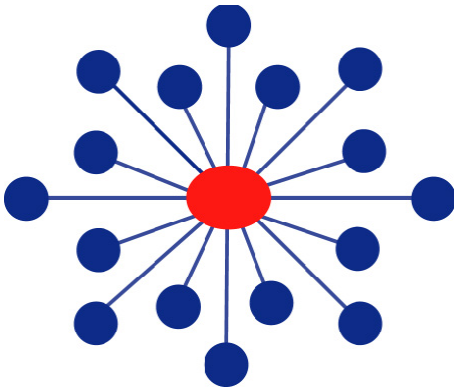

CTN-0105 Protocol

Integrating community pharmacy-based prevention and treatment of opioid and other substance use disorders: A nationwide survey of community pharmacists (Pharm-Serve-SUD)

Funded by: National Institute on Drug Abuse (NIDA)

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Lead Investigator (LI): **Li-Tzy Wu, ScD, RN, MA**
Mid-Southern Node
Duke University

Lead Investigator (LI):

Li-Tzy Wu, ScD, RN, MA
Department of Psychiatry and Behavioral Sciences Duke University School of Medicine
Mid-Southern Node

CCTN Protocol Coordinator:

Yanping Liu, MD, PhD
National Institute on Drug Abuse

Emmes (DSC):

Paul Van Veldhuisen, PhD
DSC Principal Investigator
The Emmes Company

Emmes (CCC):

Robert Lindblad, MD
CCC Principal Investigator
The Emmes Company

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1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
ASHP	American Society of Health-System Pharmacists
APhA	American Pharmacists Association
CCC	Clinical Coordinating Center
CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare & Medicaid Services
CPNP	College of Psychiatric and Neurologic Pharmacists
CRF	Case Report Form
CTN	National Drug Abuse Treatment Clinical Trials Network
DDPPQ	Drug and Drug Problems Perception Questionnaire
DSC	Data and Statistics Center
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HCS	Health Care Systems
ICC	Intraclass Correlation
IRB	Institutional Review Board
IRT	Item Response Theory
KAP	Knowledge, Attitude, and Practice
LI	Lead Investigator
LN	Lead Node
MAT	Medication-Assisted Treatment
MC	Medical Clinician
MOP	Manual of Operating Procedures
MOUD	Medication treatment for Opioid Use Disorder
NIDA	National Institute on Drug Abuse
OOKS	Opioid Overdose Knowledge Scale
OUD	Opioid Use Disorder
PDMP	Prescription Drug Monitoring Program
QA	Quality Assurance
SAMHSA	Substance Abuse and Mental Health Services Administration
SBIRT	Screening, Brief Intervention, and Referral to Treatment
SD	Standard Deviation
SRT	Screening and Referral to Treatment
SUD	Substance Use Disorder
USPSTF	US Preventive Services Task Force

2.0 STUDY SYNOPSIS AND SCHEMA

Study Objectives

The overall goal of this study is to investigate community pharmacists' knowledge of, attitudes about, and intention to provide patient care and services for Screening for substance use/misuse and Referral to Treatment (SRT) for substance use disorders (SUDs) and Medication treatment for Opioid Use Disorders (MOUD). The findings from this study will help identify specific barriers and facilitators related to pharmacist-provided services and patient care for SRT and MOUD.

Study aims are to:

Aim 1: Conduct a survey of licensed community pharmacists to study their knowledge of, attitudes about, and intention to provide patient care and services for SRT and MOUD; and

Aim 2: Conduct a qualitative interview of a sample of **up to 50** survey participants (range: 20 to 50 participants) from Aim 1 to further assess survey participants' interest in implementing preventive care services for SUDs and medication therapy management for patients with opioid use disorder (OUD) in their practice.

Together, the results will inform pharmacy-based study designs and future directions for the NIDA National Drug Abuse Treatment Clinical Trials Network (CTN) studies as well as training and educational needs for community pharmacists.

Study Design

This cross-sectional study will use a mixed methods approach that combines the strengths of a quantitative survey of a large sample of survey participants and a qualitative interview of up to 50 survey participants from Aim 1 to further identify in-depth information not available from the survey to achieve study aims.

