Addressing the Opioid Epidemic Through Community Pharmacy Engagement: Randomized Controlled Trial (Aim 2)

NCT number NCT04677387
Document Date 05/29/2024

PROTOCOL: INTERVENTIONAL STUDY

Complete Title: Addressing the Opioid Epidemic Through Community Pharmacy Engagement: Randomized Controlled Trial (Aim 2)

Short Title: Nalox-Comm: Naloxone Communication Training for Pharmacists

Drug or Device Name(s): N/A

FDA IND/IDE (if applicable): N/A

Sponsor: National Institutes of Health (NIH)

Protocol Date: 5/29/24

Sponsor
National Institutes of Health (NIH)
Bethesda, MD 20892
USA

Study Principal Investigator: Delesha Carpenter, PhD, MSPH
1 University Heights, 114G Karpen Hall
Asheville, NC 28804
Phone: 828-250-3916
Email: dmcarpenter@unc.edu

PROTOCOL TITLE: Addressing the Opioid Epidemic Through Community Pharmacy Engagement: Randomized Controlled Trial (Aim 2)

Short Title: Nalox-Comm: Naloxone Communication Training for Pharmacists

Lead Investigator:

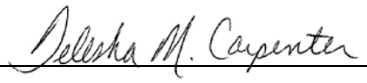
Delesha Carpenter, PhD, MSPH

University of North Carolina at Chapel Hill

Version Date: May 29, 2024

I confirm that I have read this protocol and understand it.

Principal Investigator Name: Delesha Carpenter

Principal Investigator Signature: 

Date: 5/30/2024

Table of Contents

ABBREVIATIONS AND DEFINITIONS OF TERMS 4

PROTOCOL SYNOPSIS 5
BACKGROUND AND RATIONALE 8
1. STUDY OBJECTIVES 9
2. INVESTIGATIONAL PLAN 9
3. STUDY PROCEDURES 10
4. STUDY EVALUATIONS AND MEASUREMENTS 11
5. STATISTICAL CONSIDERATIONS 13
6. STUDY INTERVENTION 14
7. SAFETY MANAGEMENT 15
8. DATA AND SAFETY MONITORING 15
9. CONSENT PROCESS 16
10. REFERENCES 16

APPENDIX 18

Abbreviations and Definitions of Terms

Abbreviation	Definition
RCT	Randomized controlled trial
SP	Simulated patient
P2P	Prescribe to Prevent
GEE	Generalized estimating equations
DSMB	Data and Safety Monitoring Board

PROTOCOL SYNOPSIS

Study Title	Addressing the Opioid Epidemic Through Community Pharmacy Engagement: Randomized Controlled Trial (Aim 2)
Funder	National Institutes of Health (NIH)
Study Rationale	• From 1999 to 2015, the drug overdose death rate in non-metropolitan rural areas increased by 325% and, by 2015, exceeded that of metropolitan urban areas[2]. • Naloxone, an opioid overdose reversal agent, is not readily accessible in many rural communities. • Community pharmacists are the most accessible healthcare professional in rural areas[4-6] and are well-positioned to increase access to naloxone in rural areas[7]. • The amount of naloxone dispensed by pharmacists has increased steadily over the past five years[8,9]. • Multiple studies[11-13] have shown that even when pharmacies stock naloxone, many pharmacists do not offer or dispense it. Reasons include barriers related to talking with patients and caregivers about the sensitive topic of overdose[14-17]. • Pharmacists' comfort communicating about naloxone is significantly associated with how often they offer it[13]. • Existing online naloxone training resources do not sufficiently address communication barriers. • The objective of our 4-state collaboration is to develop an online module (Nalox-Comm) to increase rural pharmacists' self-efficacy to engage in naloxone discussions and, ultimately, increase how often they dispense naloxone. • In Aim 1 (study #19-0998), we will gather and analyze formative data and engage in an iterative intervention development process to finalize Nalox-Comm content. • For Aim 2 (study #20-2192), which is described in this protocol, we will conduct a pilot randomized controlled trial with 60 pharmacists to evaluate whether Nalox-Comm increases the frequency with which pharmacists dispense naloxone (primary outcome).
Study Objective(s)	**Primary** • To evaluate whether Nalox-Comm increases the rate at which pharmacists dispense naloxone **Secondary** • To determine whether the Nalox-Comm module increases pharmacists' willingness to dispense naloxone

