).

## Conclusions

The current study aimed to determine the feasibility and acceptability of a novel approach to OEND by utilizing online recruitment, online opioid overdose education, and remote distribution of naloxone kits. The results of this study demonstrate support for 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. Feasibility was established as evidenced by strong recruitment and the attainment of much greater than the targeted sample size of 150 and 80 participants for each respective portion of the study within a brief 11-week time frame. Furthermore, the retention rate at the end of the 3-month follow-up period was robust (83%). Recruitment and retention rates of this study are even more impressive given its focus on a difficult to reach population such as individuals with substance use, speaking to the ability of this remote approach to expand access to those in need. The completely remote nature of the study removed logistical and transportation barriers for participants, potentially enhancing capability to remain engaged throughout the entirety of the study. The intervention was simple to deliver and could plausibly be managed by minimally trained research staff due to the automation of the online data capture system, making it feasible to conduct in a variety of settings.

In addition to feasibility, the current intervention was also acceptable, as demonstrated by high participant satisfaction. A majority of participants were at least 90% satisfied with the format of the study including the ease of answering questions via online survey, receipt of follow-up survey links through email, and viewing an electronic version of the consent document. Likewise, participants favorably rated the informativeness and effectiveness of the training, as well as their own confidence to successfully administer naloxone. The OEND group reported higher satisfaction with receiving a naloxone kit as compared to the OE group receiving information on how to obtain a kit, possibly highlighting barriers to independently acquiring naloxone.

Demographic characteristics of the participants underscore the comparability between those who elected to complete the survey or training and those who were ineligible for the survey or declined to progress to the training portion. Though females ($n$ = 69) were somewhat more likely than males ($n$ = 42) to opt for training, females are generally more inclined to participate in research studies (Becker, 2022).

Despite the noted positive outcomes of this study and its novel contributions to current OEND research, it is not without limitations. First, as a pilot study, conclusions about the efficacy of this approach cannot be made definitively. The focus of the current study was to assess potential feasibility and to provide strong preliminary data for a fully-powered randomized clinical trial. One of the principal goals for remote implementation of OEND is to expand access to this impactful intervention. However, the cost of posting recruitment advertisements online, utilizing secure data capture technology, and purchasing naloxone could prevent the adoption of this methodology in under-resourced settings where it is likely most needed. Though the online nature of the study removed in-person barriers such as transportation, it may have also introduced issues for participants with low technology literacy or for those with limited access to reliable technology.

Even with these limitations, this study tested a novel intervention that can prompt further inquiry into the efficacy of remote OEND methodologies. Though results of group comparisons are not fully reported herein, this was a randomized controlled clinical trial and comparisons between randomized groups could inform future tailoring of interventions and provide further support for harm reduction strategies such as OEND. Overall, continued research demonstrating the effectiveness of this approach could

expand access to this life-saving intervention and reduce the high and increasing morbidity of opioid overdoses in the United States.

# References

Adapt Pharma Inc. NARCAN (naloxone hydrochloride) nasal spray (package insert). Pennsylvania: Adapt Pharma Inc., 2015.

Becker, R. (2022). Gender and Survey Participation: An Event History Analysis of the Gender Effects of Survey Participation in a Probability-based Multi-wave Panel Study with a Sequential Mixed-mode Design. *Methods, Data, Analyses*, *16*(1), 30. https://doi.org/10.12758/mda.2021.08

Behar, E., Santos, G.-M., Wheeler, E., Rowe, C., & Coffin, P. O. (2015). Brief overdose education is sufficient for naloxone distribution to opioid users. *Drug and Alcohol Dependence*, *148*, 209–212. https://doi.org/10.1016/j.drugalcdep.2014.12.009

Bennett, A. S., Bell, A., Doe-Simkins, M., Elliott, L., Pouget, E., & Davis, C. (2018). From peers to lay bystanders: Findings from a decade of naloxone distribution in Pittsburgh, PA. *Journal of Psychoactive Drugs*, *50*(3), 240–246. https://doi.org/10.1080/02791072.2018.1430409

Bennett, A. S., & Elliott, L. (2021). Naloxone's role in the national opioid crisis—Past struggles, current efforts, and future opportunities. *Translational Research*, *234*, 43–57. https://doi.org/10.1016/j.trsl.2021.03.001

Carpenter, M. J., Alberg, A. J., Gray, K. M., & Saladin, M. E. (2010). Motivating the unmotivated for health behavior change: A randomized trial of cessation induction for smokers. *Clinical Trials*, *7*(2), 157–166. https://doi.org/10.1177/1740774510361533

Carpenter, M. J., Hughes, J. R., Gray, K. M., Wahlquist, A. E., Saladin, M. E., & Alberg, A. J. (2011). Nicotine therapy sampling to induce quit attempts among smokers unmotivated to quit: A randomized clinical trial. *Lifestyle Behaviors | JAMA Internal Medicine | JAMA Network.* https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/1106038

Carroll, K. M., Kiluk, B. D., Nich, C., Gordon, M. A., Portnoy, G. A., Marino, D. R., & Ball, S. A. (2014). Computer-assisted delivery of cognitive-behavioral therapy: Efficacy and durability of cbt4cbt among cocaine-dependent individuals maintained on methadone. *American Journal of Psychiatry, 171*(4), 436–444. https://doi.org/10.1176/appi.ajp.2013.13070987

Cicero, T. J., & Ellis, M. S. (2015). Abuse-deterrent formulations and the prescription opioid abuse epidemic in the United States: Lessons learned from OxyContin. *JAMA Psychiatry, 72*(5), 424–430. https://doi.org/10.1001/jamapsychiatry.2014.3043

Clark, A. K., Wilder, C. M., & Winstanley, E. L. (2014). A systematic review of community opioid overdose prevention and naloxone distribution programs. *Journal of Addiction Medicine, 8*(3), 153–163. https://doi.org/10.1097/ADM.0000000000000034

Coffin, P. O., & Sullivan, S. D. (2013). Cost-effectiveness of distributing naloxone to heroin users for lay overdose reversal. *Annals of Internal Medicine, 158*(1), 1–9. https://doi.org/10.7326/0003-4819-158-1-201301010-00003

Compton, W. M., Jones, C. M., & Baldwin, G. T. (2016). Relationship between nonmedical prescription-opioid use and heroin use. *New England Journal of Medicine*. https://www.nejm.org/doi/full/10.1056/NEJMra1508490

Darke, S., & Duflou, J. (2016). The toxicology of heroin-related death: Estimating survival times. *Addiction, 111*(9), 1607–1613. https://doi.org/10.1111/add.13429

Drainoni, M.-L., Koppelman, E. A., Feldman, J. A., Walley, A. Y., Mitchell, P. M., Ellison, J., & Bernstein, E. (2016). Why is it so hard to implement change? A qualitative examination of barriers and facilitators to distribution of naloxone for overdose prevention in a safety net environment. *BMC Research Notes, 9*(1), 465. https://doi.org/10.1186/s13104-016-2268-z

*Drug Overdose Deaths in the U.S. Top 100,000 Annually*. (2021, November 17). https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2021/20211117.htm

Gertner, A. K., Domino, M. E., & Davis, C. S. (2018). Do naloxone access laws increase outpatient naloxone prescriptions? Evidence from Medicaid. *Drug and Alcohol Dependence, 190*, 37–41. https://doi.org/10.1016/j.drugalcdep.2018.05.014

Harocopos, A., & Allen, B. (2015). Routes into opioid analgesic misuse: Emergent typologies of initiation. *Journal of Drug Issues.* https://journals.sagepub.com/doi/full/10.1177/0022042615604345

Jarlais, D. C. D., Nugent, A., Solberg, A., Feelemyer, J., Mermin, J., & Holtzman, D. (2015). Syringe service programs for persons who inject drugs in urban, suburban, and rural areas—United States, 2013. *Morbidity and Mortality Weekly Report, 64*(48), 1337–1341.

Johnson, K., Jones, C., Compton, W., Baldwin, G., Fan, J., Mermin, J., & Bennett, J. (2018). Federal response to the opioid crisis. *Current HIV/AIDS Reports*, *15*(4), 293–301. https://doi.org/10.1007/s11904-018-0398-8

Jones, J. D., Campbell, A., Metz, V. E., & Comer, S. D. (2017). No evidence of compensatory drug use risk behavior among heroin users after receiving take-home naloxone. *Addictive Behaviors*, *71*, 104–106. https://doi.org/10.1016/j.addbeh.2017.03.008

Kanouse, A. B., & Compton, P. (2015). The epidemic of prescription opioid abuse, the subsequent rising prevalence of heroin use, and the federal response. *Journal of Pain & Palliative Care Pharmacotherapy*, *29*(2), 102–114. https://doi.org/10.3109/15360288.2015.1037521

Lambdin, B. H., Davis, C. S., Wheeler, E., Tueller, S., & Kral, A. H. (2018). Naloxone laws facilitate the establishment of overdose education and naloxone distribution programs in the United States. *Drug and Alcohol Dependence*, *188*, 370–376. https://doi.org/10.1016/j.drugalcdep.2018.04.004

Lambdin, B. H., Zibbell, J., Wheeler, E., & Kral, A. H. (2017). Identifying gaps in the implementation of naloxone programs for laypersons in the United States. *International Journal on Drug Policy*, *52*, 52–55. https://doi.org/10.1016/j.drugpo.2017.11.017

McAuley, A., Aucott, L., & Matheson, C. (2015). Exploring the life-saving potential of naloxone: A systematic review and descriptive meta-analysis of take-home naloxone (THN) programmes for opioid users. *International Journal of Drug Policy*, *26*(12), 1183–1188. https://doi.org/10.1016/j.drugpo.2015.09.011

McDonald, R., & Strang, J. (2016). Are take-home naloxone programmes effective? Systematic review utilizing application of the Bradford Hill criteria. *Addiction*. https://onlinelibrary.wiley.com/doi/full/10.1111/add.13326

*Pilot Studies: Common Uses and Misuses*. (2022). NCCIH. Retrieved June 14, 2022, from https://www.nccih.nih.gov/grants/pilot-studies-common-uses-and-misuses

*Prevent an Overdose, Save a Life*. (2013). New York City Department of Health. https://www.youtube.com/watch?v=xH04qvoKkhk

Razaghizad, A., Windle, S. B., Filion, K. B., Gore, G., Kudrina, I., Paraskevopoulos, E., Kimmelman, J., Martel, M. O., & Eisenberg, M. J. (2021). The effect of overdose education and naloxone distribution: An umbrella review of systematic reviews. *American Journal of Public Health*, *111*(8), e1–e12. https://doi.org/10.2105/AJPH.2021.306306

Rosenthal, R., & Rubin, D. B. (2003). r-equivalent: A simple effect size indicator. *Psychological Methods*, *8*(4), 492–496. https://doi.org/10.1037/1082-989X.8.4.492

Rudd, R. A., Seth, P., David, F., & Scholl, L. (2016). Increases in drug and opioid-involved overdose deaths—United States, 2010–2015. *Morbidity and Mortality Weekly Report*, *65*(50 & 51), 1445–1452.

*SAVEME Steps: What to Do for a Suspected Overdose*. (2022). British Columbia Emergency Health Services. http://www.bcehs.ca/health-info/public-health/responding-to-an-overdose/what-to-do-for-a-suspected-overdose

Seal, K. H., Thawley, R., Gee, L., Bamberger, J., Kral, A. H., Ciccarone, D., Downing, M., & Edlin, B. R. (2005). Naloxone distribution and cardiopulmonary resuscitation training for injection drug users to prevent heroin overdose death: A pilot intervention study. *Journal of Urban Health*, *82*(2), 303–311. https://doi.org/10.1093/jurban/jti053

Seth, P., Scholl, L., Rudd, R. A., & Bacon, S. (2018). Overdose Deaths Involving Opioids, Cocaine, and Psychostimulants—United States, 2015–2016. *Morbidity and Mortality Weekly Report*, *67*(12), 349–358. https://doi.org/10.15585/mmwr.mm6712a1

Sisson, M. L., McMahan, K. B., Chichester, K. R., Galbraith, J. W., & Cropsey, K. L. (2019). Attitudes and availability: A comparison of naloxone dispensing across chain and independent pharmacies in rural and urban areas in Alabama. *International Journal of Drug Policy*, *74*, 229–235. https://doi.org/10.1016/j.drugpo.2019.09.021

*Synthetic Opioid Overdose Data*. (2021, September 9). Centers for Disease Control and Prevention. https://www.cdc.gov/drugoverdose/deaths/synthetic/index.html

*Understanding the Epidemic*. (2022, February 9). Centers for Disease Control and Prevention. https://www.cdc.gov/drugoverdose/epidemic/index.html

Unick, G. J., Rosenblum, D., Mars, S., & Ciccarone, D. (2013). Intertwined epidemics: National demographic trends in hospitalizations for heroin- and opioid-related overdoses, 1993–2009. *PLOS ONE*, *8*(2), e54496. https://doi.org/10.1371/journal.pone.0054496

Volkow, N. D., Frieden, T. R., Hyde, P. S., & Cha, S. S. (2014). Medication-assisted therapies—Tackling the opioid-overdose epidemic. *New England Journal of Medicine*. https://www.nejm.org/doi/full/10.1056/nejmp1402780

Wagner, K. D., Valente, T. W., Casanova, M., Partovi, S. M., Mendenhall, B. M., Hundley, J. H., Gonzalez, M., & Unger, J. B. (2010). Evaluation of an overdose prevention and response training programme for injection drug users in the Skid Row area of Los Angeles, CA. *International Journal of Drug Policy*, *21*(3), 186–193. https://doi.org/10.1016/j.drugpo.2009.01.003

Walley, A. Y., Xuan, Z., Hackman, H. H., Quinn, E., Doe-Simkins, M., Sorensen-Alawad, A., Ruiz, S., & Ozonoff, A. (2013). Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: Interrupted time series analysis. *BMJ*, *346*, f174. https://doi.org/10.1136/bmj.f174

Wheeler, E., Jones, T. S., Gilbert, M. K., & Davidson, P. J. (2015). Opioid overdose prevention programs providing naloxone to laypersons—United States, 2014. *Morbidity and Mortality Weekly Report*, *64*(23), 631–635.