Study Population and Sample Size

(a) **Pilot test**

Before implementing the survey, we will pilot test the on-line survey in 10 licensed pharmacists identified from the Community Pharmacy Enhanced Services Network (CPESN) for understanding any feasibility issues. Following completion of the on-line pilot survey, the 10 participants will participate in a virtual meeting with the investigative team to discuss their feedback and suggestions for improving the survey content and processes. The main purpose is to identify potential issues with the clarity of survey items and to identify any logistical problems, such as technical issues of navigating the on-line survey system (i.e., an electronic data capture system) to complete the questionnaire. All issues identified during the pilot survey will be corrected in collaboration with the CTN Data and Statistics Center (DSC).

(b) ***Survey***

The survey will be conducted in a sample of approximately 1062 licensed community pharmacists to collect data about community pharmacists' knowledge of, attitudes about, and intention to provide patient care and services for SRT for SUDs and MOUD. Survey participants will be licensed community pharmacists who will be identified from the CPESN. Participants may also be recruited from other related community pharmacist networks as needed to reach the recruitment goal. Data may be collected through an online survey, phone interview, and postal survey to increase the response rate (Dillman et al., 2014; Hoddinott & Bass, 1986; Kroth et al., 2009).

(c) ***Qualitative interview***

A sample of up to 50 survey participants will participate in an interview to further assess survey participants' interest in implementing preventive care services for SUDs and medication therapy management care for patients with OUD in their practice.

Study Duration

The data collection time is estimated to be about 9-14 months.

- Pilot survey for feasibility issues: approximately 2-4 months, including the time for CTN DSC to modify the electronic data capture system to address logistical or technical issues.
- Survey: approximately 5-7 months.
- Qualitative interview: approximately 2-3 months, including the time for CTN DSC to produce a list of potential participants with demographic information (sex, race, ethnicity) from Aim 1 for recruitment.

Study Assessments

Primary measures of key interests include the following domains:

- Knowledge and attitudes.
- Subjective norms/beliefs.
- Perceived social stigma.
- Perceived behavioral control.
- Practices and intention to practice patient care for MOUD.

Statistical Analyses

The analysis will examine the distribution of all study variables, including proportion estimates for variables with categorical responses and mean scores for variables of each scale and subscales. The Theory of Planned Behavior will be used to guide the analysis of the associations among pharmacists' knowledge, attitudes, beliefs/perception, and intention to practice SRT for SUDs and MOUD (Ajzen, 2011; Kelly et al. 2012; Fleming et al. 2018; Talbot et al. 2015). The analysis will be conducted separately for variables associated with practicing SRT and variables associated with practicing MOUD care. The analysis will also examine demographic and practice differences in knowledge and attitudes, subjective norms/beliefs, perceived social stigma, perceived behavioral control, barriers and facilitators, and intention to practice or practice. Sex, gender identity, age group, racial/ethnic differences in primary variables will be analyzed and reported.

To capture the potential correlation between survey responses of participants practicing in the same state, linear mixed models will be used to analyze the continuous outcomes via PROC MIXED in SAS, and binary or categorical outcomes will be analyzed using generalized linear mixed models via PROC GLIMMIX in SAS. Mixed effects models may be used to analyze the associations between the listed outcome measures and the pharmacists' characteristics where fixed effects will be included capturing the characteristics, and a random effect is included to adjust for the correlation of pharmacists from the same state. During analysis, a formal test of whether the variance of the random effect is different from zero will inform whether the random effect may be dropped from modeling. These analyses will be used to determine the strength of associations for the main hypotheses.

3.0 The STUDY AIMS

This work will be conducted in two aims.

Aim 1 is to conduct a survey of licensed community pharmacists to explore their knowledge of, attitudes about, and intention to provide patient care and services for SRT and MOUD.

Aim 2 is to conduct a qualitative interview of a sample size of up to 50 survey participants (range: 20 to 50 participants) from Aim 1 to further assess survey participants' interest in implementing preventive care services for SUDs and medication therapy management care for patients with OUD in their practice. The questionnaire of Aim 1 will include a question at the end of the survey questionnaire to ask the participant whether he/she is willing to be contacted to participate in an interview study of implementing patient care services for MOUD at the pharmacy setting. Among those who endorse "yes" to the interview study, up to 50 survey participants (range: 20-50) will be recruited to participate in the interview study (i.e., until saturation of themes for different demographic groups defined by sex, race, and ethnicity is considered adequate).