	• To determine whether the module increases pharmacists' self-efficacy to dispense naloxone • To determine whether the module improves the quality of pharmacists' naloxone communication
Test Article(s)	The Nalox-Comm training developed for this study is ~30 mins in length. It is an online module with videos, didactic content, and reflection. Content includes: • The importance of naloxone and the role of the pharmacist • Non-stigmatizing language • How to initiate an offer of naloxone • How to respond to patient & caregiver naloxone requests • How to address specific communication barriers
Study Design	This is a cluster RCT with balanced randomization by pharmacy and two parallel groups (experimental and control), conducted with pharmacists from 62 pharmacies part of a single grocery store chain in rural counties of Georgia, North Carolina, South Carolina, and Tennessee.
Subject Population key criteria for Inclusion and Exclusion:	Inclusion Criteria 1. Subjects age 18-99 years; 2. currently work at a pharmacy that stocks naloxone; 3. currently work at a rural community pharmacy; and 4. speak English. Exclusion Criteria 1. Non-staff pharmacists such as pharmacy "floaters" or fill-in pharmacists
Number Of Subjects	60 pharmacists
Study Duration	Each subject's participation will last approximately 6 months. The entire study is expected to last approximately 3 years.
Study Phases	1. Enrollment by invitation: inviting select pharmacies via email, confirming eligibility of those interested, obtaining electronic informed consent, completion of baseline survey 2. SP baseline observation: 3 SPs call each enrolled pharmacist to observe and rate the quality of their naloxone communication 3. Study intervention: participants complete either the Nalox-Comm module (experimental group) or the P2P training module (control group) based on previous randomization of pharmacies. They also complete a post-training survey. 4. SP post-training observation: 3 SPs call each enrolled pharmacist to observe and rate the quality of their naloxone communication

	5. Follow-up: 3 months post-intervention, participants complete a final follow-up survey to assess secondary outcomes
Efficacy Evaluations	Primary outcome: change in naloxone dispensing rates is measured by comparing pharmacy records of naloxone dispensed in the 3 months prior to study participation to number of naloxone dispensed in the 3 months after study completion Secondary outcomes: • Willingness – 7 items measure willingness to dispense naloxone. Pharmacists rate their willingness to engage in each item from 1= "Not at all willing" to 4 = "Very willing." • Self-efficacy – factors were identified that could impact counseling self-efficacy. On the study surveys, pharmacists rate their confidence to engage in 7 naloxone communication tasks. Response options range from 1 = "Not at all confident" to 4 = "Very confident." • Quality of naloxone counseling – SPs use a validated observation guide with 6 items to rate the pharmacist's quality of communication on a 5-point scale (1 = lowest score and 5 = highest score).
Statistical And Analytic Plan	Linear regression using GEE will be used to assess the effect of the intervention on naloxone dispensing rates (primary outcome) after adjusting for any imbalances between the treatment groups. Similar models will be used to assess the effect of the intervention on each secondary outcome.
DATA AND SAFETY MONITORING PLAN	The study PI will evaluate data collected by secret shoppers and through surveys. The PI will also meet weekly with her project director and monthly with the research team to discuss data collection, potential data quality issues if they arise, and study progress. Also, the DSMB will provide an independent and unbiased review of the study's ongoing progress.

BACKGROUND AND RATIONALE

In 2017, more than 49,000 of the 72,000 estimated drug overdose deaths in the U.S. involved opioid drugs[1]. From 1999 to 2015, the drug overdose death rate in non-metropolitan rural areas increased by 325% and, by 2015, exceeded that of metropolitan urban areas[2]. Naloxone, an opioid overdose reversal agent, is not readily accessible in many rural communities because these communities often lack substance use treatment resources and are health professional shortage areas[3]. Community pharmacists (pharmacists who work in outpatient ambulatory care settings) are the most accessible healthcare professional in rural areas[4-6] and, due to statewide standing orders that have granted pharmacists increased prescriptive authority to dispense naloxone to anyone who may benefit from it, are well-positioned to increase access to naloxone in rural areas[7].

The amount of naloxone dispensed by pharmacists has increased steadily over the past five years[8,9]. This increase is likely to continue since the Surgeon General's (SG) Advisory on Naloxone and Opioid Overdose, which was released in April 2018, specifically encourages individuals to talk with their pharmacists about naloxone.[10] Unfortunately, multiple studies[11,12], including our own[13], have shown that even when pharmacies stock naloxone, many pharmacists do not offer or dispense it. The reasons behind pharmacists' reluctance to offer and dispense naloxone often include barriers related to talking with patients and caregivers (i.e., third parties who obtain naloxone for someone at risk of overdose) about the sensitive topic of overdose[14-17]. Our own work has shown that pharmacists' comfort communicating about naloxone is significantly associated with how often they offer it[13]. Existing online naloxone training resources do not sufficiently address communication barriers that may influence pharmacists' willingness to offer and dispense naloxone, particularly barriers that are common in rural areas, such as high stigma against drug use and fear of offending patients[13,18].