Williams, A. V., Strang, J., & Marsden, J. (2013). Development of Opioid Overdose Knowledge (OOKS) and Attitudes (OOAS) Scales for take-home naloxone training evaluation. *Drug and Alcohol Dependence*, *132*(1), 383–386. https://doi.org/10.1016/j.drugalcdep.2013.02.007

Winstanley, E. L., Clark, A., Feinberg, J., & Wilder, C. M. (2016). Barriers to implementation of opioid overdose prevention programs in Ohio. *Substance Abuse*, *37*(1), 42–46. https://doi.org/10.1080/08897077.2015.1132294

Wright, J. H., Owen, J. J., Richards, D., Eells, T. D., Richardson, T., Brown, G. K., Barrett, M., Rasku, M. A., Polser, G., & Thase, M. E. (2019). Computer-assisted Cognitive-Behavior Therapy for depression: A systematic review and meta-analysis. *The Journal of Clinical Psychiatry*, *80*(2), 3573. https://doi.org/10.4088/JCP.18r12188

Xu, J., Davis, C. S., Cruz, M., & Lurie, P. (2018). State naloxone access laws are associated with an increase in the number of naloxone prescriptions dispensed in retail pharmacies. *Drug and Alcohol Dependence*, *189*, 37–41. https://doi.org/10.1016/j.drugalcdep.2018.04.020

Table 1. Demographic Characteristics of Sample (N = 304)

| | ***M*** | ***SD*** |
|---|---|---|
| Age | 37.5 | 9.6 |
| | ***n*** | ***%*** |
| Race | | |
| American Indian/Alaskan Native | 5 | 1.6% |
| Black/African American | 36 | 11.8% |
| White/Caucasian | 252 | 82.9% |
| Multiracial | 9 | 3.0% |
| Ethnicity | | |
| Hispanic | 15 | 4.9% |
| Non-Hispanic | 289 | 95.1% |
| Sex | | |
| Female | 161 | 53.0% |
| Male | 143 | 47% |
| Educational Attainment | | |
| Prefer not to answer | 2 | 0.7% |
| Less than high school | 20 | 6.6% |
| High school/GED | 188 | 61.8% |
| Technical/Associate's degree | 57 | 18.8% |
| Bachelor's degree or higher | 37 | 12.2% |
| Annual Household Income | | |
| Prefer not to answer/Don't know | 11 | 3.6% |
| Under $10,000 | 82 | 27.0% |
| $10,000 to $24,999 | 85 | 28.0% |
| $25,000 to $49,999 | 74 | 24.3% |
| $50,000 to $74,999 | 26 | 8.6% |
| $75,000 to $99,999 | 10 | 3.3% |
| $100,000 to $124,999 | 11 | 3.6% |
| $125,000 to $149,999 | 3 | 1.0% |
| Over $149,999 | 2 | 0.7% |
| Psychiatric Disorder | | |
| Prefer not to answer | 2 | 0.7% |
| No | 143 | 47.0% |
| Yes | 159 | 52.3% |

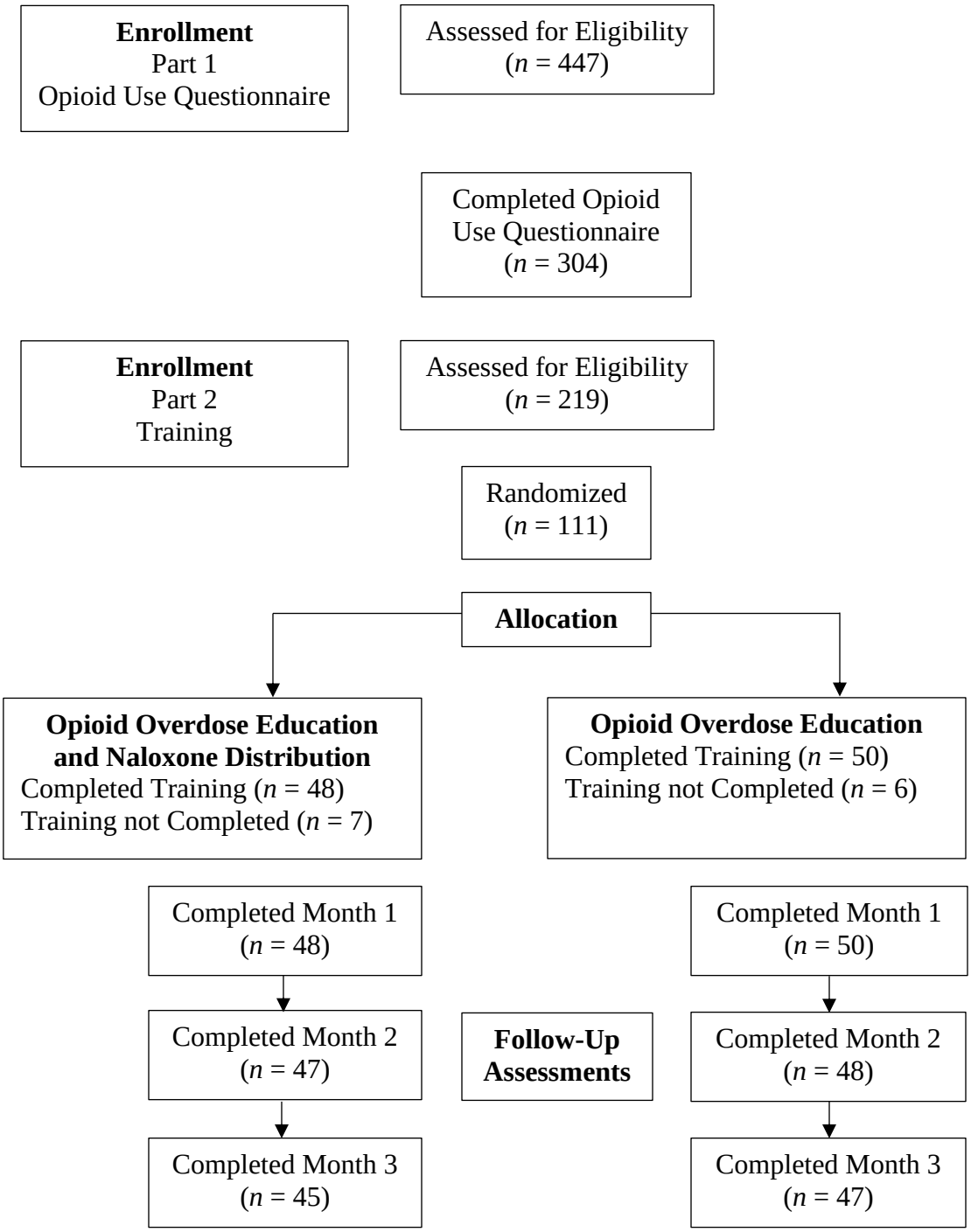


**Figure 1.** CONSORT diagram.

# CHARACTERIZING INDIVIDUALS WHO ELECT AND DECLINE OPIOID OVERDOSE EDUCATION AND NALOXONE DISTRIBUTION TO TAILOR PROGRAMS AND EXPAND IMPACT

by

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## Abstract

In response to the opioid epidemic, federal agencies have stressed the importance of targeted naloxone distribution through avenues such as Opioid Overdose Education and Naloxone Distribution (OEND) programs. OEND effectively reduces mortality by training laypersons to recognize overdose and utilize response strategies. Despite demonstrated effectiveness, OEND remains underutilized. This project aimed to characterize those who illicitly use opioids to determine avenues for future tailoring of OEND programs. Individuals who illicitly used opioids within the past six months were recruited via online social media, after which they completed an online questionnaire that assessed history of opioid and other substance use, personal and observed opioid overdoses, and opioid-related treatment. Participants were given the option to receive opioid overdose and naloxone administration training. Those who elected training (n=111) and those who declined (n=193) were compared on opioid use, severity of use, and overdose experiences. Participants (N=304) were 47% male and 83% White. Those who elected training endorsed greater intravenous administration ($X^2$=4.18, $p$=.041, Cramer's $V$=0.12). Individuals who declined training reported more frequent methadone use ($X^2$=7.51, $p$=.006, Cramer's $V$=0.16), overdose hospitalizations ($t$(298)=2.13, $p$=.034, Cohen's $d$=0.26), and observed overdoses ($t$(300)=3.01, $p$=.003, Cohen's $d$=0.36). After adjusting for multiple comparisons, only the differences in methadone use and observed overdoses remained statistically significant. Individuals who elected training reported high-risk drug use behaviors and therefore may view themselves as susceptible to overdose, thus increasing desire for training. Those who declined had witnessed more overdoses and been hospitalized more often, and may have had greater exposure to

naloxone, hence decreasing perceived need for training. Understanding characteristics of those who elect and refuse training could inform structuring of programs and recruitment approaches.

# Introduction

Opioid-related overdoses and deaths have drastically and continuously increased throughout the past two decades to a degree warranting the classification of an epidemic (*Understanding the Epidemic*, 2022). In 1999, fatal opioid overdoses accounted for approximately 8,000 annual deaths, whereas in 2021 that number exceeded 75,673 (*CDC WONDER*, 2022; *Drug Overdose Deaths in the U.S. Top 100,000 Annually*, 2021). In an effort to combat this epidemic, federal agencies have promoted the implementation of evidence-based harm reduction strategies such as targeted naloxone distribution (Carroll et al., 2018).

Naloxone is an opioid antagonist administered to acutely reverse overdoses. Naloxone can be distributed via avenues such as co-prescription with opioid analgesic medications, pharmacy dispensing with standing order prescription rights, and Opioid Overdose Education and Naloxone Distribution (OEND) training programs. OEND programs train laypersons, especially those who use opioids and interact with others who use drugs, to recognize and respond to overdose with naloxone administration when indicated (Bennett et al., 2018; Razaghizad et al., 2021; Walley et al., 2013; Wheeler et al., 2015).

The ability of OEND programs to effectively train individuals and reduce fatal opioid overdoses has been largely established (Behar et al., 2015; Bennett et al., 2018; Clark et al., 2014; Giglio et al., 2015; Razaghizad et al., 2021). Though OEND programs have become more widespread in recent years they remain underutilized, likely due in part to lingering unfounded concerns about unintended escalation of opioid use (Barocas, 2019; Bazazi et al., 2010; Bennett & Elliott, 2021; Lambdin et al., 2017; Murphy &

Russell, 2020; Sisson et al., 2019; Winograd et al., 2020). The fact that OEND programs are typically based in urban areas also undermines their accessibility and use (Bennett & Elliott, 2021; Lambdin et al., 2017; *Still Not Enough Naloxone Where It's Most Needed*, 2016). These programs may therefore fail to reach those with the highest interest or need of participating. OEND has the greatest impact when it is targeted and provided to those most likely to witness opioid overdose (Carroll et al., 2018). Perhaps the traditional OEND model could be optimized by simultaneously aiming for expanded reach and enhanced tailoring.

The current study is a secondary analysis of a novel pilot clinical trial that applied remote methodologies to OEND delivery. Participants in that trial were recruited and screened online, then completed a comprehensive questionnaire detailing their opioid and substance use related history. Following completion of the questionnaire, participants were given the opportunity to continue with the study and receive opioid overdose and naloxone administration training. The current project compares participants who elected to complete the training versus individuals who did not with an aim to characterize the population of those most interested in receiving OEND. The a priori hypotheses were that individuals who elected to participate in overdose training would be more likely than those who declined to: a) have active opioid use; b) have higher severity of opioid use; c) have experienced past personal overdose; and d) know someone who has experienced an overdose.

# Methods

## *Participants*

Participants (N = 304) were recruited through advertisements placed on Craigslist soliciting individuals with recent illicit opioid use. Recruitment advertisements were visible on Craigslist sites for 16 cities within four states in the Southeast (AL, FL, GA, TN). Inclusion criteria required that participants be at least 18 years of age, have used opioids (e.g., prescription opioids, heroin, fentanyl, methadone) illicitly within the past six months, and have access to an electronic device. This study is registered on ClinicalTrials.gov (NCT04303000) and more detailed information regarding inclusion criteria can be viewed on the site. Proposed sample size was established based on feasibility rather than outcome testing, given the pilot nature of the project (*Pilot Studies*, 2022).

## *Procedures*

Individuals interested in participating in the study were redirected from Craigslist to the screening survey housed within REDCap™ data capture system via a secure link. Eligible participants were automatically forwarded to a virtual informational consent sheet that described the content, purpose, and confidentiality aspects of the survey. After indicating consent, participants progressed to the Opioid Use Questionnaire (described below). Upon completion of the survey, participants were informed of the immediate opportunity to potentially complete online opioid overdose and naloxone administration training. Individuals who expressed interest in participating continued further to the training portion of the study. Those who declined participation were asked about their

reasons for refusing and were thanked for their time. Participants were compensated $30.00 for completing the questionnaire. Study protocol was reviewed and approved by the Institutional Review Board at the University of Alabama at Birmingham.

*Measures*

*Demographic characteristics*. Basic demographic information and participant characteristics including age, sex, race/ethnicity, education level, employment status, annual household income, marital status, living situation, and history of psychiatric diagnoses were collected.

*Opioid Use Questionnaire*. This 64-item questionnaire assessed history and current use of numerous opioids and other substances. Route of administration for each opioid was also collected. History of personal and witnessed opioid overdose, opioid overdose related hospitalizations, and substance use treatments were evaluated. Included questions were formatted following examples from published substance use screening assessments and nationally representative studies (Elliott et al., 2021; *National Adult Tobacco Survey (NATS)*, 2014; *Population Assessment of Tobacco and Health (PATH) Study*, 2014).

*Decline Survey*. A 7-item survey was administered to participants who declined to receive opioid overdose and naloxone administration training in order to evaluate reasons for refusing training. On a multiple response item, participants selected their top three reasons for deciding not to be trained (e.g., "*I do not think I need it*," "*I am afraid I will*

*be more likely to use again*," "*I am afraid of legal trouble if I carry naloxone*," "*I do not have time for training*"). The survey also assessed their preferred training format (e.g., in-person, video, written instructions), length, and provider (e.g., nurse, physician, social worker, peer) if they were to accept training.

*Data Analytic Approach*

Data analysis began with descriptive statistics for baseline participant characteristics. Descriptive statistics were also computed to delineate reasons for declining opioid overdose and naloxone administration training. Tests of between group differences (e.g., t-tests, chi-squared tests) were conducted to compare groups on opioid use, severity of use, and overdose experiences. Measures of effect size, namely Cohen's *d* for continuous variables and Cramer's *V* for binary or categorical variables, were computed (Akoglu, 2018). Confidence intervals were calculated to assist with quantifying estimates. A False Discovery Rate (FDR) approach (10% FDR level) was used to adjust the significance level for multiple exploratory analyses (Glickman et al., 2014).

Participants were considered to have active opioid use if they had illicitly used any type of opioid within the past month. Severity of opioid use was qualified with variables commonly utilized for this purpose including route of administration, polysubstance use, overdose related hospitalizations, and inpatient substance use treatment (Guarino et al., 2021; McLellan et al., 1992; Sundaresh et al., 2022; Villalobos-Gallegos et al., 2015). Route of administration was dichotomized to indicate never or ever use of intravenous injection, given its status as the most hazardous form of drug administration (Mathers et al., 2013). The number of hospitalizations secondary to opioid

overdose and times treated at an inpatient substance use program ranged on a scale from "*Never*" to "*More than three times*." This same scale was used for reporting number of personal and observed opioid overdoses.

## Results

### *Participant Characteristics*

The total study sample consisted of 304 individuals who all reported illicit opioid use during the past six months. Participant age ranged from 18 to 77 ($M$ = 37.5; $SD$ = 9.6). Sex was divided relatively evenly with 53% of participants reporting female biological sex (47% male). In terms of race and ethnicity, 11.8% of the sample identified as Black/African American, 82.9% as white/Caucasian, and 4.9% as Hispanic. A majority of participants reported high school education or equivalent (61.8%) and an annual household income under $49,999 (79.3%). Just over half (52.3%) of the sample reported being formally diagnosed with a psychiatric disorder, not including substance use disorders.

Participants who elected to participate in training (n = 111) and those who declined (n = 193) did not statistically differ on age, race, ethnicity, educational attainment, income, or psychiatric diagnosis history. Females were marginally more likely to elect training ($X^2$ = 5.94, $p$ = .015, Cramer's $V$ = 0.14). See Table 1 for a comprehensive summary of participant characteristics. After correction for multiple inferences, $p$-values <.015 were considered statistically significant at the 10% FDR level.

*Group Comparisons*

Group differences in opioid use, severity of use (e.g., intravenous administration, polysubstance use, hospitalization for overdose, inpatient substance use treatment), and overdose experiences were examined between participants who elected to advance further in the study to receive training and those who declined. Self-reported active opioid use was almost identical between those who elected ($n$ = 95, 85.6%) and declined ($n$ = 164, 85.0%) OEND training ($X^2$ = 0.11, $p$ = .739, Cramer's $V$ = 0.02, 95% CI[0.44, 1.79]). Lifetime illicit usage of prescription opioids, heroin, fentanyl, and buprenorphine/naloxone were also very similar. Those who declined ($n$ = 108, 56.0%) were more likely than those who elected training ($n$ = 44, 39.6%) to endorse illicit ever use of methadone ($X^2$ = 7.51, $p$ = .006, Cramer's $V$ = 0.16, 95% CI[0.32, 0.83]). This group difference had a strong effect that remained significant even after an FDR adjustment.