4.0 INTRODUCTION

4.1 Background

The opioid and other drug overdose death epidemic in the United States has escalated for approximately two decades, and affects men, women, and all racial ethnic populations (Hedegaard et al., 2019; Scholl et al. 2019). Identifying ways to increase the use of Screening and Referral to Treatment (SRT) and MOUD is a key priority to improve preventive care and treatment services for SUDs (Volkow et al. 2014). Given the magnitude of the opioid and other drug overdose death epidemic (Hedegaard et al., 2019; Scholl et al. 2019), multiple approaches to expand access to treatment must be researched and identified to increase use of MOUD and other SUD treatment services for people from diverse geographical locations. Regrettably, federal and local efforts aimed at improving access to MOUD are thwarted by the shortage of MOUD providers. Almost 20 million US residents live in a county without a DEA-waivered buprenorphine provider (Andrilla et al. 2019). Thus, sustainable models for expanding MOUD and other SUD services must also address the uptake of SRT and the MOUD workforce issues through increasing the number of healthcare professionals involved in the provision of SRT and patient care for SUDs.

Community pharmacists, as dispensers of and gatekeepers to opioid and other psychoactive medications, including those used for OUD treatment, are natural partners of other healthcare providers. Community pharmacists are widely available even in rural areas. As many as 89% of Americans live within 5 miles of a community pharmacy, and 91% of surveyed participants reported “confidence in pharmacist-provided advice” (Haberkorn, 2018; NACDS, 2013). Community pharmacists have actively participated in the rescue efforts for opioid deaths via dispensing naloxone and/or community naloxone distribution initiatives (CDC, 2019). Sufficient numbers of community pharmacists are available to meet the future healthcare demand. For example, there are over 309,000 trained pharmacists in the US (NASPA, 2018). The supply of pharmacists is expected to increase 35% by 2025, and the demand for pharmacists will grow by 16% (HRSA, 2013).

The ubiquity of community pharmacies indicates that community pharmacies should be researched to identify effective ways to enable community pharmacists as access points for components of OUD treatment, particularly in suburban or rural areas lacking OUD treatment facilities (Look et al., 2019). Recent data showed that community pharmacies were more prevalent and more likely to be located in rural counties with higher rates of opioid-related overdose deaths than addiction treatment facilities (Look et al., 2019). This finding also provides a compelling rationale for further studying community pharmacists’ knowledge of, attitudes about, and intention to provide patient care and services for SRT for SUDs and MOUD.

A buprenorphine treatment multiplier approach, which involves collaboration between MOUD physicians and community pharmacists to provide MOUD maintenance care, offers the possibility to expand MOUD treatment access in large areas of the country where waivered physicians, physician assistants, and nurse practitioners are scarce. A prior study showed that physicians and pharmacists can successfully collaborate to provide effective medication management for OUD, and results indicated that patient care for OUD was improved by enhanced communication and continuity of care, reduced physician burden, enhanced monitoring of diversion, and reduced costs (DiPaula & Menachery, 2015). In countries that introduced buprenorphine treatment earlier than the US, like France, community pharmacists not only routinely supervise buprenorphine dosing and urine monitoring of drug use, but also facilitate the prevention of diversion and misuse efforts (Fatseas & Auriacombe, 2007).

4.2 Significance to the Field

Screening for substance use/misuse, treatment initiation, and referral to treatment provides a framework that can be integrated into regular check-ups or clinical encounters in any healthcare setting to initially screen for substance misuse, use screening results to “engage” a patient showing unhealthy substance use or misuse in a short conversation and provide feedback, refer to treatment as needed, and monitor changes in the

problem. SAMHSA recommends universal screening all patients for SUDs in primary care (SAMHSA, 1997; USPSTF, 2019). Since 2015, the USPSTF has recommended that clinicians ask all adults about tobacco use, advise them to stop using tobacco, and provide behavioral interventions and

U.S. Food and Drug Administration (FDA)–approved pharmacotherapy for cessation to adults who use tobacco (USPSTF, 2015). The USPSTF also has recommended screening for unhealthy alcohol use in primary care settings in adults age ≥18 years, including pregnant women, and providing persons engaged in risky or hazardous drinking with brief behavioral counseling interventions to reduce unhealthy alcohol use (USPSTF, 2018).