The objective of our 4-state collaboration is to develop an online module (Nalox-Comm) to increase rural pharmacists' self-efficacy to engage in naloxone discussions and, ultimately, increase how often they dispense naloxone. For Aim 1 (study #19-0998), we will gather formative data on barriers to engaging in naloxone conversations and preferences for module content from rural pharmacists, patients, and caregivers (i.e., third parties who obtain naloxone for someone who takes opioids). We will then analyze formative data and engage in an iterative intervention development process with a stakeholder development panel and expert consultants to finalize Nalox-Comm content. For Aim 2 (study #20-2192), which is described in this protocol, we will conduct a pilot randomized controlled trial with 60 pharmacists to evaluate whether Nalox-Comm increases the frequency with which pharmacists dispense naloxone (primary outcome). We will also assess whether the module increases pharmacists' willingness and self-efficacy to dispense naloxone and improves the quality of their naloxone communication (secondary outcomes).

1. STUDY OBJECTIVES

We are conducting a RCT to evaluate whether Nalox-Comm training increases how often rural pharmacists dispense naloxone compared to completing a more basic online naloxone training that includes minimal communication content. We hypothesize that pharmacists who complete Nalox-Comm will dispense more naloxone in the three months post-intervention (primary outcome) and will report greater willingness to dispense naloxone, higher naloxone counseling self-efficacy, as well as demonstrate higher quality communication about naloxone (secondary outcomes).

2. INVESTIGATIONAL PLAN

2.1 Study Design

This is a cluster RCT with balanced randomization by store and two parallel groups (experimental and control), conducted with pharmacists from 62 pharmacies part of a single grocery store chain in rural counties of Georgia, North Carolina, South Carolina, and Tennessee. These 62 pharmacies comprise all of the pharmacies in the grocery store chain that are in rural areas, defined by a Rural-Urban Commuting Area (RUCA) code of 4–10 and/or a county that is at least 33% rural according to the 2010 U.S. Census Bureau data[19]. Figure 1 provides an overview of the study design, including completion of a baseline survey, simulated patient baseline observations, an online experimental or control naloxone training, a post-training survey, simulated patient post-training observations, and a three-month follow-up survey.

2.2 Randomization and Allocation to Treatment Groups

All 62 rural pharmacies were matched based on their county's opioid prescribing rate and level of rurality (33% or greater). The county opioid prescribing rate for each pharmacy was identified using the Centers for Disease Control and Prevention's opioid prescribing rates[20].

Pharmacies were first ordered by opioid prescribing rate (primary matching variable) and then level of rurality. Pharmacies with exact matches were paired first and then the rest of the pairs were matched using the closest value. Using computer-generated random numbers, one pharmacy in each matched pair was randomized to either the control or experimental group.

2.3 Number of Subjects, Study Duration, and Enrollment

60 pharmacists, 30 for the experimental group (Nalox-Comm) and 30 for the control group (Prescribe to Prevent) will participate. The overall time commitment for participants is less than 2 hours spread out over a 6 month period. We will keep the study active until all aims are completed (approximately 3 years). The Clinical Coordinator for the grocery store pharmacy chain will distribute an email to the 62 rural pharmacy stores to notify pharmacists that the chain is participating in an evaluation of naloxone training materials and introduce them to the study team. The study team will then email the pharmacies' store email addresses with more information about the study and a link to an online baseline survey. The first page of the baseline survey contains a consent form, which notifies pharmacists that, should they choose to participate, they will be asked to complete surveys before and

after completing the training and will be observed by simulated patients. Pharmacists who provide electronic informed consent and complete the baseline survey are considered to be enrolled in the study. Upon completion of the baseline survey, they automatically receive an email confirmation detailing next steps.

2.4 Study Population

The recruitment goal is 60 pharmacists. Each of the 62 pharmacies employs two full-time pharmacists, both of whom can participate. Thus, participants for the RCT (N = 60) will be recruited from a total sample of 124 pharmacists. Eligible pharmacists must meet the following criteria: 1) be age 18 years or older, 2) speak English, 3) work as a full-time pharmacist at one of the participating 62 rural grocery store chain pharmacies. In addition, individuals who are a floater, or non-staff, pharmacist are ineligible.

3. STUDY PROCEDURES

3.1 Simulated patient pre-training observation

After completing the baseline survey and before receiving an invitation to complete the online naloxone training, three SPs who are blinded to group assignment call each enrolled pharmacist to observe and rate the quality of their naloxone communication. These SPs act as "Secret Shoppers", whereby the pharmacist does not know the call is not a real patient. The SPs were trained using procedures that have been used in previous pharmacy SP studies[21-23]. SPs were trained to present one of three realistic naloxone cases (i.e., scenarios). SPs were provided with a script, which they reviewed and practiced with the study team until their presentation felt genuine.

During and immediately after the interaction with the pharmacist, each SP rates several aspects of the encounter using an observation guide. SPs then enter their observation guide responses for each pharmacist into a secure Qualtrics survey where they do not have access to other SPs' ratings for the same participant.