Route of opioid administration differed such that those who elected training ($n$ = 74, 66.7%) indicated somewhat greater ever use of intravenous administration than those who declined ($n$ = 105, 54.4%); but this moderate effect did not remain significant when adjusting for multiple inferences ($X^2$ = 4.18, $p$ = .041, Cramer's $V$ = 0.12, 95% CI[1.02, 2.72]). Similarly, elect individuals ($n$ = 82, 73.9%) endorsed lifetime polysubstance use more than decline ($n$ = 121, 62.7%), though the moderate effect was not statistically significant ($X^2$ = 3.32, $p$ = .069, Cramer's $V$ = 0.11, 95% CI[0.96, 2.77]). Those who declined training ($M$ = 0.94, $SD$ = 1.32) had been hospitalized for opioid overdose more frequently than those who elected training ($M$ = 0.62, $SD$ = 1.07) with a small effect that did not remain significant after multiple comparisons adjustment ($t$(298) = 2.13, $p$ = .034,

Cohen's *d* = 0.26, 95% CI[0.02, 0.49]). Inpatient treatment was also slightly more common for decliners (*M* = 1.22, *SD* = 1.44) as compared to electors (*M* = 0.98, *SD* = 1.38), with a small effect that was not significant (*t*(301) = 1.39, *p* = .165, Cohen's *d* = 0.17, 95% CI[-0.07, 0.40]).

In terms of opioid overdose experiences, those who declined training (*M* = 2.06, *SD* = 1.61) had marginally more personal overdoses than those who elected (*M* = 1.99, *SD* = 1.61). However, the effect was small and not significant (*t*(296) = 0.38, *p* = .708, Cohen's *d* = 0.05, 95% CI[-0.19, 0.28]). Participants in the decline group (*M* = 2.61, *SD* = 1.59) also reported witnessing others overdose slightly more frequently than in the elect group (*M* = 2.05, *SD* = 1.58). The significance of this difference remained after controlling for multiple inferences, though the effect was small (*t*(300) = 3.01, *p* = .003, Cohen's *d* = 0.36, 95% CI[0.12, 0.60]).

*Reasons for Declining Training*

Completion of the Decline Survey was not required, given that participants had just indicated a lack of desire to advance further with the study. A total of 34 participants chose to complete the survey. Interpretations cannot be made due to the small response rate, and data are thus presented solely for descriptive purposes. The most cited reasons for these participants refusing training were lack of need (*n* = 8, 23.5%), fear of others thinking they use opioids (*n* = 7, 20.6%), and ability to obtain naloxone through another venue (*n* = 7, 20.6%). Most preferred training formats included video (*n* = 8, 23.5%), website (*n* = 6, 17.6%), and in-person (*n* = 6, 17.6%). In terms of ideal length of training, most chose 21-30 minutes (*n* = 11, 32.4%).

# Discussion

This study compared individuals who elected or declined to participate in online opioid overdose and naloxone administration training as a means to provide preliminary characterization of a target population for these programs. Identifying characteristics of those most interested in accepting training could increase utilization and impact of OEND programs. This project seems to be the first to explore and report differences among individuals who choose or reject to partake in OEND.

Demographically, females were slightly more likely to elect training, which is consistent with general findings elsewhere that show stronger research engagement among women (Becker, 2022). All other demographic characteristics were comparable between groups, potentially indicating that interest in online training is not skewed toward any particular demographic.

The hypothesis that participants who opted for training would be more likely to have active opioid use, higher severity of use, experience of past overdose, and know someone who has experienced an overdose, was largely unsupported. Within this sample, rates of active opioid use were effectively uniform between those who elected training and those who declined. Individuals who elected training did endorse somewhat more lifetime intravenous administration and polysubstance use. On the other hand, those who declined training reported slightly more frequent opioid overdose-related hospitalizations and engagement in inpatient substance use treatment. Lifetime occurrences of both personal and witnessed opioid overdoses were marginally higher among training refusers. While the various types of opioids reportedly used were generally similar between the groups, lifetime illicit use of methadone was greater for those who declined training .

Overall, those who chose to take part in training reported riskier behaviors during actual drug use, as intravenous administration and concurrent use of multiple substances have each been associated with amplified risk of fatal overdose (Cicero et al., 2020; Crummy et al., 2020; Mathers et al., 2013; Riley et al., 2016). Curiously, however, they indicated fewer personal overdoses than their counterparts. Those with riskier drug use behaviors may perceive themselves as more vulnerable to overdose and therefore engage in protective behaviors (e.g., test shots; Bonar & Bohnert, 2016). Given the small sample size, the disparity in number of overdoses between groups may simply not be meaningful. Or those interested in training could be more likely to have fatal overdoses, which would not be accounted for among already deceased individuals who could not participate in the study. In addition to reporting more frequent personal overdoses, those who declined training also witnessed more overdoses and more often utilized emergent and inpatient treatment. These individuals may have more exposure to naloxone through witnessing its administration to others or because some emergency departments and treatment facilities offer take home naloxone (Dora-Laskey et al., 2022; Katzman et al., 2020). Greater exposure to overdose response procedures and naloxone could increase confidence in one's ability to appropriately react in an overdose situation and decrease perceived need for training.

Comparisons inferred within this sample cannot be extrapolated due to the pilot nature of the study. With the small pilot sample and potential lack of power to identify true differences, group comparisons were interpreted with measures of effect size even without indicated statistical significance. Greater illicit methadone use and more frequently observed overdoses for those who declined training were the only group

differences that were statistically significant after adjusting for multiple comparisons. Data included in these analyses are derived from a self-report questionnaire without any form of secondary validation. Scales for responses related to frequencies were truncated (e.g., "*More than three times*") rather than allowing for open-ended number answers. The decline survey was not a required piece of the study, thus diminishing potential response rate and interpretability. Even with these limitations, this study utilized a comprehensive questionnaire to innovatively explore characteristics of those most interested in OEND programs as a means to potentially increase the impact of this life-saving intervention.

## Conclusion

This project provides preliminary data for a future fully powered study to characterize the population most inclined to engage in OEND programs. Understanding differences between individuals who elect and decline training could help tailor how OEND programs present their information. Knowing characteristics of those who opt for and refuse training could also allow OEND programs to better highlight training benefits for those who might not recognize its value for them personally. Tailoring recruitment approaches for OEND programs could increase its impact and further prevention efforts against fatal overdose.

# References

Akoglu, H. (2018). User's guide to correlation coefficients. *Turkish Journal of Emergency Medicine*, *18*(3), 91–93. https://doi.org/10.1016/j.tjem.2018.08.001

Barocas, J. A. (2019). Commentary on Irvine et al. (2019): Barriers to implementing a successful roadmap for preventing opioid-related overdose deaths. *Addiction*, *114*(9), 1614–1615. https://doi.org/10.1111/add.14738

Bazazi, A. R., Zaller, N. D., Fu, J. J., & Rich, J. D. (2010). Preventing opiate overdose deaths: Examining objections to take-home naloxone. *Journal of Health Care for the Poor and Underserved*, *21*(4), 1108–1113. https://doi.org/10.1353/hpu.2010.0935

Becker, R. (2022). Gender and survey participation: An event history analysis of the gender effects of survey participation in a probability-based multi-wave panel study with a sequential mixed-mode design. *Methods, Data, Analyses*, *16*(1), 30. https://doi.org/10.12758/mda.2021.08

Behar, E., Santos, G.-M., Wheeler, E., Rowe, C., & Coffin, P. O. (2015). Brief overdose education is sufficient for naloxone distribution to opioid users. *Drug and Alcohol Dependence*, *148*, 209–212. https://doi.org/10.1016/j.drugalcdep.2014.12.009

Bennett, A. S., Bell, A., Doe-Simkins, M., Elliott, L., Pouget, E., & Davis, C. (2018). From peers to lay bystanders: Findings from a decade of naloxone distribution in Pittsburgh, PA. *Journal of Psychoactive Drugs*, *50*(3), 240–246. https://doi.org/10.1080/02791072.2018.1430409

Bennett, A. S., & Elliott, L. (2021). Naloxone's role in the national opioid crisis—Past struggles, current efforts, and future opportunities. *Translational Research, 234*, 43–57. https://doi.org/10.1016/j.trsl.2021.03.001

Bonar, E. E., & Bohnert, A. S. B. (2016). Perceived severity of and susceptibility to overdose among injection drug users: Relationships with overdose history. *Substance Use & Misuse, 51*(10), 1379–1383. https://doi.org/10.3109/10826084.2016.1168447

Carroll, J., Green, T., & Noonan, R. (2018). *Evidence-Based Strategies for Preventing Opioid Overdose: What's Working in the United States, 2018* (p. 40). Centers for Disease Control and Prevention.

*CDC WONDER*. (2022). Centers for Disease Control and Prevention. https://wonder.cdc.gov/

Cicero, T. J., Ellis, M. S., & Kasper, Z. A. (2020). Polysubstance use: A broader understanding of substance use during the opioid crisis. *American Journal of Public Health, 110*(2), 244–250. https://doi.org/10.2105/AJPH.2019.305412

Clark, A. K., Wilder, C. M., & Winstanley, E. L. (2014). A systematic review of community opioid overdose prevention and naloxone distribution programs. *Journal of Addiction Medicine, 8*(3), 153–163. https://doi.org/10.1097/ADM.0000000000000034

Crummy, E. A., O'Neal, T. J., Baskin, B. M., & Ferguson, S. M. (2020). One is not enough: Understanding and modeling polysubstance use. *Frontiers in Neuroscience, 14*. https://www.frontiersin.org/article/10.3389/fnins.2020.00569

Dora-Laskey, A., Kellenberg, J., Dahlem, C. H., English, E., Gonzalez Walker, M., Brummett, C. M., & Kocher, K. E. (2022). Piloting a statewide emergency department take-home naloxone program: Improving the quality of care for patients at risk of opioid overdose. *Academic Emergency Medicine*, *29*(4), 442–455. https://doi.org/10.1111/acem.14435

*Drug Overdose Deaths in the U.S. Top 100,000 Annually*. (2021, November 17). https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2021/20211117.htm

Elliott, L., Crasta, D., Khan, M., Roth, A., Green, T., Kolodny, A., & Bennett, A. S. (2021). Validation of the Opioid Overdose Risk Behavior Scale, version 2 (ORBS-2). *Drug and Alcohol Dependence*, *223*, 108721. https://doi.org/10.1016/j.drugalcdep.2021.108721

Giglio, R. E., Li, G., & DiMaggio, C. J. (2015). Effectiveness of bystander naloxone administration and overdose education programs: A meta-analysis. *Injury Epidemiology*, *2*(1), 10. https://doi.org/10.1186/s40621-015-0041-8

Glickman, M. E., Rao, S. R., & Schultz, M. R. (2014). False discovery rate control is a recommended alternative to Bonferroni-type adjustments in health studies. *Journal of Clinical Epidemiology*, *67*(8), 850–857. https://doi.org/10.1016/j.jclinepi.2014.03.012

Guarino, H., Mateu-Gelabert, P., Quinn, K., Sirikantraporn, S., Ruggles, K. V., Syckes, C., Goodbody, E., Jessell, L., & Friedman, S. R. (2021). Adverse childhood experiences predict early initiation of opioid use behaviors. *Frontiers in Sociology*, *6*, 620395. https://doi.org/10.3389/fsoc.2021.620395

Katzman, J. G., Takeda, M. Y., Greenberg, N., Moya Balasch, M., Alchbli, A., Katzman, W. G., Salvador, J. G., & Bhatt, S. R. (2020). Association of take-home naloxone and opioid overdose reversals performed by patients in an opioid treatment program. *JAMA Network Open*, *3*(2), e200117. https://doi.org/10.1001/jamanetworkopen.2020.0117

Lambdin, B. H., Zibbell, J., Wheeler, E., & Kral, A. H. (2017). Identifying gaps in the implementation of naloxone programs for laypersons in the United States. *International Journal on Drug Policy*, *52*, 52–55. https://doi.org/10.1016/j.drugpo.2017.11.017

Mathers, B. M., Degenhardt, L., Bucello, C., Lemon, J., Wiessing, L., & Hickman, M. (2013). Mortality among people who inject drugs: A systematic review and meta-analysis. *Bulletin of the World Health Organization*, *91*(2), 102–123. https://doi.org/10.2471/BLT.12.108282

McLellan, A. T., Carise, D., Coyne, T. H., Jackson, T. R., & Categories, H. (n.d.). *Addiction Severity Index—5th Edition*. *1*, 15.

Murphy, J., & Russell, B. (2020). Police officers' views of naloxone and drug treatment: Does greater overdose response lead to more negativity? *Journal of Drug Issues*, *50*(4), 455–471. https://doi.org/10.1177/0022042620921363

*National Adult Tobacco Survey (NATS)*. (2014). Centers for Disease Control and Prevention. https://www.cdc.gov/tobacco/data_statistics/surveys/nats/

*Pilot Studies: Common Uses and Misuses*. (2022). NCCIH. Retrieved June 14, 2022, from https://www.nccih.nih.gov/grants/pilot-studies-common-uses-and-misuses

*Population Assessment of Tobacco and Health (PATH) Study*. (2014). National Institutes of Health (NIH). https://pathstudyinfo.nih.gov/

Razaghizad, A., Windle, S. B., Filion, K. B., Gore, G., Kudrina, I., Paraskevopoulos, E., Kimmelman, J., Martel, M. O., & Eisenberg, M. J. (2021). The effect of overdose education and naloxone distribution: An umbrella review of systematic reviews. *American Journal of Public Health*, *111*(8), e1–e12. https://doi.org/10.2105/AJPH.2021.306306

Riley, E. D., Evans, J. L., Hahn, J. A., Briceno, A., Davidson, P. J., Lum, P. J., & Page, K. (2016). A longitudinal study of multiple drug use and overdose among young people who inject drugs. *American Journal of Public Health*, *106*(5), 915–917. https://doi.org/10.2105/AJPH.2016.303084

Sisson, M. L., McMahan, K. B., Chichester, K. R., Galbraith, J. W., & Cropsey, K. L. (2019). Attitudes and availability: A comparison of naloxone dispensing across chain and independent pharmacies in rural and urban areas in Alabama. *International Journal of Drug Policy*, *74*, 229–235. https://doi.org/10.1016/j.drugpo.2019.09.021

Sundaresh, S., Sadananda, G. B., & Bailit, J. L. (2022). Trends in the severity of opioid use disorder during pregnancy over time. *Journal of Perinatology*, 1–6. https://doi.org/10.1038/s41372-022-01336-2

*Understanding the Epidemic*. (2022, February 9). Centers for Disease Control and Prevention. https://www.cdc.gov/drugoverdose/epidemic/index.html

Villalobos-Gallegos, L., Pérez, A., Mendoza, R., Graue, J., Marín-Navarrete, R. (2015). Psychometric and diagnostic properties of the Drug Abuse Screening Test (DAST): Comparing the DAST-20 vs. the DAST-10. *Salud Mental*, *38*(2), 89–94. https://doi.org/10.17711/SM.0185-3325.2015.012

*Vital Signs*. (2016, January 1). CDC Newsroom. https://www.cdc.gov/media/releases/2019/p0806-naloxone.html

Walley, A. Y., Xuan, Z., Hackman, H. H., Quinn, E., Doe-Simkins, M., Sorensen-Alawad, A., Ruiz, S., & Ozonoff, A. (2013). Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: Interrupted time series analysis. *BMJ*, *346*, f174. https://doi.org/10.1136/bmj.f174

Wheeler, E., Jones, T. S., Gilbert, M. K., & Davidson, P. J. (2015). Opioid overdose prevention programs providing naloxone to laypersons—United States, 2014. *Morbidity and Mortality Weekly Report*, *64*(23), 631–635.