Recently, the USPSTF has released the report that recommends screening adults age ≥18 years for illicit and nonmedical drug use (USPSTF, 2020). Using an SRT approach to identify severe or untreated individuals with SUD to provide the referral and SUD treatment information, make the referral to behavioral health services or providers, and/or help engage them in treatment is an important step to help prevent SUD problems and increase access to SUD treatment services, including MOUD. Community pharmacists, as medication experts, are well-trained to expand access to SRT and MOUD efforts by screening patients for drug misuse, checking the prescription drug monitoring program (PDMP), communicating with patients about safety of medication use, identifying red flags of opioid misuse, communicating with providers, conducting patient education as needed, monitoring medication use and outcomes, and providing diversion prevention and referral services (APhA, 2014; Compton et al. 2019; DiPaula & Menachery, 2015). In Virginia, Centers for Medicare & Medicaid Service (CMS) reimburses pharmacist-provided screening for substance misuse. Successful collaboration between physicians and pharmacists can help to reduce physician burden and optimize patient care.

As early as 2003, the American Society of Health-System Pharmacists (ASHP) published a position statement on the pharmacist's role in substance misuse prevention, education, and assistance, which indicates that pharmacists have the unique knowledge, skills, and responsibilities for assuming an important role in substance misuse prevention, education, and assistance (Baldwin & Dole, 2003). Specifically, ASHP endorses that pharmacists, as health care providers, should be actively involved in reducing the negative effects that substance misuse has on society, health systems, and the pharmacy profession (Baldwin & Dole, 2003).

In addition, the American Pharmacists Association (APhA) released a position statement to advocate pharmacists' role in addressing opioid misuse, addiction, and diversion (APhA, 2014). APhA highlights the data showing that opioid misuse, addiction, and diversion has grown dramatically since the early 1990s and affects public health considerably (e.g., more individuals died from drug overdoses than from motor vehicle accidents). APhA's statement discusses strategies and tools that pharmacists can use to reduce the likelihood of opioid misuse, addiction, and diversion through the following practices: (1) the assessment of prescriptions that are presented for opioid medications, (2) the management of patients receiving opioids, and (3) follow-up options when misuse, addiction, or diversion has been identified (APhA, 2014).

The College of Psychiatric and Neurologic Pharmacists (CPNP) also recognizes the critical role of community pharmacists in providing safe and appropriate access to opioids, while protecting the public from the hazards of misuse and addiction (CPNP, 2017). CPNP released a clinical guideline "Opioid use disorders: Interventions for community pharmacists" to educate them on interventions and strategies they can employ to provide safe and appropriate access to opioids and engage in providing care to patients with SUD, mainly OUD. This OUD interventions guideline for community pharmacists provides information on the following areas: Talking to your patients about substance use disorder; Three-Step process for screening opioid prescriptions for safe use; Improving the health of patients with SUDs (e.g., promote naloxone access, encourage medication-assisted treatment [MAT: buprenorphine, methadone, naltrexone], MAT counseling points, provide access to clean needles); developing a local resource list; and helpful resources. Community pharmacists can do the following to improve patient care and reduce drug misuse: collaborate with the prescriber to ensure opioid prescriptions are for a legitimate medical purpose in the usual course of professional treatment; perform

pill counts; review the PDMP; enforce a policy of no early refills for controlled substances; hold the patient accountable to the treatment agreement; assist with monitoring severity of pain and functional status of the patient; and monitor for indicators of misuse, addiction, or diversion (CPNP, 2017).

Despite the strong support from these professional pharmacists' associations, little is known about community pharmacists' knowledge of, attitudes about, and intention to provide patient care and services for SRT for SUDs and MOUD in the United States (Bratberg, 2019; Cooper et al., 2020; Shonesy et al., 2019). Thus, a mixed methods approach combining a quantitative survey and a qualitative interview following the survey will be used to understand such barriers and facilitators of pharmacist-provided SRT and MOUD services. This study will provide timely new data to better identify facilitators and barriers to engaging community pharmacist-provided services for SRT and MOUD. The results will identify research gaps for further research and inform clinical and research strategies for providing community pharmacist- provided services for SRT, drug overdose prevention, and care for MOUD.