3.2 Naloxone online training

Once enrolled pharmacists have been observed by all three SPs, they receive an email invitation to complete either the Nalox-Comm module (experimental group) or the P2P training module (control group). The email includes a link to the respective training, instructions on how to navigate and complete the module, and the process for receiving continuing education (CE) credit. For those in the control group, the email also contains the link to the post-training survey, which is completed after training. The first question of this survey asks pharmacists if they completed the P2P training and will not allow them to continue the survey if they check "No." Those assigned to the Nalox-Comm module (experimental group) are directed to the post-training survey within the module in order to coordinate CE credit and track completion.

3.3 Simulated patient post-training observation

Up to four weeks after pharmacists have completed training, the three blinded SPs observe their naloxone communication by phone a second time. In order to prevent pharmacists from recognizing

SPs, the three scenarios were adapted to be similar in nature to the pre-intervention scenarios, but different enough so as to not cause suspicion on the part of the pharmacist. SPs use the same observation guide to rate the pharmacists' naloxone communication and enter their responses into a secure Qualtrics survey.

To ensure SP scenarios are enacted with fidelity, research assistants observe two of each SP's baseline observations and two of their post-intervention observations, using an SP assessment guide to rate the quality of the SP's performance. Items in the guide were adapted from previously validated SP assessments[24,25] and ask raters to indicate if all script content is covered and whether the SP sounds authentic and stays in his/her role. Additionally, research assistants describe any deviations and provide an overall rating from 1 to 9 of the SP's portrayal, where low numbers indicate "needs improvement" and high numbers indicate a "great" portrayal.

3.4 Three-month post-intervention follow-up

When three months has passed since training, pharmacists receive an email invitation to complete their final follow-up survey, which assesses the study's secondary outcomes.

3.5 Remuneration and participant follow-up

Participants can receive up to $150 in Amazon eGift cards for completing the study: $50 for completing each of the surveys (baseline, post-training, and three-month follow-up). To help reach the enrollment goal of 60 pharmacists, as well as ensure a 100% completion rate for those enrolled, up to five follow-up email reminders are sent to non-completers of each survey. If no response is received after the reminder emails, pharmacists receive one phone call. Additionally, recruitment flyers were mailed to each pharmacy.

4. STUDY EVALUATIONS AND MEASUREMENTS

4.1 Primary outcome

Our primary outcome is change in naloxone dispensing rates measured by comparing pharmacy records of naloxone dispensed in the three months prior to study participation to number of naloxone dispensed in the three months after study completion (Table 2). The grocery store pharmacy chain has agreed to provide us with these naloxone dispensing rates from each of the participating pharmacies at the conclusion of the study. We hypothesize that pharmacies in the experimental group will dispense more naloxone in the three months post-intervention compared to pharmacies in the control group.

4.2 Secondary outcomes

Willingness to dispense naloxone: Seven items measure willingness to dispense naloxone; four items came from the Nielsen et al. (2016) naloxone attitudes survey and two items from the Wilson et al. (2016) HOPE measure[26,27]. A seventh item was created to reflect initiating a conversation about naloxone. At baseline, immediately post-intervention, and three months post-intervention, pharmacists indicate how willing they are to engage in activities such as "proactively identify customers who are candidates for naloxone" and "dispense naloxone to patients and caregivers."

Response options range from 1 = “Not at all willing” to 4 = “Very willing.” Items are averaged to create a mean willingness score, with higher scores indicating more willingness to dispense naloxone.

Naloxone counseling self-efficacy: There are no validated instruments to measure pharmacists’ naloxone counseling self-efficacy. Thus, we referred to the qualitative literature on pharmacists’ barriers to dispensing naloxone[11,15-17,26,28,29] and identified factors that could impact counseling self-efficacy. On the baseline, immediate post-intervention, and three-month post-intervention surveys, pharmacists rate their confidence to engage in seven naloxone communication tasks, including engaging in naloxone counseling when the pharmacy is busy and discussing naloxone in a way that does not offend customers. Response options range from 1 = “Not at all confident” to 4 = “Very confident.” Items are averaged to create a mean self-efficacy score (range = 1 to 4), with higher scores indicating greater naloxone counseling self-efficacy.

Quality of naloxone counseling: SPs assess pharmacists’ quality of naloxone counseling at baseline and four weeks post-intervention. During a phone interaction with the pharmacist, SPs use a validated observation guide with six items to rate the pharmacist’s quality of communication on a 5-point scale (1 = lowest score and 5 = highest score). These items specifically assess satisfaction with communication (e.g., listened carefully, showed respect, and actively engaged with their case). This method for measuring impressions of communication has been used previously to assess the effect of training on pharmacists’ ability to communicate about antidepressants[21].

Three separate SPs rate each pharmacist both pre-intervention and post-intervention. The three ratings are averaged to create summary scores for quality of communication before and after training (range = 1 to 5), with higher scores indicating higher quality of communication.

In addition to the six items, the observation guide asks if the pharmacist encouraged or made a personal recommendation for naloxone, what term the pharmacist used to describe naloxone’s use (e.g., overdose, opioid emergency), and which analogy or comparison was used to describe naloxone (e.g., EpiPen, fire extinguisher).