Winograd, R. P., Werner, K. B., Green, L., Phillips, S., Armbruster, J., & Paul, R. (2020). Concerns that an opioid antidote could "make things worse": Profiles of risk compensation beliefs using the Naloxone-Related Risk Compensation Beliefs (NaRRC-B) scale. *Substance Abuse*, *41*(2), 245–251. https://doi.org/10.1080/08897077.2019.1616348

Table 1. Demographic Characteristics of Sample at Baseline by Group (Elect Training vs. Decline)

| | **Elect Training (*n* = 111)** | | **Decline Training (*n* = 193)** | | **Effect Size** | |
|---|---|---|---|---|---|---|
| | ***M/n*** | ***SD/%*** | ***M/n*** | ***SD/%*** | **Cramer's *V*/ Cohen's *d*** | ***p*** |
| Age, (*M*, *SD*) | 37.99 | 9.86 | 37.24 | 9.46 | 0.08 | .512 |
| Race | | | | | 0.10 | .657 |
| American Indian/Alaskan Native | 1 | 0.9% | 3 | 1.6% | | |
| Black/African American | 12 | 10.8% | 23 | 11.9% | | |
| White/Caucasian | 91 | 82.0% | 160 | 82.9% | | |
| Multiracial | 7 | 6.3% | 7 | 3.6% | | |
| Ethnicity | | | | | 0.06 | .326 |
| Hispanic | 4 | 3.6% | 12 | 6.2% | | |
| Non-Hispanic | 107 | 96.4% | 181 | 93.8% | | |
| Sex | | | | | 0.14 | .015* |
| Female | 69 | 62.2% | 92 | 47.7% | | |
| Male | 42 | 37.8% | 101 | 52.3% | | |
| Educational Attainment | | | | | 0.11 | .492 |
| Prefer not to answer | 1 | 0.9% | 1 | 0.5% | | |
| Less than high school | 8 | 7.2% | 12 | 6.2% | | |
| High school/GED | 69 | 62.2% | 119 | 61.7% | | |
| Technical/Associate's degree | 24 | 21.6% | 33 | 17.1% | | |
| Bachelor's degree or higher | 9 | 8.1% | 28 | 14.5% | | |
| Psychiatric Disorder | | | | | 0.09 | .320 |
| Prefer not to answer | 1 | 0.9% | 1 | 0.5% | | |
| Yes | 64 | 57.7% | 95 | 49.2% | | |
| No | 46 | 41.4% | 97 | 50.3% | | |

*Note*. *Statistically significant at a 10% False Discovery Rate level

Table 2. Illicit Opioid Use, Severity of Use, and Overdose Experience Characteristics of Sample by Group (Elect Training vs. Decline)

| | **Elect Training (*n* = 111)** | | **Decline Training (*n* = 193)** | | **Effect Size** | |
|---|---|---|---|---|---|---|
| | ***n*** | ***%*** | ***n*** | ***%*** | **Cramer's *V*** | ***p*** |
| Active Opioid Use | 95 | 85.6% | 164 | 85.0% | 0.02 | .739 |
| Prescription Opioid Use (Ever) | 108 | 97.3% | 182 | 94.3% | 0.07 | .437 |
| Heroin Use (Ever) | 80 | 72.1% | 146 | 75.6% | 0.04 | .492 |
| Fentanyl Use (Ever; Not Laced) | 64 | 57.6% | 116 | 60.1% | 0.05 | .671 |
| Methadone Use (Ever) | 44 | 39.6% | 108 | 56.0% | 0.16 | .006* |
| Buprenorphine/Naloxone Use (Ever) | 76 | 68.5% | 127 | 65.8% | 0.03 | .635 |
| Intravenous Administration (Ever) | 74 | 66.7% | 105 | 54.4% | 0.12 | .041 |
| Polysubstance Use (Ever) | 82 | 73.9% | 121 | 62.7% | 0.11 | .069 |
| | ***M*** | ***SD*** | ***M*** | ***SD*** | **Cohen's *d*** | ***p*** |
| Number of Hospitalizations for OD | 0.62 | 1.07 | 0.94 | 1.32 | 0.26 | .034 |
| Number of Inpatient Treatments | 0.98 | 1.38 | 1.22 | 1.44 | 0.17 | .165 |
| Number of Personal Overdoses | 1.99 | 1.61 | 2.06 | 1.61 | 0.05 | .708 |
| Number of Observed Overdoses | 2.05 | 1.58 | 2.61 | 1.59 | 0.36 | .003* |

*Note*. OD = Overdose; *Statistically significant at a 10% False Discovery Rate level

# PRELIMINARY EFFECTIVENESS OF ONLINE OPIOID OVERDOSE AND NALOXONE ADMINISTRATION TRAINING AND IMPACT OF NALOXONE POSSESSION ON OPIOID USE

by

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## Abstract

Importance: This study evaluated the effectiveness of online opioid overdose and naloxone administration education and impact of naloxone possession.

Objective: A priori hypotheses: 1) knowledge will improve subsequent to training; 2) possession of naloxone will be lower for the group instructed to obtain it from a pharmacy; 3) no group differences will exist between individuals who obtained naloxone and not in regard to overdoses, opioid use, and treatment interest.

Design: Secondary analysis from a pilot randomized clinical trial that included three monthly follow-ups. Data collection occurred between July 2021 and January 2022.

Setting: Participation in the study occurred entirely online.

Participants: All enrolled subjects had reported illicit use of opioids within the past six months and were required to be at least 18 years old with access to an electronic device. Out of the 447 individuals assessed for initial eligibility, 304 completed the first portion, 219 were screened for the training portion, 111 were randomized, and 98 completed the training.

Intervention: Participants viewed a video outlining signs of and responses to opioid overdose, and how to administer naloxone.

Main Outcomes and Measures: Effectiveness of training was measured with pre- and post-training knowledge questionnaires. Naloxone kit possession, overdoses, opioid use frequency, and treatment interest were self-reported on follow-up assessments.

Results: Participants (N=98) consisted of 61.2% female (38.8% male), 84.7% Caucasian, and 9.2% Black/African American, and were on average 38.7 years of age. Mean knowledge scores significantly increased from 6.82/9.00 to 8.22 after training

(*t*(194)=6.85, *p* <.001, 95% CI[1.00, 1.81], Cohen's *d*=0.85). Difference in naloxone possession between randomized groups was significant with a large effect size (*p* < .001, diff=0.60, 95% CI[0.47, 0.73]). A bidirectional relationship was found between naloxone possession and frequency of opioid use. Overdoses and treatment interest were similar across possession status.

Conclusions and Relevance: Opioid overdose education is effective in online video format. Disparity in naloxone possession across groups indicates barriers to obtaining naloxone from pharmacies. Naloxone possession did not influence risky opioid use or treatment interest and its impact on frequency of use warrants further investigation.

Trial Registration: Clinitaltrials.gov- NCT04303000

# Introduction

Over the past two decades, more than 500,000 people in the United States have died from opioid overdose (*Opioid Data Analysis and Resources*, 2021). During that time period, deaths related to opioid overdose increased eight-fold with over 207 people currently dying every day (*Data Overview*, 2022; *Understanding the Epidemic*, 2022). With this rapid rise in mortality rates, federal agencies have responded with enhanced efforts to collect overdose data and implement effective harm reduction strategies (*About OD2A*, 2021). In connection with their recent cooperative aimed at preventing fatal opioid overdose, the Centers for Disease Control and Prevention (CDC) stressed the importance of utilizing evidence-based prevention approaches, with targeted naloxone distribution topping their list (Carroll et al., 2018).

Naloxone is an opioid antagonist that reverses the effects of excessive opioid intake including respiratory depression, hypotension, and sedation. Originally employed in emergency department settings, naloxone is now able to be administered on site by trained first responders or laypersons as a means to reduce the crucial window between overdose onset and treatment (Darke & Duflou, 2016). Numerous studies have demonstrated the efficacy of programs that train laypersons to recognize the signs of opioid overdose, execute response protocol, and deliver naloxone (Bennett et al., 2018; Clark et al., 2014; McAuley et al., 2015; McDonald & Strang, 2016; Razaghizad et al., 2021; Wheeler et al., 2015). Opioid Overdose Education and Naloxone Distribution (OEND) programs have been found to effectively improve participants' knowledge of overdose risk factors, indications, and response procedures when comparing pre- and post-training assessment scores, or comparing scores to those of non-trained participants

(Clark et al., 2014; Giglio et al., 2015; Razaghizad et al., 2021). The same benefits have been observed with trainings delivered through computer-based intervention, remaining consistent at long-term follow-up (Clark et al., 2014; Giglio et al., 2015; Huhn et al., 2018; Razaghizad et al., 2021). In addition to enhancing participants' knowledge, OEND programs increase the use of recommended response strategies and considerably decrease opioid overdose mortality (Bennett et al., 2018; Bird et al., 2016; Clark et al., 2014; Giglio et al., 2015; McAuley et al., 2015; McDonald & Strang, 2016; Razaghizad et al., 2021; Walley et al., 2013; Wheeler et al., 2015).

Despite the demonstrated value of OEND, these programs remain underutilized especially given the current severity of opioid-related morbidity and mortality. Established OEND programs are usually executed by large medical research institutions, county health departments, or treatment programs, resulting in a paucity of access in rural areas and for individuals who have not yet presented for treatment (Bennett & Elliott, 2021; Jarlais et al., 2015; Jones et al., 2017; Lambdin et al., 2017, 2018). Additionally, the concept of naloxone possession continues to face unfounded criticisms that negatively impact policy enactment and distribution. Policy makers, police officers, and even pharmacists have endorsed the view that naloxone allows for continued, increased, or riskier opioid use (Barocas, 2019; Bazazi et al., 2010; Lai et al., 2021; Murphy & Russell, 2020; Sisson et al., 2019; Winograd et al., 2020). OEND follow-up assessments continually indicate a lack of increase in opioid use or even demonstrate a decrease in use, as harm reduction interventions often connect participants to treatment options (Doe-Simkins et al., 2014; Ellis et al., 2021; Giglio et al., 2015; Jones et al., 2017; Seal et al., 2005; Tse et al., 2022; Wagner et al., 2010; Walley et al., 2013).

Even with unsubstantiated concerns regarding unintended consequences of naloxone possession, most states have passed standing order laws that allow pharmacies prescriptive authority to dispense naloxone without an individual prescription being presented (Gertner et al., 2018; Lambdin et al., 2018; Xu et al., 2018). However, stocking of naloxone can be limited, especially for rural, independent pharmacies (Cid et al., 2021; Egan et al., 2020; Guadamuz et al., 2019; Guy et al., 2019, 2021; Pollini et al., 2022; Sisson et al., 2019). If naloxone is in stock and available for purchase, the price can vary from fifty to hundreds of dollars, making cost a considerable barrier. Many persons who use opioids do not have insurance and those who do often encounter policies that place restrictions on the coverage of naloxone (Huskamp et al., 2018). Pharmacists holding negative attitudes toward naloxone has been associated with decreased dissemination from their pharmacy (Sisson et al., 2019). Overall, these barriers to optimally implementing OEND and obtaining naloxone from pharmacies prevent high-risk individuals from accessing this life-saving treatment.

The current study examines secondary outcomes of a pilot clinical trial that assessed feasibility of a novel approach to OEND with employment of completely remote methodologies. The training procedures included review of an educational video along with supplemental materials in addition to an assessment of participants' knowledge prior to and after training. Randomized assignment to group was conducted such that one group was provided naloxone and the other guided to procure naloxone through standing order pharmacies. Repeated follow-up assessments examined opioid use behaviors in relation to naloxone possession. A priori hypotheses were as follows: 1) opioid overdose and naloxone knowledge will significantly improve subsequent to training; 2) possession

of naloxone will be lower for the group instructed to obtain it from a pharmacy as compared to the group with study disseminated naloxone; 3) no group differences will exist between individuals who obtained naloxone versus those who did not in regard to reported overdoses, opioid use, and interest in substance use treatment.

## Methods

### *Participants*

Individuals who had illicitly used opioids within the past six months were recruited via online advertisements placed on Craigslist within 16 cities in the Southeast. The advertisement contained a secure link to an online eligibility survey housed within REDCap™ data capture software. Eligibility criteria required that participants be at least 18 years of age, used opioids in an illicit manner within the past six months, had accessibility to an electronic device with internet capabilities, and did not currently own a naloxone kit or have a known contraindication to naloxone. This study is registered with ClinicalTrials.gov and full eligibility criteria can be found on the site (NCT04303000).

### *Procedures*

Eligible individuals were automatically directed to a virtual informational consent sheet describing the first of two portions of the study, which consisted of a survey pertaining to history of opioid and other substance use, overdose experiences, familiarity with naloxone, and substance use treatment history. Indicating consent advanced the participant to the online survey, at the end of which they could opt to continue with the

second portion of the study to receive opioid overdose and naloxone administration training.

Interested and eligible participants viewed a comprehensive virtual consent document, signed electronically, and were sent a copy of the completed form. Immediately following completion of the consent process, participants were sent an individualized, secure REDCap link to the training module via email. First, participants completed a brief questionnaire assessing their knowledge related to aspects of opioid overdose and naloxone. Next, they watched a 10-minute training video in which medical professionals and individuals with personal experience of opioid use outline characteristics of opioid overdose as well as actions to take in an overdose situation (*Prevent an Overdose, Save a Life*, 2013). In the video, a medical professional also performs a demonstration of how to administer intramuscular injection and nasal spray forms of naloxone. After watching the video, participants were provided with an acronym (SAVE ME) to facilitate recall of appropriate steps to follow during an opioid overdose scenario (e.g., **S**timulate-**A**irway-**V**entilate-**E**valuate-**M**uscular Injection/Nasal Spray-**E**valuate/Support; *SAVEME Steps: What to Do for a Suspected Overdose*, 2022). Participants completed the aforementioned knowledge questionnaire a second time after viewing the video and acronym to assess training effectiveness.

Participants were randomized to one of two conditions. Those randomized to the first group (Opioid Overdose Education and Naloxone Distribution [OEND]) were provided with a 4mL naloxone nasal spray. Individuals randomized to the second group (Opioid Overdose Education [OE]) were given a list of pharmacies in their area where

they could obtain a naloxone kit. Randomization was executed through REDCap software with 1:1 allotment and randomization blocks size 4.

Both randomized groups engaged in monthly follow-up assessments one, two, and three-months after training completion. REDCap automatically distributed individualized links to follow-up surveys via email at each time point and sent reminder emails for any unfinished surveys. Follow-up assessments focused on naloxone kit usage and in the event that an overdose had occurred, the circumstances and outcomes. Participants' current opioid use and interest or engagement in treatment was also assessed. All study procedures were reviewed and approved by the Institutional Review Board at the University of Alabama at Birmingham.

*Measures*

*Opioid Use Questionnaire.* This 64-item questionnaire assesses use history of various opioids including illicit prescription opioids, heroin, fentanyl, and those used for medication assisted treatment. Past and current use of other substances is also included. The questionnaire inquires about previous overdoses, hospitalizations, and substance use treatments. Knowledge of and past experience with naloxone is also assessed. Items included were modeled after standardized questions from nationally representative studies and substance use screening assessments (*National Adult Tobacco Survey (NATS)*, 2014; *NIDA-Modified ASSIST (NM ASSIST)*, 2020; *Population Assessment of Tobacco and Health (PATH) Study*, 2014).

*Pre- and Post-Training Knowledge Questionnaire.* This 9-item questionnaire was administered prior to and following training in order to evaluate effectiveness. Items are multiple choice format and concentrate on risk factors for opioid overdose, signs of overdose, essential actions during an overdose situation, and functionality of naloxone. All content presented on the questionnaire was addressed in the training. Each question counted as one point for a total possible score of nine points. Questions were derived from a previously validated scale (Williams et al., 2013).

*Follow-up assessments.* A 21-item questionnaire that includes questions about whether the participant had used their naloxone kit, who received the naloxone, who administered the naloxone, whether suggested steps (e.g., calling 911) were followed, and outcomes. The questionnaire also inquires about the participants' current opioid use, whether they had experienced overdose since the last assessment, and whether they were considering or had entered substance use treatment. The OE group had a slightly modified version of the questionnaire that integrated five additional questions related to attainment of a naloxone kit.