4.3 Study rationale and feasibility within the CTN

Recognizing the pharmacist's essential role in the care of people with substance misuse problems or SUD, the Multidisciplinary Education and Research in Substance Use and Addiction (AMERSA) has developed core competencies for pharmacists to address substance use in the 21st century (Bratberg, 2019). The core skills required for pharmacists includes (a) screening patients for substance misuse and conducting brief interventions as needed, (b) optimizing pain control with providers via the CDC Guidelines for Prescribing Opioids for Chronic Pain, (c) reducing harm through syringe provision and naloxone, (d) managing medications used for patients with SUD (e.g., MOUD), ideally in collaboration with other SUD providers/prescribers, and (e) referring patients to treatment resources (Bratberg, 2019). As medication safety specialists, pharmacists have specialized knowledge about both prescription and illicit psychoactive substances and are trained on how best to communicate their potential and expected harms and benefits to patients and other family stakeholders (Bratberg, 2019). Community pharmacists in the United States are currently underutilized healthcare professionals for engaging in the SRT efforts. This study will produce timely data to inform the development of strategies to reduce barriers and enhance facilitators for engaging pharmacists in the SRT efforts noted by the AMERSA's mission.

This study can also help identify means to address a critical barrier to expanding access to SUD treatments (e.g., MOUD) and reducing drug-related overdoses due to the shortage of MOUD providers (Andrilla et al. 2019; Compton et al., 2019). It directly supports NIDA's interests in engaging community pharmacists for addiction research and addiction care. Within the CTN, NIDA has supported a novel, multisite pilot trial to study the feasibility of "Buprenorphine Physician and Community Pharmacist Collaboration in the Management of Patients with Opioid Use Disorder (CTN-0075)" (Wu et al., 2021). This CTN multisite trial (3 paired office-based buprenorphine treatment clinic and community pharmacy sites) is the first multisite trial designed specifically to understand the feasibility and acceptability of transitioning office-based buprenorphine care from office-based buprenorphine treatment providers to licensed community pharmacists in the United States. Results of CTN-0075 demonstrate the success of engaging 6 buprenorphine-waivered physicians and 6 community pharmacists in the CTN trial. Of note, all study sites of CTN-0075 performed well in study participant recruitment, enrollment, treatment retention and treatment adherence, and satisfaction measures.

Key results of CTN-0075 are summarized below:

- CTN-0075 results showed a high success rate in pre-screening, screening, and recruitment for the study. Of the 96 adult patients approached for pre-screening, only 4 patients (4.2%) declined the pre- screening. Among the 92 patients pre-screened, 85 patients were eligible pre-screens, and 76 patients (82.6%) met the inclusion criteria and enrolled in the screening phase. The overall proportion of eligible pre-screens who were screened was 89.4% (range: 77.4% to 100% across sites). The overall proportion of screens who screen failed was 6.6%. The overall proportion of screened participants who

were enrolled in the maintenance phase where their care was managed by pharmacists was 93.4% (71/76; range: 84.6% to 100% across sites).

- The results revealed success in the recruitment rate. The overall actual enrollment rate (actual/proposed) was 108.6% (range: 104.3% to 113.0% across the three clinics).
- A high proportion of participants completed the study at Month 6 (88.7%, n = 63). All three paired sites had similarly high rates of treatment retention at the end of the study (range: 87.0% to 90.9%).
- All three paired clinic-pharmacy sites had very high rates of treatment attendance/adherence (range: 94.9% to 95.5% across sites). During the 6-month maintenance phase, 6 treatment visits were expected per participant. The overall treatment attendance during the 6-month maintenance phase was 95.3%, where 406 out of 426 expected visits were attended by participants.
- The results revealed a very high rate of treatment fidelity. Of the monitored Buprenorphine Visit Checklists during the study, the physician/pharmacist adherence to completing all required checklist items (i.e., visit assessment items) was 100% (i.e., proportion of visits showing 80% adherence or higher). The mean adherence was 99.9% (range: 94.1-100%).
- The results indicated a very high level of satisfaction by study participants (i.e., patients with OUD). Of note, 98.5% of study participants were either satisfied (4.8%) or very satisfied (93.7%) with their experience in this study at Month 6, and 94.4% of study participants were either satisfied (7.9%) or very satisfied (90.5%) with the quality of treatment offered in this study at Month 6. The vast majority of participants also reported that treatment transfer from physician's office to the pharmacy was not difficult (96.8%), and that holding the buprenorphine visits at the same place the medication is dispensed was either extremely useful/convenient (82.5%) or very useful/convenient (12.7%).
- Almost all participants (98.4%) endorsed that they would choose to participate in the study again if they were given the opportunity. Reasons for influencing participants' decision to participate in the future study were:
    - My participation may help to improve and expand treatment delivery/options (100%).
    - Pharmacy is the right location for this type of treatment (96.8%).
    - The treatment offered was of better quality than the usual treatment (85.7%).
    - It was easy to understand/distinguish patient, physician, and pharmacist roles (96.8%).