4.3 Other measures

Naloxone knowledge: Six multiple-choice questions and two true/false questions based on the content of the naloxone training modules assess participants’ naloxone knowledge. Correct answers are totaled to create a summary score (range = 0 to 6), with higher scores indicating greater naloxone knowledge.

Attitudes toward dispensing naloxone: Eight items from the Wilson et al. (2016) HOPE measure assess participants’ attitudes toward naloxone[27]. Items relate to attitudes toward substance abuse (e.g., “I believe chemical dependency is a disease”) and naloxone (e.g., “Giving patients naloxone for overdose reversal will cause them to use more drugs”). Response options range from 1 = “Strongly disagree” to 4 = “Strongly agree”. Items are reverse scored as necessary and averaged to create a mean score (range = 1 to 4), with higher scores indicating more negative attitudes toward naloxone.

Barriers to dispensing naloxone: This construct is assessed using items from the HOPE measure[27]. Pharmacists report how much of a concern 10 attitudinal and environmental barriers are for dispensing naloxone, including not wanting to insult the patient and lack of time to counsel. Response options range from 1 = "Not at all concerned" to 5 = "Extremely concerned." Items are averaged to create a mean score (range = 1 to 5), with higher scores indicating more barriers to dispensing naloxone.

Previous naloxone training: At baseline, pharmacists indicate whether they have ever received naloxone training (yes/no) and on the three-month post-intervention survey whether they have received any naloxone training in addition to the training completed as part of the study (yes/no).

Pharmacist characteristics: At baseline, pharmacists report their age, gender, race, ethnicity, how long they have worked in pharmacy practice and at their current pharmacy, and whether they have previously dispensed naloxone (yes/no).

Pharmacy characteristics: At baseline, pharmacists report the number of pharmacists and technicians who are typically at the pharmacy at one time, as well as the estimated daily prescription volume at their pharmacy.

Social desirability bias: The validated short version of the Marlowe-Crowne Social Desirability Scale, Cronbach alpha = 0.65[30], assesses pharmacists' social desirability bias. From 10 statements such as "I'm always willing to admit when I make a mistake" and "I never resent being asked to return a favor", respondents select statements that are true for them (coded as 1). Unchecked, or "false" statements, are coded as 0. Items are summed so that scores range from 0 to 10, with higher values indicating greater social desirability bias.

5. STATISTICAL CONSIDERATIONS

Characteristics of pharmacies and pharmacists will be presented by treatment group. Unadjusted statistical comparisons using two sample t-tests and chi-square tests will be made between treatment groups (control vs. intervention group). Generalized estimating equations, (i.e., the GEE method), will be used to analyze the effects of the intervention on the primary and secondary outcome variables, while accounting for the fact that pharmacists are nested within pharmacies.

5.1 Primary outcome

The GEE method will be used to detect a significant difference in our primary outcome variable of frequency of naloxone dispensing. Specifically, we will evaluate change in naloxone dispensing from the 3 months pre-intervention to the 3 months post-intervention. Our multivariable model will be nested by pharmacy and will include several covariates, including the county's opioid prescribing rate, pharmacy rurality, average daily script fill rate, and demographic characteristics of the pharmacist. Alpha will be set at 0.05.

5.2 Secondary outcomes

We will also conduct similar GEE models as the one described above to assess if the intervention improves our secondary outcomes of willingness to dispense naloxone, naloxone counseling self-efficacy, and quality of naloxone counseling.

5.3 Sample size and power

Pharmacies in this grocery store chain dispense naloxone once for every 250 opioid prescriptions, on average. With 60 pharmacists, 30 per treatment arm, we have at least 80% power at the 0.05 significance level to detect an increase in naloxone dispensing to 1 for every 100 opioid prescriptions dispensed, assuming a standard deviation of 0.008 (2 in 250 or 0.8 in 100) and depending on the intraclass (within pharmacy) correlation. In other words, we expect the intervention to increase the naloxone dispensing rate from 1 in 250 (0.4%) to 1 in 100 (1%), an increase of 0.6%. So, the sample size is based on a mean difference of 0.6%.

6. STUDY INTERVENTION

6.1 Control group: Prescribe to Prevent online module

Participants randomized to the control group complete the 55-min online Prescribe to Prevent (P2P) module. P2P consists of videos, didactic content, and quizzes, covering the key naloxone topics listed in Table 1. Two videos included in P2P demonstrate a pharmacist communicating about a potentially fatal opioid drug interaction with: 1) a patient and 2) a provider. Of note, none of the P2P videos demonstrate effective naloxone communication with patients. Pharmacists in the control group can receive 0.125 continuing education units (CEUs) for completing the course.