### *Data Analytic Approach*

Descriptive statistics were utilized for participant demographic characteristics, naloxone kit possession and usage quantities, and particular naloxone use outcomes. Frequencies and percentages of follow-up outcomes (e.g., use of naloxone kit, who received the naloxone, experience of personal or observed overdose, substance use treatment entry, and current illicit opioid use) were calculated with respective confidence

intervals. With the sample size of the study and number of reported naloxone kits used, this pilot project was not sufficiently powered to examine differences between participants who used their kit or not.

Balance between randomized groups across demographic variables and participant characteristics was assessed through chi-square and t-test analyses with examination of effect size measures. Baseline factors for participants lost to follow-up were not used as adjusting covariates, as only six participants did not complete the study.

Mean scores of pre- and post-training knowledge questionnaires were calculated and compared using a mixed-effects model and a measure of effect size (Cohen's *d* with *SD* estimated with variance components). Uncertainty about the estimate is qualified with a confidence interval.

Generalized estimated equations (GEE) with an exchangeable covariance for subject were fitted to repeated measures data in order to compare groups on naloxone kit possession, current opioid use, risk behavior, and interest in or seeking treatment across follow-up times. Separation in binary models was addressed with a Firth's correction approach. Probit links were utilized for binary outcomes, and model estimated proportions and mean differences were used for interpretation. Pairwise contrasts were estimated and examined. Inverse-link estimates were computed to facilitate interpretation. A false discovery rate (FDR) approach was utilized to adjust for multiple inferences. Confidence intervals were computed to quantify uncertainty about estimates (Glickman et al., 2014). A cross-lagged panel model was conducted in R statistical software with the "lavaan" (i.e., latent variable analysis) package (Rosseel, 2012) for structural equation modeling to estimate directional effects of correlated variables. A

fitting method robust to deviations in normality was used due to the inclusion of binary variables. All available data was used without any list-wise deletion. Standard errors were computed using non-parametric methods (e.g., bootstrapping).

All participants randomized to the OEND group were provided with a naloxone kit while those in the OE group self-selected to obtain naloxone at their local pharmacy. For opioid use, risk behavior, and treatment interest, GEE analyses were conducted comparing participants with and without naloxone for the entire sample (69 naloxone kits vs. 29 without naloxone) as well as selectively examining OE group participants (21 naloxone kits vs. 29 without naloxone). Separately analyzing the OE group was done as a means to ecologically evaluate the effect of self-selecting naloxone possession.

Eight response options for current opioid use ranged from "*Not at all*" to "*Multiple times per day*." Six response options for interest in substance use treatment included "*No*," "*Not sure*," "*Maybe one day*," "*Yes*," "*Currently in treatment*," and "*Recently completed treatment*." Personal overdose experience was used as a proxy measure of risky opioid use, as high-risk substance use behaviors heighten the possibility of overdose (Elliott et al., 2021; Krawczyk et al., 2020; Webster, 2017).

## Results

In terms of demographic characteristics of the sample (N = 98), the average age was 38.7 years (*SD* = 9.9), 61.2% were female, 38.8% were male, 9.2% were Black/African American, and 84.7% were white/Caucasian. There were no statistically significant differences between randomized groups in terms of age, sex, or race. See Table 1 for baseline demographic characteristics of the sample partitioned by group.

With regard to randomization, 55 were allotted to the OEND group and 56 to the OE group. Of the 111 participants that were randomized, 13 did not complete the training and related questionnaires. Between those who did not finish the training and those who did, there were no statistical differences in assigned group or demographic characteristics. Of the 98 participants (48 OEND, 50 OE) who successfully finished the training, 100% completed the first follow-up assessment, 86% ($n$ = 95) completed the two-month follow-up, and 83% ($n$ = 92) completed the three-month follow-up. Of the six participants that were lost to attrition, five were male and one was female, four identified as white and two as multiracial.

Prior to completing the training, participants' mean knowledge questionnaire score was 6.82 ($SD$ = 1.66) out of 9.00. The average knowledge questionnaire score post-training increased to 8.22 ($SD$ = 1.17). This improvement in knowledge subsequent to training completion was statistically significant with a large effect size ($t(194) = 6.85$, $p < .001$, 95% CI [1.00, 1.81], Cohen's $d$ = 0.85), supporting the hypothesis that opioid overdose and naloxone knowledge would increase with training.

Each participant in the OEND group ($n$ = 48) received a naloxone nasal spray. Of the 50 individuals in the OE group, only 21 (42%) reported obtaining their own naloxone kit. See Table 1 for demographic characteristics divided by naloxone kit possession status. In the OE group, those who obtained a kit did not statistically differ on any demographic characteristics in comparison to individuals who did not obtain a kit. The hypothesis that possession of naloxone would be lower for the OE group as compared to the OEND group was supported. A binary GEE analysis with probit links showed that the time averaged difference in naloxone kit possession between the OEND group ($M$ = 0.98)

and the OE group ($M$ = 0.38) was significant with a large effect size ($p$ < .001, $df$ = 1, diff = 0.60, 95% CI [0.47, 0.73]). Pairwise comparisons indicated that the mean difference between groups on naloxone possession was significant with a large effect size at Month 1 ($p$ < .001, $df$ = 1, diff = 0.63, 95% CI [0.50, 0.77]), Month 2 ($p$ < .001, $df$ = 1, diff = 0.61, 95% CI [0.48, 0.75]), and Month 3 ($p$ < .001, $df$ = 1, diff = 0.55, 95% CI [0.41, 0.69]) follow-up assessments.

Overall, 16 participants reported using their naloxone kit in an overdose situation over the three-month follow-up period. Naloxone kit utilization was exactly evenly split between the OEND and OE groups. Out of the 16 naloxone kits used, three were used on the participant by a friend or family member. The remaining kits were administered to friends/family members ($n$ = 9) of the participant or a third-party individual ($n$ = 4). All naloxone kits used resulted in a life reportedly being saved. For participants with indicated naloxone possession, five (2.6%) personal overdoses were reported during the follow-up period, in comparison to four (4.5%) personal overdoses for those without naloxone. Binomial GEE analyses with probit links and pairwise contrasts were conducted to investigate group differences in reported overdoses across the three follow-up time points. When examining the entire sample, GEE pairwise comparisons did not show a difference in overdose incidents between participants with or without naloxone at Month 1 ($p$ = .705, $df$ = 1, diff = 0.02, 95% CI [-0.06, 0.09]), Month 2 ($p$ = .486, $df$ = 1, diff = 0.04, 95% CI [-0.08, 0.17]), or Month 3 ($p$ = .515, $df$ = 1, diff = 0.03, 95% CI [-0.11, 0.06]). Similarly, there was no difference in reported overdoses between groups at Month 1 ($p$ = .936, $df$ = 1, diff = 0.01, 95% CI [-0.10, 0.11]), Month 2 ($p$ = .465, $df$ = 1, diff = 0.06, 95% CI [-0.07, 0.18]), or Month 3 ($p$ = .101, $df$ = 1, diff = 0.12, 95% CI [-

0.27, 0.02]) when comparing only individuals in the OE group who obtained a kit versus not.

In terms of current opioid use frequency during the follow-up period, a majority of individuals both with (47%) and without (46%) naloxone kit possession endorsed daily use. Linear GEE analyses with pairwise contrasts were conducted to investigate group differences in reported frequency of opioid use across the three follow-up time points. For the entire sample, the GEE model indicated that participants who owned a naloxone kit were marginally more likely to report more frequent opioid use, but the effect was not significant ($p$ = .155, $df$ = 1, 95% CI [-1.48, 0.24], Cohen's $d$ = 0.26). However, this difference becomes significant with a moderate effect size when solely examining individuals in the OE group who were able to self-select to obtain a naloxone kit or not ($p$ = .007, $df$ = 1, 95% CI [0.33, 2.12], Cohen's $d$ = 0.54). Pairwise comparisons showed this difference at Month 1 ($p$ = .024, $df$ = 1, 95% CI [0.15, 2.11], Cohen's $d$ = 0.49), Month 2 ($p$ = .026, $df$ = 1, 95% CI [0.15, 2.34], Cohen's $d$ = 0.54), and Month 3 ($p$ = .027, $df$ = 1, 95% CI [0.15, 2.48], Cohen's $d$ = 0.57).

A cross-lagged panel model was conducted to examine the directionality of the association between naloxone kit possession and opioid use frequency among participants in the OE group ($n$ = 50). The overall model fit was good ($X^2$ = 8.88, $p$ = .064). At the one-month follow-up, 34% of participants possessed a naloxone kit. Possession increased to 38% at Month 2 and 45% at Month 3. On a scale from 0 ("*Not at all*") to 7 ("*Multiple times per day*"), mean opioid use frequency was 4.76 ($SD$ = 2.25) at Month 1, 4.94 ($SD$ = 2.35) at Month 2, and 4.63 ($SD$ = 2.43) at Month 3. Naloxone kit possession was correlated between Month 1 and Month 2 ($r$ = 0.78, $p$ < .001), Month 1 and Month 3 ($r$ =

0.84, $p < .001$), and Month 2 and Month 3 ($r = 0.88$, $p < .001$). Similarly, opioid use frequency was correlated between Month 1 and Month 2 ($r = 0.83$, $p < .001$), Month 1 and Month 3 ($r = 0.60$, $p < .001$), and Month 2 and Month 3 ($r = 0.57$, $p < .001$). The associations between kit possession at Month 1 and opioid use at Month 2 ($r = 0.02$, $p = .30$) and kit possession at Month 2 and opioid use at Month 3 ($r = 0.09$, $p = .15$) were small and not significant. The associations between opioid use at Month 1 and kit possession at Month 2 ($r = 0.05$, $p = .10$) and opioid use at Month 2 and kit possession at Month 3 ($r = 0.01$, $p = .15$) were also small and not statistically significant. See Figure 1 to view the full path model.

Across the follow-up period, most participants endorsed potential (29.6%) or definite interest (25.4%) in substance use treatment. Linear GEE analyses with pairwise contrasts were conducted to examine group differences in substance use treatment interest across the three follow-up time points. Results showed that participants who owned a naloxone kit were marginally more likely to have greater levels of interest in treatment, but the effect was not significant for the entire sample ($p = .741$, $df = 1$, 95% CI [-0.54, 0.38], Cohen's $d = 0.06$), nor for the OE group alone ($p = .888$, $df = 1$, 95% CI [-0.52, 0.45], Cohen's $d = 0.03$). Overall, the hypothesis that no significant group differences would exist between individuals with and without naloxone in terms of reported overdoses, opioid use, and interest in substance use treatment was partially supported. See Table 2 for group differences across follow-up time points for each repeated measures variable of interest. For GEE models, $p$-values <.027 are significant at a 10% FDR level.

# Discussion

This pilot randomized clinical trial examined outcomes from a novel approach to OEND implementation that exclusively utilized online and remote methodologies as a mechanism to broaden its application. Identifying and offering OEND to unreached, high-risk individuals through these methods could significantly expand access to this life-saving intervention, as traditional OEND programs have generally been siloed to institutions found in urban areas that likely draw subjects who have already presented for treatment (Bennett & Elliott, 2021; Jarlais et al., 2015; Jones et al., 2017; Lambdin et al., 2017, 2018). Remote OEND could circumvent access barriers such as rurality, pharmacy issues, fear of stigma, and unreadiness for treatment. The current study appears to be the first to recruit, consent, and train participants entirely online and report related outcomes. While this project is procedurally unique compared to other OEND studies, findings concerning the efficacy of these programs and those that dispute naloxone criticisms were largely consistent with past research.

Effectiveness of opioid overdose education is often gauged via knowledge assessments comparing intervention and control groups or within subjects repeated evaluation following training. In the current study, participants' understanding of naloxone and risk factors, indicators, and response procedures for opioid overdose significantly improved consequent to training with mean scores rising from 75.7% to 91.4%. Similar to previous research, this study demonstrates that non-medical laypersons can learn to effectually recognize an opioid overdose and learn appropriate emergency procedures, even after a brief (~10 minute) intervention (Clark et al., 2014; Giglio et al., 2015; Huhn et al., 2018; Razaghizad et al., 2021). This study also provides support for

education being successfully administered in an online video format without any in-person requirement, alleviating location related access barriers.

Barriers to obtaining naloxone from a pharmacy persist despite widespread standing order laws and a substantial increase in naloxone availability within pharmacies (Cid et al., 2021; Egan et al., 2020; Gertner et al., 2018; Guadamuz et al., 2019; Guy et al., 2019, 2021; Lambdin et al., 2018; Pollini et al., 2022; Sisson et al., 2019; Xu et al., 2018). Randomization of participants to either receive naloxone or guidance to acquire it from a pharmacy illustrated disparity in naloxone ownership with the latter group possessing less than half the number of kits as the former. Reasons for not securing a naloxone kit at any point during the three-month follow-up period were not investigated. However, participants who were required to seek naloxone from a pharmacy being significantly less likely to have it suggests potential issues with naloxone accessibility through these venues.

Information from monthly follow-up assessments replicates past work indicating that naloxone distribution prevents fatal opioid overdoses (Bennett et al., 2018; Bird et al., 2016; Clark et al., 2014; Giglio et al., 2015; McAuley et al., 2015; McDonald & Strang, 2016; Razaghizad et al., 2021; Walley et al., 2013; Wheeler et al., 2015). Over the course of the follow-up period, 16 naloxone kits were reportedly used with successful overdose reversal. This 23.2% naloxone kit usage rate is much higher than the 8-18% characteristically reported from in-person studies (Chichester et al., 2020; Doe-Simkins et al., 2014; Katzman et al., 2020; McAuley et al., 2015; Walley et al., 2013; Wheeler et al., 2015), possibly alluding to the ability of remote OEND to reach those in need who are neglected by the current scope of these programs.

Evidence against common criticisms of naloxone has been well-established but comparing opioid use and treatment variables across individuals with and without naloxone expands this investigation (Barocas, 2019; Bazazi et al., 2010; Lai et al., 2021; Murphy & Russell, 2020; Sisson et al., 2019; Winograd et al., 2020). The number of personal overdoses reported did not differ based on naloxone possession status. Though desire to engage in substance use treatment was marginally higher for participants who owned naloxone, this effect was miniscule, not statistically significant, and a crude comparison given the sample size. Frequency of opioid use was greater for those with reported naloxone possession when comparing individuals who self-selected to obtain naloxone and those who did not. However, including participants who were randomly assigned to be provided a naloxone kit diminishes this observed difference. Further, the directionality of the effect is unclear, as a follow-up analysis did not reveal significant relationships between the two variables in either direction across time points. Specially, it is uncertain whether having naloxone eases fear of negative outcomes thereby increasing opioid use, or if those who use opioids at higher levels have safety concerns regarding their use, making them more likely to seek out naloxone. The pilot nature of this study prevents generalizable inferences. In this sample, it appears that having naloxone available to use does not increase risky opioid use behaviors, nor does it result in avoidance of treatment. However, naloxone possession may be bidirectionally related to high frequency of opioid use.

As a pilot study, it should be noted that these results are preliminary implications that necessitate further examination within a fully powered clinical trial. Information related to overdose incidents, ability to obtain a naloxone kit, and frequency of opioid use

were self-reported without secondary validation. Socially desirable responding or fear of stigma could have influenced participants' answers, though the impact of these issues should be lower given there were no in-person interactions. Reasons as to why many of the participants in the OE group were unable to obtain naloxone were not queried and could have provided valuable information related to pharmacy dispensing. Ideally, analyses examining opioid use severity would have incorporated other data in addition to experience of personal overdose, namely route of administration and quantity used. Despite these limitations, this study tested an innovative intervention and demonstrated effectiveness of online opioid overdose education. Including a comparator group with ecological validity was a unique strength for the study. Finally, impressive completion rates for the training and strong retention rates across multiple follow-up time points (~85% at three months) highlight the feasibility of this novel approach to OEND.