- The results also showed a very high level of satisfaction indicators by participating physicians and pharmacists. At the end of the study, 100% of participating physicians and pharmacists reported being very satisfied with their experience in this study. All participating physicians and pharmacists were either satisfied (8.3%) or very satisfied (91.7%) with the quality of treatment offered in this study. The vast majority of participating physicians and pharmacists reported that treatment transfer from physician's office to the pharmacy was not difficult (83.3%). All participating physicians and pharmacists (100%) reported that holding the buprenorphine visits at the same place the medication is dispensed was either very (25%) or extremely useful/convenient (75%).
- All participating physicians and pharmacists (100%) endorsed that they would choose to participate in the study again if they were given the opportunity. Reasons for influencing their decision to participate in the future study were:
    - My participation may help to improve and expand treatment delivery/options (100%).
    - Pharmacy is the right location for this type of treatment (91.7%).
    - The treatment offered was of better quality than the usual treatment (58.3%).
    - It was easy to understand/distinguish patient, physician, and pharmacist roles (91.7%).

- These positive findings from CTN-0075 confirm the importance of studying the feasibility of community pharmacist-provided care for SUDs (Wu et al., 2021). Results from this study will provide critical background data to the CTN as new studies are considered.

5.0 OBJECTIVES

The overall objective is to use a mixed-methods design to study pharmacists' knowledge of, attitudes about, and intention to provide patient care and services for SRT for SUDs and MOUD.

Aim 1 Objective

Aim 1: To conduct the survey of licensed pharmacists to collect data about community pharmacists' knowledge of, attitudes about, and intention to provide patient care and services for SRT for SUDs and MOUD.

Participants: Survey participants will be licensed community pharmacists who will be identified from the CPESN. Participants may also be recruited from other related community pharmacist networks as needed to reach the recruitment goal. Data will be collected through an online or web-based survey, and phone interviews may also be used to increase the response rate. Email and text messaging reminders, phone call reminders, and mailed surveys will also be used to maximize the response rate contingent upon IRB approval.

Aim 2 Objective

Aim 2: To conduct a qualitative interview of a sample size of up to 50 survey participants from Aim 1 to further assess survey participants' interest in implementing preventive care services for SUDs and medication therapy management care for patients with OUD in their practice.

Participants: The survey questionnaire of Aim 1 will include a question at the end of the survey questionnaire to ask the participant whether he/she is willing to be contacted to participate in an interview study of implementing patient care services for patients with SUD at the pharmacy setting. Among those who endorse "yes" to the interview study, up to 50 survey participants will be recruited to participate in the interview study (i.e., until saturation of themes for different demographic groups defined by sex, race, and ethnicity is considered adequate). The main purpose is to obtain in-depth information about barriers and facilitators related to pharmacist-provided preventive care services for SUDs and medication therapy management care for patients with OUD in their practice. A **Qualitative Interview Guide** will be developed for Aim 2.