6.2 Experimental group: Nalox-Comm online module

Pharmacists in the experimental group complete the approximately 30-minute Nalox-Comm online module. The module was developed during Aim 1 of the NIDA-funded study (study #19-0998). Formative data to guide Nalox-Comm content were collected from interviews with 40 pharmacists, 40 patients at-risk of opioid overdose, and 40 caregivers of individuals at-risk of overdose from pharmacies located in rural counties with high rates of opioid-related overdose deaths in Alabama, Iowa, North Carolina, and Wisconsin. Logistical and attitudinal barriers to pharmacists engaging in naloxone counseling with their patients were identified, including: privacy (patients often do not want others to know they take prescription opioids), cost (patients may not be interested in something they cannot afford), safety (patients may be wary about new medications), and stigma (naloxone has some negative associations from news headlines or television shows). Thus, Nalox-Comm includes three separate, approximately 10-min lessons on how to initiate and conduct a conversation about naloxone that addresses these specific communication barriers. Throughout Aim 1 (study #19-0998), a stakeholder development panel of rural community pharmacists advised on module content to ensure relevancy for rural populations.

Nalox-Comm includes multiple video examples of pharmacists conversing with patients about naloxone, in which they demonstrate a stepwise communication approach (C.A.R.E.). C.A.R.E. stands for: show that you Care or have Concern; Ask the patient for permission to counsel them about naloxone; Relate naloxone to patients by explaining their specific risk factors; and Encourage and

Educate patients by making a personal and/or professional recommendation that they get naloxone. Pharmacists in the experimental group can receive 0.10 CEUs for completing the course.

7. SAFETY MANAGEMENT

The primary risk is breach of confidentiality. The study consent form will inform pharmacists that their responses to the surveys and secret shopper observations will not be shared with their employer, results will be reported in aggregate, and will not affect their employment. The online consent will include a check box that states, 'I agree to participate in this research study.' All data will be stored in a secure fashion with password-protected files and secure servers.

We do not anticipate any adverse events (AEs) since the surveys and intervention assess naloxone knowledge, attitudes, and communication/training preferences and scenarios will be realistic and not outside the range of what pharmacists would be asked to navigate as part of their normal professional duties. However, the secret shopper interactions may still cause the pharmacist to feel uncomfortable, and thus potential mild AEs include pharmacist discomfort and possible emotional outburst when engaging in the secret shopper encounter. Secret shoppers will be trained to handle possible negative reactions from the pharmacist, although the likelihood of a negative reaction is low. Due to the nature of our study, we do not anticipate encountering situations in which confidentiality could be breached because of mandatory reporting. However, if the pharmacist reacts negatively to the scenario and it is clear that they need medical assistance or counseling, confidentiality may be breached to ensure the safety of the pharmacist. The consent form will state that confidentiality will be breached in the case that a pharmacist needs medical assistance or counseling.

The study research team members are trained in confidentiality procedures. Identification numbers will be assigned to pharmacists and any information that could identify individuals participating in this project will not be included in any data sets. The data will only be given to the PI and research staff. Data will not be shared with the pharmacists' employers.

8. DATA AND SAFETY MONITORING

The study PI will evaluate data collected by secret shoppers and through surveys. The PI will also meet weekly with her project director and monthly with the research team to discuss data collection, potential data quality issues if they arise, and study progress. These meetings will serve as a forum to discuss issues related to data collection and implementation of the data collection protocol. Meetings will be held more frequently if needed.

Additionally, an independent and unbiased review of the study's ongoing progress will be provided by the DSMB. The DSMB is well-qualified to comment on the appropriateness of the RCT protocol and make recommendations related to any AEs or adjustments to study procedures. The investigator(s) will appoint a DSMB chairperson. S/He is responsible for overseeing the meetings and developing the agenda in consultation with the investigator(s). The DSMB will meet at least once per year and will schedule additional meetings, if deemed necessary. A quorum of more than half the DSMB members is required in order to convene a meeting of the DSMB.

9. CONSENT PROCESS

Informed consent documents for this study include a specific statement that information from the trial will be posted on ClinicalTrials.gov. Consent will be obtained on the online baseline survey. The first page of the baseline survey will contain a study consent form that includes the requirements, risks, and benefits of participation. The consent form will also include a checkbox stating that "I agree to participate in this research study" that pharmacists check to consent to participate in the study. Pharmacists will have the ability to opt out of the study. The consent form will notify pharmacists that secret shoppers will observe their communication over the 3-month study period. The consent form will also state that the secret shopper will not disclose their identity, but the pharmacist will be notified after the study has been completed of when the phone calls occurred. The consent form will also state that data collected during the secret shopper visit will not be shared with their employers. Pharmacists who do not wish to participate in the research study will not be penalized by their employer.