## Conclusions

Overall, the current study provided support for the effectiveness of implementing opioid overdose education via online video format. The disproportion of naloxone possession between randomized groups speaks to the need for examination and potential restructuring of current pharmacy dispensing practices. Lack of influence in this sample from naloxone possession on risky opioid use and interest in treatment further refutes outdated criticisms of this harm reduction strategy. The effect of naloxone possession on quantity of opioid use needs to be examined with a fully randomized design to parse out directionality of this relationship. Preliminary results from this pilot trial indicate potential feasibility of implementing optimized, remote OEND to expand access to this

life-saving intervention and reduce the high and increasing morbidity of opioid overdoses in the United States.

# References

*About OD2A | Drug Overdose | CDC Injury Center*. (2021, November 8). https://www.cdc.gov/drugoverdose/od2a/about.html

Barocas, J. A. (2019). Commentary on Irvine et al. (2019): Barriers to implementing a successful roadmap for preventing opioid-related overdose deaths. *Addiction, 114*(9), 1614–1615. https://doi.org/10.1111/add.14738

Bazazi, A. R., Zaller, N. D., Fu, J. J., & Rich, J. D. (2010). Preventing opiate overdose deaths: Examining objections to take-home naloxone. *Journal of Health Care for the Poor and Underserved, 21*(4), 1108–1113. https://doi.org/10.1353/hpu.2010.0935

Bennett, A. S., Bell, A., Doe-Simkins, M., Elliott, L., Pouget, E., & Davis, C. (2018). From peers to lay bystanders: Findings from a decade of naloxone distribution in Pittsburgh, PA. *Journal of Psychoactive Drugs, 50*(3), 240–246. https://doi.org/10.1080/02791072.2018.1430409

Bennett, A. S., & Elliott, L. (2021). Naloxone's role in the national opioid crisis—Past struggles, current efforts, and future opportunities. *Translational Research, 234*, 43–57. https://doi.org/10.1016/j.trsl.2021.03.001

Bird, S. M., McAuley, A., Perry, S., & Hunter, C. (2016). Effectiveness of Scotland's National Naloxone Programme for reducing opioid-related deaths: A before (2006–10) versus after (2011–13) comparison. *Addiction, 111*(5), 883–891. https://doi.org/10.1111/add.13265

Carroll, J., Green, T., & Noonan, R. (2018). *Evidence-Based Strategies for Preventing Opioid Overdose: What's Working in the United States, 2018* (p. 40). Centers for Disease Control and Prevention.

Chichester, K., Sisson, M. L., Schiavon, S. P., Hugley, M. J., Hendricks, P. S., Shelton, R. C., & Cropsey, K. L. (2020). Naloxone training from nonmedical personnel: Benefits before, during, and after overdose events. *Journal of Addiction Medicine*, *14*(5), e220. https://doi.org/10.1097/ADM.0000000000000645

Cid, A., Daskalakis, G., Grindrod, K., & Beazely, M. A. (2021). What is known about community pharmacy-based take-home naloxone programs and program interventions? A scoping review. *Pharmacy*, *9*(1), 30. https://doi.org/10.3390/pharmacy9010030

Clark, A. K., Wilder, C. M., & Winstanley, E. L. (2014). A systematic review of community opioid overdose prevention and naloxone distribution programs. *Journal of Addiction Medicine*, *8*(3), 153–163. https://doi.org/10.1097/ADM.0000000000000034

Darke, S., & Duflou, J. (2016). The toxicology of heroin-related death: Estimating survival times. *Addiction, 111*(9), 1607–1613. https://doi.org/10.1111/add.13429

*Data Overview*. (2022, April 9). Centers for Disease Control and Prevention. https://www.cdc.gov/opioids/data/index.html

Doe-Simkins, M., Quinn, E., Xuan, Z., Sorensen-Alawad, A., Hackman, H., Ozonoff, A., & Walley, A. Y. (2014). Overdose rescues by trained and untrained participants and change in opioid use among substance-using participants in overdose education and naloxone distribution programs: A retrospective cohort study. *BMC Public Health*, *14*(1), 297. https://doi.org/10.1186/1471-2458-14-297

Egan, K. L., Foster, S. E., Knudsen, A. N., & Lee, J. G. L. (2020). Naloxone availability in retail pharmacies and neighborhood inequities in access. *American Journal of Preventive Medicine*, *58*(5), 699–702. https://doi.org/10.1016/j.amepre.2019.11.009

Elliott, L., Crasta, D., Khan, M., Roth, A., Green, T., Kolodny, A., & Bennett, A. S. (2021). Validation of the Opioid Overdose Risk Behavior Scale, version 2 (ORBS-2). *Drug and Alcohol Dependence*, *223*, 108721. https://doi.org/10.1016/j.drugalcdep.2021.108721

Ellis, M. S., Kasper, Z. A., & Cicero, T. J. (2021). Destigmatizing naloxone: Associations of perceived availability on opioid use patterns. *Annals of Emergency Medicine*, *77*(1), 134–135. https://doi.org/10.1016/j.annemergmed.2020.08.027

Gertner, A. K., Domino, M. E., & Davis, C. S. (2018). Do naloxone access laws increase outpatient naloxone prescriptions? Evidence from Medicaid. *Drug and Alcohol Dependence*, *190*, 37–41. https://doi.org/10.1016/j.drugalcdep.2018.05.014

Giglio, R. E., Li, G., & DiMaggio, C. J. (2015). Effectiveness of bystander naloxone administration and overdose education programs: A meta-analysis. *Injury Epidemiology*, *2*(1), 10. https://doi.org/10.1186/s40621-015-0041-8

Glickman, M. E., Rao, S. R., & Schultz, M. R. (2014). False discovery rate control is a recommended alternative to Bonferroni-type adjustments in health studies. *Journal of Clinical Epidemiology*, *67*(8), 850–857. https://doi.org/10.1016/j.jclinepi.2014.03.012

Guadamuz, J. S., Alexander, G. C., Chaudhri, T., Trotzky-Sirr, R., & Qato, D. M. (2019). Availability and cost of naloxone nasal spray at pharmacies in Philadelphia, Pennsylvania, 2017. *JAMA Network Open*, *2*(6), e195388. https://doi.org/10.1001/jamanetworkopen.2019.5388

Guy, G. P., Haegerich, T. M., Evans, M. E., Losby, J. L., Young, R., & Jones, C. M. (2019). Vital signs: Pharmacy-based naloxone dispensing — United States, 2012–2018. *Morbidity and Mortality Weekly Report*, *68*(31), 679–686. https://doi.org/10.15585/mmwr.mm6831e1

Guy, G. P., Khushalani, J. S., Jackson, H., Sims, R. St. C., & Arifkhanova, A. (2021). Trends in state-level pharmacy-based naloxone dispensing rates, 2012–2019. *American Journal of Preventive Medicine*, *61*(6), e289–e295. https://doi.org/10.1016/j.amepre.2021.05.042

Huhn, A. S., Garcia-Romeu, A. P., & Dunn, K. E. (2018). Opioid overdose education for individuals prescribed opioids for pain management: Randomized comparison of two computer-based interventions. *Frontiers in Psychiatry*, *9*. https://www.frontiersin.org/article/10.3389/fpsyt.2018.00034

Huskamp, H. A., Riedel, L. E., Barry, C. L., & Busch, A. B. (2018). Coverage of medications that treat opioid use disorder and opioids for pain management in marketplace plans, 2017. *Medical Care*, *56*(6), 505–509. https://doi.org/10.1097/MLR.0000000000000918

Jarlais, D. C. D., Nugent, A., Solberg, A., Feelemyer, J., Mermin, J., & Holtzman, D. (2015). Syringe service programs for persons who inject drugs in urban, suburban, and rural areas—United States, 2013. *Morbidity and Mortality Weekly Report*, *64*(48), 1337–1341.

Jones, J. D., Campbell, A., Metz, V. E., & Comer, S. D. (2017). No evidence of compensatory drug use risk behavior among heroin users after receiving take-home naloxone. *Addictive Behaviors*, *71*, 104–106. https://doi.org/10.1016/j.addbeh.2017.03.008

Katzman, J. G., Takeda, M. Y., Greenberg, N., Moya Balasch, M., Alchbli, A., Katzman, W. G., Salvador, J. G., & Bhatt, S. R. (2020). Association of take-home naloxone and opioid overdose reversals performed by patients in an opioid treatment program. *JAMA Network Open*, *3*(2), e200117. https://doi.org/10.1001/jamanetworkopen.2020.0117

Krawczyk, N., Eisenberg, M., Schneider, K. E., Richards, T. M., Lyons, B. C., Jackson, K., Ferris, L., Weiner, J. P., & Saloner, B. (2020). Predictors of overdose death among high-risk emergency department patients with substance-related encounters: A data linkage cohort study. *Annals of Emergency Medicine*, *75*(1), 1–12. https://doi.org/10.1016/j.annemergmed.2019.07.014

Lai, J. T., Goldfine, C. E., Chapman, B. P., Taylor, M. M., Rosen, R. K., Carreiro, S. P., & Babu, K. M. (2021). Nobody wants to be Narcan'd: A pilot qualitative analysis of drug users' perspectives on naloxone. *Western Journal of Emergency Medicine*, *22*(2), 339–345. https://doi.org/10.5811/westjem.2020.10.48768

Lambdin, B. H., Davis, C. S., Wheeler, E., Tueller, S., & Kral, A. H. (2018). Naloxone laws facilitate the establishment of overdose education and naloxone distribution programs in the United States. *Drug and Alcohol Dependence*, *188*, 370–376. https://doi.org/10.1016/j.drugalcdep.2018.04.004

Lambdin, B. H., Zibbell, J., Wheeler, E., & Kral, A. H. (2017). Identifying gaps in the implementation of naloxone programs for laypersons in the United States. *International Journal on Drug Policy*, *52*, 52–55. https://doi.org/10.1016/j.drugpo.2017.11.017

McAuley, A., Aucott, L., & Matheson, C. (2015). Exploring the life-saving potential of naloxone: A systematic review and descriptive meta-analysis of take-home naloxone (THN) programmes for opioid users. *International Journal of Drug Policy*, *26*(12), 1183–1188. https://doi.org/10.1016/j.drugpo.2015.09.011

McDonald, R., & Strang, J. (2016). Are take-home naloxone programmes effective? Systematic review utilizing application of the Bradford Hill criteria. *Addiction*. https://onlinelibrary.wiley.com/doi/full/10.1111/add.13326

Murphy, J., & Russell, B. (2020). Police officers' views of naloxone and drug treatment: does greater overdose response lead to more negativity? *Journal of Drug Issues, 50*(4), 455–471. https://doi.org/10.1177/0022042620921363

*NARCAN (naloxone hydrochloride) nasal spray*. (2015). The American Society of Health-System Pharmacists.

*National Adult Tobacco Survey (NATS)*. (2014). Centers for Disease Control and Prevention. https://www.cdc.gov/tobacco/data_statistics/surveys/nats/

*NIDA-Modified ASSIST (NM ASSIST): Clinician's Screening Tool for Drug Use in General Medical Settings*. (2020). Retrieved June 10, 2022, from https://www.samhsa.gov/resource/ebp/nida-modified-assist-nm-assist-clinicians-screening-tool-drug-use-general-medical

*Opioid Data Analysis and Resources | CDC's Response to the Opioid Overdose Epidemic | CDC*. (2021, October 15). https://www.cdc.gov/opioids/data/analysis-resources.html

Pollini, R. A., Ozga, J. E., Joyce, R., Xuan, Z., & Walley, A. Y. (2022). Limited access to pharmacy-based naloxone in West Virginia: Results from a statewide purchase trial. *Drug and Alcohol Dependence*, *231*, 109259. https://doi.org/10.1016/j.drugalcdep.2021.109259

*Population Assessment of Tobacco and Health (PATH) Study*. (2014). National Institutes of Health (NIH). https://pathstudyinfo.nih.gov/

*Prevent an Overdose, Save a Life*. (2013). New York City Department of Health. https://www.youtube.com/watch?v=xH04qvoKkhk

Razaghizad, A., Windle, S. B., Filion, K. B., Gore, G., Kudrina, I., Paraskevopoulos, E., Kimmelman, J., Martel, M. O., & Eisenberg, M. J. (2021). The effect of overdose education and naloxone distribution: An umbrella review of systematic reviews. *American Journal of Public Health*, *111*(8), e1–e12. https://doi.org/10.2105/AJPH.2021.306306

Rosseel, Y. (2012). lavaan: An R Package for Structural Equation Modeling. *Journal of Statistical Software*, *48*, 1–36. https://doi.org/10.18637/jss.v048.i02

*SAVEME Steps: What to Do for a Suspected Overdose*. (2022). British Columbia Emergency Health Services. http://www.bcehs.ca/health-info/public-health/responding-to-an-overdose/what-to-do-for-a-suspected-overdose

Seal, K. H., Thawley, R., Gee, L., Bamberger, J., Kral, A. H., Ciccarone, D., Downing, M., & Edlin, B. R. (2005). Naloxone distribution and cardiopulmonary resuscitation training for injection drug users to prevent heroin overdose death: A pilot intervention study. *Journal of Urban Health*, *82*(2), 303–311. https://doi.org/10.1093/jurban/jti053

Sisson, M. L., McMahan, K. B., Chichester, K. R., Galbraith, J. W., & Cropsey, K. L. (2019). Attitudes and availability: A comparison of naloxone dispensing across chain and independent pharmacies in rural and urban areas in Alabama. *International Journal of Drug Policy*, *74*, 229–235. https://doi.org/10.1016/j.drugpo.2019.09.021

Tse, W. C., Djordjevic, F., Borja, V., Picco, L., Lam, T., Olsen, A., Larney, S., Dietze, P., & Nielsen, S. (2022). Does naloxone provision lead to increased substance use? A systematic review to assess if there is evidence of a 'moral hazard' associated with naloxone supply. *International Journal of Drug Policy*, *100*, 103513. https://doi.org/10.1016/j.drugpo.2021.103513

*Understanding the Epidemic*. (2022, February 9). Centers for Disease Control and Prevention. https://www.cdc.gov/drugoverdose/epidemic/index.html

Wagner, K. D., Valente, T. W., Casanova, M., Partovi, S. M., Mendenhall, B. M., Hundley, J. H., Gonzalez, M., & Unger, J. B. (2010). Evaluation of an overdose prevention and response training programme for injection drug users in the Skid Row area of Los Angeles, CA. *International Journal of Drug Policy*, *21*(3), 186–193. https://doi.org/10.1016/j.drugpo.2009.01.003

Walley, A. Y., Xuan, Z., Hackman, H. H., Quinn, E., Doe-Simkins, M., Sorensen-Alawad, A., Ruiz, S., & Ozonoff, A. (2013). Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: Interrupted time series analysis. *BMJ*, *346*, f174. https://doi.org/10.1136/bmj.f174

Webster, L. R. (2017). Risk factors for opioid-use disorder and overdose. *Anesthesia & Analgesia*, *125*(5), 1741–1748. https://doi.org/10.1213/ANE.0000000000002496

Wheeler, E., Jones, T. S., Gilbert, M. K., & Davidson, P. J. (2015). Opioid overdose prevention programs providing naloxone to laypersons—United States, 2014. *Morbidity and Mortality Weekly Report*, *64*(23), 631–635.