10. REFERENCES

1. Centers for Disease Control and Prevention. CDC WONDER. Retrieved from https://wonder.cdc.gov/. Accessed Nov 14, 2018.
2. Mack KA, Jones CM, Ballesteros MF. Illicit drug use, illicit drug use disorders, and drug overdose deaths in metropolitan and nonmetropolitan areas—United States. American journal of transplantation. 2017;17(12):3241-3252.
3. Thomas KC, Ellis AR, Konrad TR, Holzer CE, Morrissey JP. County-level estimates of mental health professional shortage in the United States. Psychiatric Services. 2009;60(10):1323-1328.
4. Knapp KK, Paavola FG, Maine LL, Sorofman B, Politzer RM. Availability of primary care providers and pharmacists in the United States. Journal of the American Pharmaceutical Association (1996). 1999;39(2):127-135.
5. Casey MM, Klingner J, Moscovice I. Pharmacy services in rural areas: is the problem geographic access or financial access? The Journal of Rural Health. 2002;18(3):467-477.
6. Lin SJ. Access to community pharmacies by the elderly in Illinois: a geographic information systems analysis. Journal of Medical Systems. 2004;28(3):301-309.
7. Roberts AW, Carpenter DM, Smith A, Look KA. Reviewing state-mandated training requirements for naloxone-dispensing pharmacists. Research in Social and Administrative Pharmacy. 2018.
8. Morton KJ, Harrand B, Floyd CC, et al. Pharmacy-based statewide naloxone distribution: A novel "topdown, bottom-up" approach. Journal of the American Pharmacists Association. 2017;57(2):S99-S106.e105.
9. Jones CM, Lurie PG, Compton WM. Increase in naloxone prescriptions dispensed in US retail pharmacies since 2013. American journal of public health. 2016;106(4):689-690.
10. U.S. Department of Health and Human Services. Surgeon General's Advisory on Naloxone and Opioid Overdose. 2018. Retrieved from https://www.surgeongeneral.gov/priorities/opioid-overdoseprevention/naloxone-advisory.html. Accessed June 11, 2018.
11. Thornton JD, Lyvers E, Scott VGG, Dwibedi N. Pharmacists' readiness to provide naloxone in community pharmacies in West Virginia. Journal of the American Pharmacists Association. 2017;57(2):S12-S18.e14.
12. Bailey AM, Wermeling DP. Naloxone for opioid overdose prevention: pharmacists' role in community- based practice settings. Annals of Pharmacotherapy. 2014;48(5):601-606.
13. Carpenter DM, Dhamanaskar AK, Gallegos KL, Shepherd G, Mosley SL, Roberts CA. Factors associated with how often community pharmacists offer and dispense naloxone. Research in Social and Administrative Pharmacy. 2018.

14. Cochran G, Field C, Lawson K, Erickson C. Pharmacists' knowledge, attitudes and beliefs regarding screening and brief intervention for prescription opioid abuse: a survey of Utah and Texas pharmacists. Journal of Pharmaceutical Health Services Research. 2013;4(2):71-79.
15. Hagemeier NE, Murawski MM, Lopez NC, Alamian A, Pack RP. Theoretical exploration of Tennessee community pharmacists' perceptions regarding opioid pain reliever abuse communication. Research in Social and Administrative Pharmacy. 2014;10(3):562-575.
16. Gamm L, Stone S, Pittman S. Mental health and mental disorders—A rural challenge: A literature review. Rural healthy people. 2010;1:97-114.
17. Browne T, Priester MA, Clone S, Iachini A, DeHart D, Hock R. Barriers and Facilitators to Substance Use Treatment in the Rural South: A Qualitative Study. The Journal of Rural Health. 2016;32(1):92-101.
18. Carpenter DM, Roberts CA, Westrick SC, et al. A content review of online naloxone Continuing Education courses for pharmacists in states with standing orders. Research in Social and Administrative Pharmacy. 2018;14(10):968-978.
19. United States Census Bureau, Percent Urban and Rural in 2010 by State and County. https://www.census.gov/programs-surveys/geography/guidance/geo-areas/urban-rural/2010-urban-rural.html.
20. Centers for Disease Control and Prevention, Prescription Opioid Data. https://www.cdc.gov/drugoverdose/data/prescribing.html.
21. Liekens S, Vandael E, Roter D, et al. Impact of training on pharmacists' counseling of patients starting antidepressant therapy, Patient Educ. Couns 94 (1) (2014) 110–115.
22. Alte D, Weitschies W, Ritter CA, Evaluation of consultation in community pharmacies with mystery shoppers, Ann. Pharmacother 41 (6) (2007) 1023–1030.
23. Weiss MC, Booth A, Jones B, Ramjeet S, Wong E. Use of simulated patients to assess the clinical and communication skills of community pharmacists, Pharm. World Sci 32 (3) (2010) 353–361.
24. Wind LA, Van Dalen J, Muijtjens AM, Rethans JJ. Assessing simulated patients in an educational setting: the MaSP (Maastricht assessment of simulated patients), Med. Educ 38 (1) (2004) 39–44.
25. Cross WF, West JC, Crean HF, Rosenberg E, LaVigne T, Caine ED. Measurement of primary care providers' suicide prevention skills following didactic education, Suicide Life Threat Behav (2022), 10.1111/sltb.12827.
26. Nielsen S, Menon N, Larney S, Farrell M, Degenhardt L. Community pharmacist knowledge, attitudes and confidence regarding naloxone for overdose reversal, Addiction 111 (12) (2016) 2177–2186.
27. Wilson JD, Spicyn N, Matson P, Alvanzo A, Feldman L. Internal medicine resident knowledge, attitudes, and barriers to naloxone prescription in hospital and clinic settings, Subst. Abus 37 (3) (2016) 480–487.
28. Freeman PR, Goodin A, Troske S, Strahl A, Fallin A, Green TC. Pharmacists' role in opioid overdose: Kentucky pharmacists' willingness to participate in naloxone dispensing, Journal of the American Pharmacists Association 57 (2) (2017) S28–S33.
29. Mueller SR, Koester S, Glanz JM, Gardner EM, Binswanger IA. Attitudes toward naloxone prescribing in clinical settings: a qualitative study of patients prescribed high dose opioids for chronic non-cancer pain. J. Gen. Intern. Med 32 (3) (2017) 277–283.
30. Strahan R, Gerbasi K, Short. Homogenous version of the Marlowe-Crowne social desirability scale. J. Clin. Psychol 28 (191) (1972) 193.

APPENDIX

Figure 1: Study Design

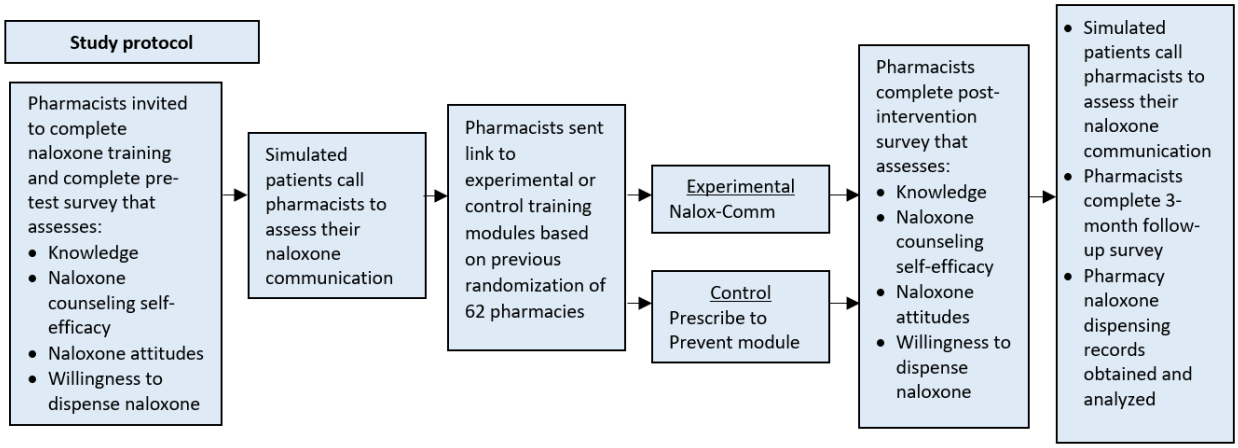


Table 1: Summary of the P2P and Nalox-Comm Modules

	Prescribe to Prevent	**Nalox-Comm**
Length	55 minutes	~30 minutes
Format	Online module with videos, didactic content, quizzes	Online module with videos, didactic content, reflection
Topics covered	• Risk factors for overdose • How to respond to overdose • How naloxone works • Types of naloxone • How to administer naloxone • Medico-legal issues • How to stock, fill, and bill for naloxone	• The importance of naloxone and the role of the pharmacist • Non-stigmatizing language • How to initiate an offer of naloxone • How to respond to patient & caregiver naloxone requests • How to address specific communication barriers

Table 2: Study measures

Variable	Source	# of items	Baseline	Immediate post-intervention	Within 4 weeks post-intervention	3-month follow-up
Primary Outcome						
Naloxone dispensing rate	Pharmacy records	-	X			X
Secondary Outcomes						
Willingness to dispense naloxone	Self-report survey	7	X	X		X
Naloxone counseling self-efficacy	Self-report survey	7	X	X		X
Quality of naloxone counseling	Direct observation	6	X		X	
Other Measures						
Naloxone knowledge	Self-report survey	8	X	X		X
Attitudes toward dispensing naloxone	Self-report survey	8	X	X		X
Barriers to dispensing naloxone	Self-report survey	10	X	X		X
Previous naloxone training	Self-report survey	1	X			X
Pharmacist characteristics	Self-report survey	7	X			
Pharmacy characteristics	Self-report survey	3	X			
Social desirability bias	Self-report survey	10	X			