Williams, A. V., Strang, J., & Marsden, J. (2013). Development of Opioid Overdose Knowledge (OOKS) and Attitudes (OOAS) Scales for take-home naloxone training evaluation. *Drug and Alcohol Dependence*, *132*(1), 383–386. https://doi.org/10.1016/j.drugalcdep.2013.02.007

Winograd, R. P., Werner, K. B., Green, L., Phillips, S., Armbruster, J., & Paul, R. (2020). Concerns that an opioid antidote could "make things worse": Profiles of risk compensation beliefs using the Naloxone-Related Risk Compensation Beliefs (NaRRC-B) scale. *Substance Abuse*, *41*(2), 245–251. https://doi.org/10.1080/08897077.2019.1616348

Xu, J., Davis, C. S., Cruz, M., & Lurie, P. (2018). State naloxone access laws are associated with an increase in the number of naloxone prescriptions dispensed in retail pharmacies. *Drug and Alcohol Dependence*, *189*, 37–41. https://doi.org/10.1016/j.drugalcdep.2018.04.020

Table 1. Demographic Characteristics of Sample at Baseline by Randomized Group and Naloxone Kit Possession

| | **OEND Group (*n* = 55)** | | **OE Group (*n* = 56)** | | **Effect Size** | |
|---|---|---|---|---|---|---|
| | ***M/n*** | ***SD/%*** | ***M/n*** | ***SD/%*** | **Cramer's *V*/ Cohen's *d*** | ***p*** |
| Age | 37.4 | 9.1 | 38.5 | 10.5 | 0.11 | .558 |
| Race | | | | | 0.15 | .674 |
| American Indian/Alaskan Native | 1 | 0.9% | - | - | | |
| Black/African American | 5 | 4.5% | 7 | 6.3% | | |
| White/Caucasian | 46 | 41.4% | 45 | 40.5% | | |
| Multiracial | 3 | 2.7% | 4 | 3.6% | | |
| Ethnicity | | | | | 0.002 | .985 |
| Hispanic | 2 | 1.8% | 2 | 1.8% | | |
| Non-Hispanic | 53 | 47.7% | 54 | 48.6% | | |
| Sex | | | | | 0.03 | .751 |
| Female | 35 | 31.5% | 34 | 30.6% | | |
| Male | 20 | 18.0% | 22 | 19.8% | | |
| Educational Attainment | | | | | 0.18 | .299 |
| Less than high school | 5 | 4.5% | 3 | 2.7% | | |
| High school/GED | 31 | 28.2% | 38 | 34.5% | | |
| Technical/Associate's degree | 15 | 13.6% | 9 | 8.2% | | |
| Bachelor's degree or higher | 3 | 2.7% | 6 | 5.5% | | |
| | **Possess Kit (*n* = 69)** | | **No Kit (*n* = 29)** | | **Effect Size** | |
| | ***M/n*** | ***SD/%*** | ***M/n*** | ***SD/%*** | **Cramer's *V*/ Cohen's *d*** | ***p*** |
| Age | 38.1 | 10.3 | 40.4 | 9.3 | 0.23 | .299 |
| Race | | | | | 0.13 | .657 |
| American Indian/Alaskan Native | 1 | 1.0% | - | - | | |
| Black/African American | 5 | 5.1% | 4 | 4.1% | | |
| White/Caucasian | 59 | 60.2% | 24 | 24.5% | | |
| Multiracial | 4 | 4.1% | 1 | 1.0% | | |
| Ethnicity | | | | | 0.07 | .523 |
| Hispanic | 1 | 1.0% | 1 | 1.0% | | |
| Non-Hispanic | 68 | 69.4% | 28 | 28.6% | | |
| Sex | | | | | 0.13 | .211 |
| Female | 45 | 45.9% | 15 | 15.3% | | |
| Male | 24 | 24.5% | 14 | 14.3% | | |
| Educational Attainment | | | | | 0.15 | .550 |
| Less than high school | 6 | 6.2% | 2 | 2.1% | | |
| High school/GED | 39 | 40.2% | 21 | 21.6% | | |
| Technical/Associate's degree | 17 | 17.5% | 4 | 4.1% | | |
| Bachelor's degree or higher | 6 | 6.2% | 2 | 2.1% | | |

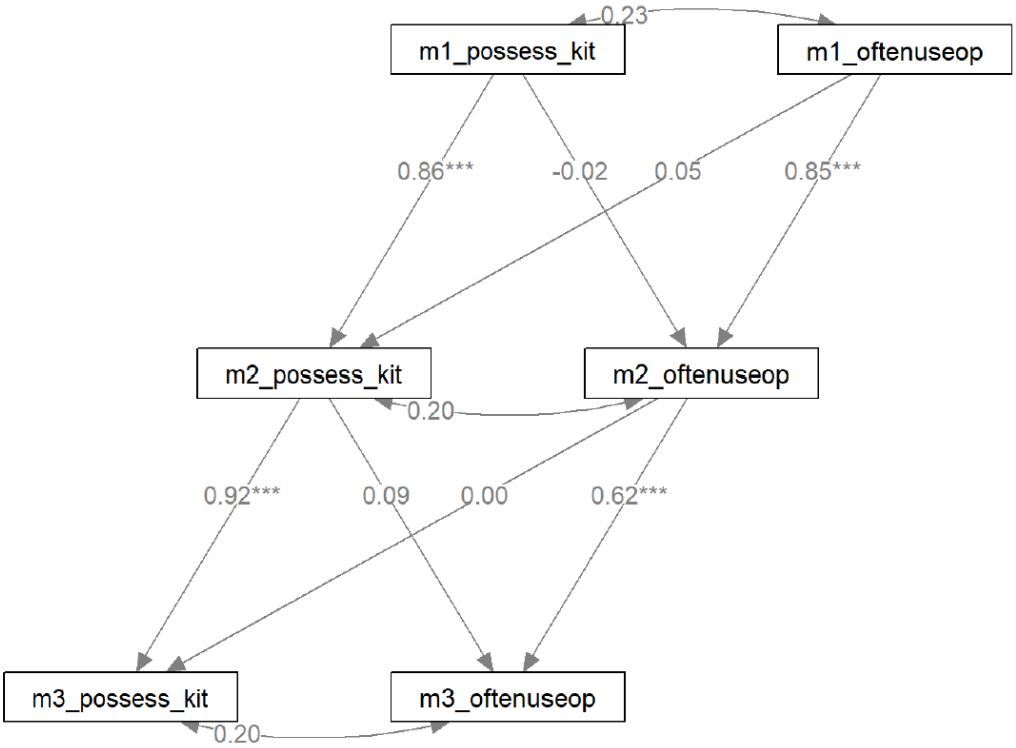
*Note*. OEND = Opioid Overdose Education and Naloxone Distribution; OE = Opioid Overdose Education

Table 2. Differences in Kit Possession, Overdoses, Opioid Use Frequency, and Interest in Treatment by Randomized Group and Naloxone Kit Possession

| **Variable** | **Time Point** | **OEND Group (*n* = 48)** | | **OE Group (*n* = 50)** | | **Effect Size** | |
|---|---|---|---|---|---|---|---|
| | | ***n*** | ***%*** | ***n*** | ***%*** | **% Difference** | ***p*** |
| Kit Possession | Time Ave. | | | | | 60% | <.001* |
| | Month 1 | 48 | 100.0% | 17 | 34.0% | 63% | <.001* |
| | Month 2 | 47 | 100.0% | 18 | 36.0% | 61% | <.001* |
| | Month 3 | 45 | 100.0% | 21 | 42.0% | 55% | <.001* |
| **Variable** | **Time Point** | **Possess Kit Full Sample (*n* = 69)** | | **No Kit Full Sample (*n* = 29)** | | **Effect Size** | |
| | | ***n*** | ***%*** | ***n*** | ***%*** | **% Difference** | ***p*** |
| Overdoses | Time Ave. | | | | | 1.0% | .921 |
| | Month 1 | 1 | 3.0% | 1 | 5.0% | 2.0% | .705 |
| | Month 2 | 2 | 5.0% | 3 | 10.0% | 4.0% | .486 |
| | Month 3 | 2 | 5.0% | 0 | 2.0% | 3.0% | .515 |
| | | ***M*** | ***SE*** | ***M*** | ***SE*** | **Cohen's *d*** | ***p*** |
| Opioid Use | Time Ave. | | | | | 0.26 | .155 |
| | Month 1 | 4.78 | 0.27 | 4.18 | 0.40 | 0.26 | .192 |
| | Month 2 | 4.88 | 0.25 | 4.20 | 0.45 | 0.29 | .179 |
| | Month 3 | 4.42 | 0.28 | 3.83 | 0.51 | 0.25 | .293 |
| Treatment Interest | Time Ave. | | | | | 0.06 | .741 |
| | Month 1 | 2.01 | 0.16 | 2.00 | 0.22 | 0.01 | .940 |
| | Month 2 | 2.01 | 0.17 | 1.87 | 0.26 | 0.10 | .628 |
| | Month 3 | 2.00 | 0.16 | 1.93 | 0.28 | 0.05 | .809 |
| **Variable** | **Time Point** | **Possess Kit OE Group (*n* = 21)** | | **No Kit OE Group (*n* = 29)** | | **Effect Size** | |
| | | ***n*** | ***%*** | ***n*** | ***%*** | **% Difference** | ***p*** |
| Overdoses | Time Ave. | | | | | 6.0% | .307 |
| | Month 1 | 0 | 5.0% | 1 | 6.0% | 1.0% | .936 |
| | Month 2 | 2 | 17.0% | 3 | 11.0% | 6.0% | .465 |
| | Month 3 | 2 | 15.0% | 0 | 3.0% | 12.0% | .101 |
| | | ***M*** | ***SE*** | ***M*** | ***SE*** | **Cohen's *d*** | ***p*** |
| Opioid Use | Time Ave. | | | | | 0.54 | .007* |
| | Month 1 | 5.50 | 0.35 | 4.38 | 0.41 | 0.49 | .024* |
| | Month 2 | 5.64 | 0.38 | 4.39 | 0.44 | 0.54 | .026* |
| | Month 3 | 5.30 | 0.37 | 3.99 | 0.50 | 0.57 | .027* |
| Treatment Interest | Time Ave. | | | | | 0.03 | .888 |
| | Month 1 | 1.92 | 0.24 | 1.98 | 0.22 | 0.04 | .851 |
| | Month 2 | 1.87 | 0.24 | 1.86 | 0.27 | 0.01 | .973 |
| | Month 3 | 2.06 | 0.23 | 1.91 | 0.28 | 0.11 | .654 |

*Note*. Discrepancies between observed frequencies and percentages from models are due to Firth's correction; "Time Ave." = "Time-Averaged"; **p*-values <.027 are significant at a 10% FDR level.

Figure 1. Cross-Lagged Panel Model Between Naloxone Kit Possession and Opioid Use Frequency




*Note*. Standardized coefficients shown; “m1” = Month 1; “m2” = Month 2; “m3” = Month 3; “possess_kit” = whether participant possessed naloxone; “oftenuseop” = frequency of opioid use.

# SUMMARY AND CONCLUSIONS

## Overall Findings

The overall goal of this project was to provide preliminary information for potential avenues to expand access to OEND. Primarily, the project aimed to evaluate the feasibility of applying remote methodologies to the OEND model. Secondary aims included examining criticisms of naloxone possession in addition to identifying characteristics of those most interested in OEND.

This study demonstrated feasibility and acceptability of implementing remote OEND through online recruitment, online virtual opioid overdose and naloxone administration training, and postal distribution of naloxone kits. Recruitment via online advertising was successful, with a larger than targeted sample size obtained within a brief timeframe. Robust retention through completion of the study provides further support for the feasibility of online administration of questionnaires, training, and follow-up assessments. Online training consisting of a brief video effectively improved participants' knowledge of overdose risk factors, signs, and response procedures, as well as their understanding of naloxone. Gauging of participants' satisfaction with the remote format of study procedures indicated acceptability, as a majority of participants endorsed high satisfaction. Satisfaction ratings were generally uniform across randomized groups. However, participants in the first group indicated much higher satisfaction with receiving a study provided naloxone kit in comparison to those in the second group who received

specific information on how to obtain a kit via pharmacy. Relatedly, a majority of individuals in the second group did not acquire naloxone during the three-month follow-up period, demonstrating a significant disparity in kit possession across randomized groups.

In response to criticism that naloxone kit possession encourages opioid use and avoidance of treatment, participants with and without naloxone were compared on reported personal overdoses, frequency of opioid use, and interest in substance use treatment across the follow-up period. No difference was found in the number of reported personal overdoses based on status of naloxone possession. Individuals who obtained naloxone had greater frequency of opioid use than those who did not. There was a stronger relationship between higher opioid use preceding naloxone acquirement as opposed to the inverse relationship. Interest in treatment was slightly higher for those who possessed naloxone, though the difference was not significant.

Naloxone distribution is most effectual when it is targeted, equipping those most likely to witness and respond to opioid overdose with the ability to do so successfully (Carroll et al., 2018). As such, this study not only aimed to identify methods to expand OEND access but also sought to provide preliminary characterization of those most interested in participating in order to promote targeted tailoring of these programs. Within this sample, individuals who elected to participate in training and those who declined had similar rates of current opioid use. Those who elected to participate endorsed more intravenous drug administration and polysubstance use. Individuals who declined to engage in training reported somewhat greater frequency of personal and

observed overdose, overdose-related hospitalizations, and inpatient substance use treatments. Decliners also indicated more illicit use of methadone.

## Interpretation of Findings

Overall, feasibility and acceptability of remote OEND was supported as evidenced by strong recruitment and retention, improvement in participant knowledge, and notable participant satisfaction. Recruitment and retention were robust even with a traditionally difficult to reach population such as individuals with substance use. The impressive engagement of this population potentially indicates ability of an online approach to reach those in need who are missed through traditional recruitment and to maintain their involvement. Remote application of OEND eliminates transportation and related cost or time barriers, especially for individuals in rural areas, likely enhancing engagement. Similar to in-person studies, participant knowledge regarding opioid overdose risks, indications, and response strategies improved subsequent to training (Clark et al., 2014; Giglio et al., 2015; Razaghizad et al., 2021). This provides support for training being effectively administered via a brief online video. Acceptability was demonstrated by participants' high satisfaction with the online format of the consent document, surveys, and training video. Moreover, participants largely perceived the training as effective and felt confident in their ability to administer naloxone after receiving guidance.

The lower satisfaction ratings and kit possession for participants given information on how to obtain a kit through a pharmacy indicate barriers to acquiring naloxone through this route. The similarity in reported number of personal overdoses and

interest in treatment across naloxone possession status provides further refuting evidence against the concern that having naloxone promotes opioid use and avoidance of treatment. Frequency of opioid use was higher for individuals with naloxone, but greater opioid use more often preceded naloxone purchase. Thus, a relationship between naloxone and higher opioid use may be explained by safety concerns regarding usage amount increasing the likelihood of obtaining naloxone, rather than possession reducing the fear of fatal overdose and subsequently encouraging use.

Perceiving oneself as more vulnerable to fatal opioid overdose may also increase desire to participate in opioid overdose and naloxone administration training. Individuals in this study who elected training indicated greater intravenous administration and polysubstance use, both of which are associated with increased risk of fatal overdose (Cicero et al., 2020; Crummy et al., 2020; Mathers et al., 2013; Riley et al., 2016). Those who declined participation in training had more experience with opioid overdose and related treatment. Having greater exposure to overdose response procedures by frequently witnessing others overdose may increase one's confidence in responding to these situations and decrease perceived need for training. Similarly, individuals having more experience with emergent or inpatient treatment in relation to opioid overdose or use could equate to a belief that they can recover without having possession of naloxone.

## Conclusions

In summary, this study provided support for the feasibility and acceptability of online opioid overdose and naloxone administration training and postal distribution of naloxone. Implementing this methodology could greatly expand access to this life-saving

intervention and reduce fatal overdoses. Modest obtainment of naloxone from pharmacies illuminates limits to accessibility through this setting and potential need for restructuring of naloxone access legislation. Naloxone possession did not appear to negatively impact opioid use or interest in treatment, adding to preexisting evidence against these concerns and further suggesting that they should not inhibit policy enactment. OEND programs may benefit from understanding characteristics of individuals who refuse training in order to tailor information and better highlight the value of training for those who perceive it as unneeded. Given the pilot nature of this study, findings and interpretations are preliminary and further examination within a fully powered trial is necessary.

# REFERENCES

Barocas, J. A. (2019). Commentary on Irvine et al. (2019): Barriers to implementing a successful roadmap for preventing opioid-related overdose deaths. *Addiction, 114*(9), 1614–1615. https://doi.org/10.1111/add.14738

Bazazi, A. R., Zaller, N. D., Fu, J. J., & Rich, J. D. (2010). Preventing opiate overdose deaths: Examining objections to take-home naloxone. *Journal of Health Care for the Poor and Underserved, 21*(4), 1108–1113. https://doi.org/10.1353/hpu.2010.0935

Behar, E., Santos, G.-M., Wheeler, E., Rowe, C., & Coffin, P. O. (2015). Brief overdose education is sufficient for naloxone distribution to opioid users. *Drug and Alcohol Dependence, 148*, 209–212. https://doi.org/10.1016/j.drugalcdep.2014.12.009

Bennett, A. S., & Elliott, L. (2021). Naloxone's role in the national opioid crisis—Past struggles, current efforts, and future opportunities. *Translational Research, 234*, 43–57. https://doi.org/10.1016/j.trsl.2021.03.001

Bird, S. M., McAuley, A., Perry, S., & Hunter, C. (2016). Effectiveness of Scotland's National Naloxone Programme for reducing opioid-related deaths: A before (2006–10) versus after (2011–13) comparison. *Addiction, 111*(5), 883–891. https://doi.org/10.1111/add.13265

Carroll, J., Green, T., & Noonan, R. (2018). *Evidence-Based Strategies for Preventing Opioid Overdose: What's Working in the United States, 2018* (p. 40). Centers for Disease Control and Prevention.

*CDC WONDER*. (2022). Centers for Disease Control and Prevention. https://wonder.cdc.gov/

Cicero, T. J., & Ellis, M. S. (2015). Abuse-deterrent formulations and the prescription opioid abuse epidemic in the United States: Lessons learned from OxyContin. *JAMA Psychiatry, 72*(5), 424–430. https://doi.org/10.1001/jamapsychiatry.2014.3043

Cicero, T. J., Ellis, M. S., & Kasper, Z. A. (2020). Polysubstance Use: A broader understanding of substance use during the opioid crisis. *American Journal of Public Health, 110*(2), 244–250. https://doi.org/10.2105/AJPH.2019.305412

Clark, A. K., Wilder, C. M., & Winstanley, E. L. (2014). A systematic review of community opioid overdose prevention and naloxone distribution programs. *Journal of Addiction Medicine, 8*(3), 153–163. https://doi.org/10.1097/ADM.0000000000000034

Coffin, P. O., & Sullivan, S. D. (2013). Cost-effectiveness of distributing naloxone to heroin users for lay overdose reversal. *Annals of Internal Medicine, 158*(1), 1–9. https://doi.org/10.7326/0003-4819-158-1-201301010-00003

Compton, W. M., Jones, C. M., & Baldwin, G. T. (2016). relationship between nonmedical prescription-opioid use and heroin use. *New England Journal of Medicine*. https://www.nejm.org/doi/full/10.1056/NEJMra1508490

Crummy, E. A., O'Neal, T. J., Baskin, B. M., & Ferguson, S. M. (2020). One is not enough: Understanding and modeling polysubstance use. *Frontiers in Neuroscience, 14*. https://www.frontiersin.org/article/10.3389/fnins.2020.00569

Darke, S., & Duflou, J. (2016). The toxicology of heroin-related death: Estimating survival times. *Addiction, 111*(9), 1607–1613. https://doi.org/10.1111/add.13429

*Data Overview*. (2022, April 9). Centers for Disease Control and Prevention. https://www.cdc.gov/opioids/data/index.html

*Death Rate Maps & Graphs*. (2022, June 2). Centers for Disease Control and Prevention. https://www.cdc.gov/drugoverdose/deaths/index.html

Evoy, K. E., Hill, L. G., & Davis, C. S. (2021). Considering the potential benefits of over-the-counter naloxone. *Integrated Pharmacy Research & Practice, 10,* 13–21. https://doi.org/10.2147/IPRP.S244709

Gertner, A. K., Domino, M. E., & Davis, C. S. (2018). Do naloxone access laws increase outpatient naloxone prescriptions? Evidence from Medicaid. *Drug and Alcohol Dependence, 190,* 37–41. https://doi.org/10.1016/j.drugalcdep.2018.05.014

Giglio, R. E., Li, G., & DiMaggio, C. J. (2015). Effectiveness of bystander naloxone administration and overdose education programs: A meta-analysis. *Injury Epidemiology, 2*(1), 10. https://doi.org/10.1186/s40621-015-0041-8

Graves, R. L., Andreyeva, E., Perrone, J., Shofer, F., Merchant, R. M., & Meisel, Z. F. (2019). Naloxone availability and pharmacy staff knowledge of standing order for naloxone in Pennsylvania pharmacies. *Journal of Addiction Medicine, 13*(4), 272–278. https://doi.org/10.1097/ADM.0000000000000492

Guadamuz, J. S., Alexander, G. C., Chaudhri, T., Trotzky-Sirr, R., & Qato, D. M. (2019). Availability and cost of naloxone nasal spray at pharmacies in Philadelphia, Pennsylvania, 2017. *JAMA Network Open*, *2*(6), e195388. https://doi.org/10.1001/jamanetworkopen.2019.5388

Gupta, R., Shah, N. D., & Ross, J. S. (2016). The rising price of naloxone—Risks to efforts to stem overdose deaths. *New England Journal of Medicine, 375*(23), 2213–2215. https://doi.org/10.1056/NEJMp1609578

Guy, G. P., Haegerich, T. M., Evans, M. E., Losby, J. L., Young, R., & Jones, C. M. (2019). Vital signs: Pharmacy-based naloxone dispensing — United States, 2012–2018. *Morbidity and Mortality Weekly Report*, *68*(31), 679–686. https://doi.org/10.15585/mmwr.mm6831e1

Guy, G. P., Khushalani, J. S., Jackson, H., Sims, R. St. C., & Arifkhanova, A. (2021). Trends in state-level pharmacy-based naloxone dispensing rates, 2012–2019. *American Journal of Preventive Medicine*, *61*(6), e289–e295. https://doi.org/10.1016/j.amepre.2021.05.042

Harocopos, A., & Allen, B. (2015). Routes into opioid analgesic misuse: Emergent typologies of initiation. *Journal of Drug Issues*, *45*(4), 385–395. https://doi.org/10.1177/0022042615604345

Jarlais, D. C. D., Nugent, A., Solberg, A., Feelemyer, J., Mermin, J., & Holtzman, D. (2015). Syringe service programs for persons who inject drugs in urban, suburban, and rural areas—United States, 2013. *Morbidity and Mortality Weekly Report*, *64*(48), 1337–1341.

Jones, J. D., Campbell, A., Metz, V. E., & Comer, S. D. (2017). No evidence of compensatory drug use risk behavior among heroin users after receiving take-home naloxone. *Addictive Behaviors*, *71*, 104–106. https://doi.org/10.1016/j.addbeh.2017.03.008

Kanouse, A. B., & Compton, P. (2015). The epidemic of prescription opioid abuse, the subsequent rising prevalence of heroin use, and the federal response. *Journal of Pain & Palliative Care Pharmacotherapy*, *29*(2), 102–114. https://doi.org/10.3109/15360288.2015.1037521

Lambdin, B. H., Davis, C. S., Wheeler, E., Tueller, S., & Kral, A. H. (2018). Naloxone laws facilitate the establishment of overdose education and naloxone distribution programs in the United States. *Drug and Alcohol Dependence*, *188*, 370–376. https://doi.org/10.1016/j.drugalcdep.2018.04.004

Lambdin, B. H., Zibbell, J., Wheeler, E., & Kral, A. H. (2017). Identifying gaps in the implementation of naloxone programs for laypersons in the United States. *International Journal on Drug Policy*, *52*, 52–55. https://doi.org/10.1016/j.drugpo.2017.11.017

Mathers, B. M., Degenhardt, L., Bucello, C., Lemon, J., Wiessing, L., & Hickman, M. (2013). Mortality among people who inject drugs: A systematic review and meta-analysis. *Bulletin of the World Health Organization*, *91*(2), 102–123. https://doi.org/10.2471/BLT.12.108282

McAuley, A., Aucott, L., & Matheson, C. (2015). Exploring the life-saving potential of naloxone: A systematic review and descriptive meta-analysis of take-home naloxone (THN) programmes for opioid users. *International Journal of Drug Policy*, *26*(12), 1183–1188. https://doi.org/10.1016/j.drugpo.2015.09.011

McDonald, R., & Strang, J. (2016). Are take-home naloxone programmes effective? Systematic review utilizing application of the Bradford Hill criteria. *Addiction*, *111*(7), 1177–1187. https://doi.org/10.1111/add.13326

Mell, H. K., Mumma, S. N., Hiestand, B., Carr, B. G., Holland, T., & Stopyra, J. (2017). Emergency medical services response times in rural, suburban, and urban areas. *JAMA Surgery*, *152*(10), 983–984. https://doi.org/10.1001/jamasurg.2017.2230

Murphy, J., & Russell, B. (2020). Police officers' views of naloxone and drug treatment: does greater overdose response lead to more negativity? *Journal of Drug Issues*, *50*(4), 455–471. https://doi.org/10.1177/0022042620921363

Pollini, R. A., Ozga, J. E., Joyce, R., Xuan, Z., & Walley, A. Y. (2022). Limited access to pharmacy-based naloxone in West Virginia: Results from a statewide purchase trial. *Drug and Alcohol Dependence*, *231*, 109259. https://doi.org/10.1016/j.drugalcdep.2021.109259

Puzantian, T., & Gasper, J. J. (2018). Provision of naloxone without a prescription by California pharmacists 2 years after legislation implementation. *JAMA*, *320*(18), 1933–1934. https://doi.org/10.1001/jama.2018.12291

Razaghizad, A., Windle, S. B., Filion, K. B., Gore, G., Kudrina, I., Paraskevopoulos, E., Kimmelman, J., Martel, M. O., & Eisenberg, M. J. (2021). The effect of overdose education and naloxone distribution: An umbrella review of systematic reviews. *American Journal of Public Health*, *111*(8), e1–e12. https://doi.org/10.2105/AJPH.2021.306306

Riley, E. D., Evans, J. L., Hahn, J. A., Briceno, A., Davidson, P. J., Lum, P. J., & Page, K. (2016). A longitudinal study of multiple drug use and overdose among young people who inject drugs. *American Journal of Public Health*, *106*(5), 915–917. https://doi.org/10.2105/AJPH.2016.303084

Sisson, M. L., McMahan, K. B., Chichester, K. R., Galbraith, J. W., & Cropsey, K. L. (2019). Attitudes and availability: A comparison of naloxone dispensing across chain and independent pharmacies in rural and urban areas in Alabama. *International Journal of Drug Policy*, *74*, 229–235. https://doi.org/10.1016/j.drugpo.2019.09.021

Smart, R., Pardo, B., & Davis, C. S. (2021). Systematic review of the emerging literature on the effectiveness of naloxone access laws in the United States. *Addiction*, *116*(1), 6–17. https://doi.org/10.1111/add.15163

Stone, R. H., Hur, S., & Young, H. N. (2020). Assessment of naloxone availability in Georgia community pharmacies. *Journal of the American Pharmacists Association*, *60*(2), 357–361. https://doi.org/10.1016/j.japh.2019.11.003

*Synthetic Opioid Overdose Data*. (2021, September 9). Centers for Disease Control and Prevention. https://www.cdc.gov/drugoverdose/deaths/synthetic/index.html

Townsend, T., Blostein, F., Doan, T., Madson-Olson, S., Galecki, P., & Hutton, D. W. (2020). Cost-effectiveness analysis of alternative naloxone distribution strategies: First responder and lay distribution in the United States. *International Journal of Drug Policy*, *75*, 102536. https://doi.org/10.1016/j.drugpo.2019.07.031

Tse, W. C., Djordjevic, F., Borja, V., Picco, L., Lam, T., Olsen, A., Larney, S., Dietze, P., & Nielsen, S. (2022). Does naloxone provision lead to increased substance use? A systematic review to assess if there is evidence of a 'moral hazard' associated with naloxone supply. *International Journal of Drug Policy*, *100*, 103513. https://doi.org/10.1016/j.drugpo.2021.103513

*Understanding the Epidemic*. (2022, February 9). Centers for Disease Control and Prevention. https://www.cdc.gov/drugoverdose/epidemic/index.html

Unick, G. J., Rosenblum, D., Mars, S., & Ciccarone, D. (2013). Intertwined epidemics: National demographic trends in hospitalizations for heroin- and opioid-related overdoses, 1993–2009. *PLOS ONE*, *8*(2), e54496. https://doi.org/10.1371/journal.pone.0054496

Van Zee, A. (2009). The promotion and marketing of OxyContin: Commercial triumph, public health tragedy. *American Journal of Public Health*, *99*(2), 221–227. https://doi.org/10.2105/AJPH.2007.131714

Volkow, N. D., Frieden, T. R., Hyde, P. S., & Cha, S. S. (2014). Medication-assisted therapies—Tackling the opioid-overdose epidemic. *New England Journal of Medicine*, *370*(22), 2063–2066. https://doi.org/10.1056/NEJMp1402780

Wagner, K. D., Valente, T. W., Casanova, M., Partovi, S. M., Mendenhall, B. M., Hundley, J. H., Gonzalez, M., & Unger, J. B. (2010). Evaluation of an overdose prevention and response training programme for injection drug users in the Skid Row area of Los Angeles, CA. *International Journal of Drug Policy*, *21*(3), 186–193. https://doi.org/10.1016/j.drugpo.2009.01.003

Winograd, R. P., Werner, K. B., Green, L., Phillips, S., Armbruster, J., & Paul, R. (2020). Concerns that an opioid antidote could "make things worse": Profiles of risk compensation beliefs using the Naloxone-Related Risk Compensation Beliefs (NaRRC-B) scale. *Substance Abuse*, *41*(2), 245–251. https://doi.org/10.1080/08897077.2019.1616348

Wood, C. A., Duello, A., Horn, P., Winograd, R., Jackson, L., Mayen, S., & Wallace, K. (2021). Overdose response training and naloxone distribution among rural first responders. *Journal of Rural Mental Health*, *45*(3), 207–218. https://doi.org/10.1037/rmh0000166

Xu, J., Davis, C. S., Cruz, M., & Lurie, P. (2018). State naloxone access laws are associated with an increase in the number of naloxone prescriptions dispensed in retail pharmacies. *Drug and Alcohol Dependence*, *189*, 37–41. https://doi.org/10.1016/j.drugalcdep.2018.04.020

# APPENDIX A

## INSTITUTIONAL REVIEW BOARD APPROVAL LETTER

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Office of the Institutional Review Board for Human Use

470 Administration Building
701 20th Street South
Birmingham, AL 35294-0104
205.934.3789 | Fax 205.934.1301 |
irb@uab.edu

## APPROVAL LETTER

**TO:** Sisson, Michelle L

**FROM:** University of Alabama at Birmingham Institutional Review Board
Federalwide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)
IORG Registration # IRB00012550 (IRB 03)

**DATE:** 09-Apr-2022

**RE:** IRB-300004762
IRB-300004762-018
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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The IRB reviewed and approved the Personnel Amendment submitted on 07-Apr-2022 for the above referenced project. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services.

**Type of Review:** Expedited
**Expedited Categories:** b2
**Determination:** Approved
**Approval Date:** 09-Apr-2022
**Expiration Date:** 20-Apr-2022

**Linked Records:**

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