6.0 STUDY DESIGN

6.1 Overview of Study Design

The study uses a mixed methods approach to investigate under-studied areas of addiction treatment services in an under-studied population. The study will involve 3 main steps. First, a survey assessing barriers and facilitators related to pharmacist-provided services and patient care for SRT and MOUD will be piloted among a small sample (N=10) of licensed pharmacists who will subsequently participate in a remote meeting with the investigative team to provide feedback about the survey's feasibility (Aim 1). The information gained from this pilot will be used to identify and address any potential feasibility issues of the survey. Next, the refined version of the survey will be administered among a large sample of licensed pharmacists (Aim 1). Participants who complete the survey from Aim 1 will then be recruited to complete a qualitative interview to further assess barriers, facilitators, and interest in implementing pharmacy-based preventive care services for SUDs (Aim 2). The study design is summarized in **Table 1.**

Table 1: Summary of Study Design

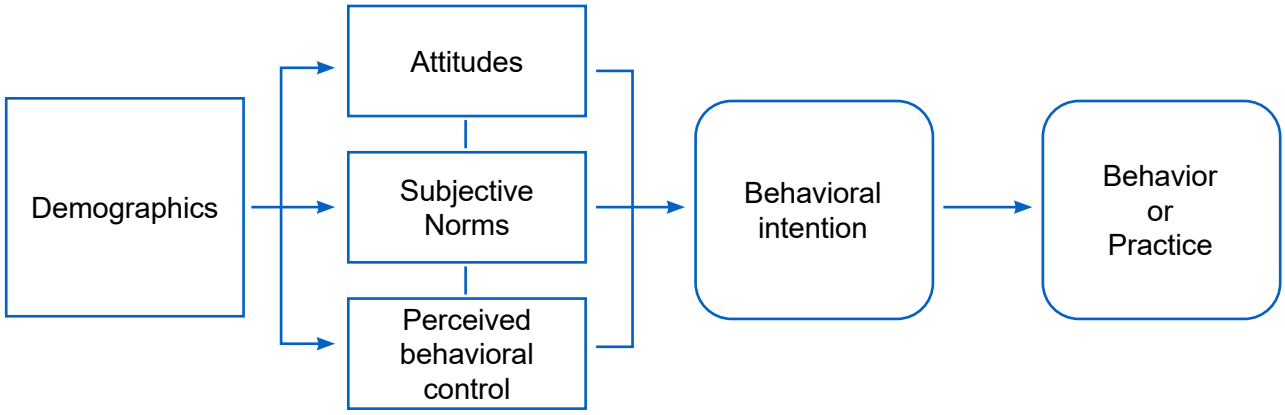
Aim	Sample size	Recruitment methods	Consent approach	Type of data collection	Compensation
Aim 1 **Pilot test the survey for feasibility issues**	N=10 (licensed pharmacists)	Email, phone call, and/or postal mail	Electronic, Telephone, WebEx, or Zoom consent / waiver of documentation of consent	Participants self-administer the survey and participate in a virtual interview following the survey (approximately 1.5 hours)	$300 per participant ($150 for completing the survey; $150 for completing a remote meeting)
Aim 1 **Conduct the survey**	N=1062 (licensed pharmacists)	Email, phone call, text message, and/or postal mail	Electronic, Telephone, WebEx, or Zoom consent / waiver of documentation of consent	Electronic on-line survey (via email or text messaging links), mailed survey (postal mail), **or** phone or virtual interview by research staff (up to 1 hour)*	$150 per participant
Aim 2 **Conduct the qualitative interview**	N=up to 50 (range: 20-50) (licensed pharmacists from survey participants)	Email, phone call, and/or postal mail	Electronic, Telephone, WebEx, or Zoom consent / waiver of documentation of consent	Recorded phone or virtual interview by research staff (up to 1.5 hours)	$250 per participant

* For those who provide the informed consent, we will conduct up to 7 electronic reminders or phone calls if needed

6.2 The Conceptual model:

The Theory of Planned Behavior (**Figure 1**) assumes that attitudes toward a behavior, subjective norms or beliefs (e.g., perceived social pressure to perform or not to perform the behavior), and perceived behavioral control (e.g., an individual's perceptions of his/her ability to perform a given behavior or self- efficacy) influence the intention to perform a task and that intention predicts the actual behavior or practice (Ajzen, 2011). The Theory of Planned Behavior is the model commonly used in the literature to study pharmacists' knowledge, attitude, and/or practice (KAP) as well as healthcare professional's intentions to provide substance use treatment services (Dowling-McClay et al., 2019; Fleming et al. 2018; Hagemeier et al., 2014; Kelly et al. 2012; Talbot et al. 2015).

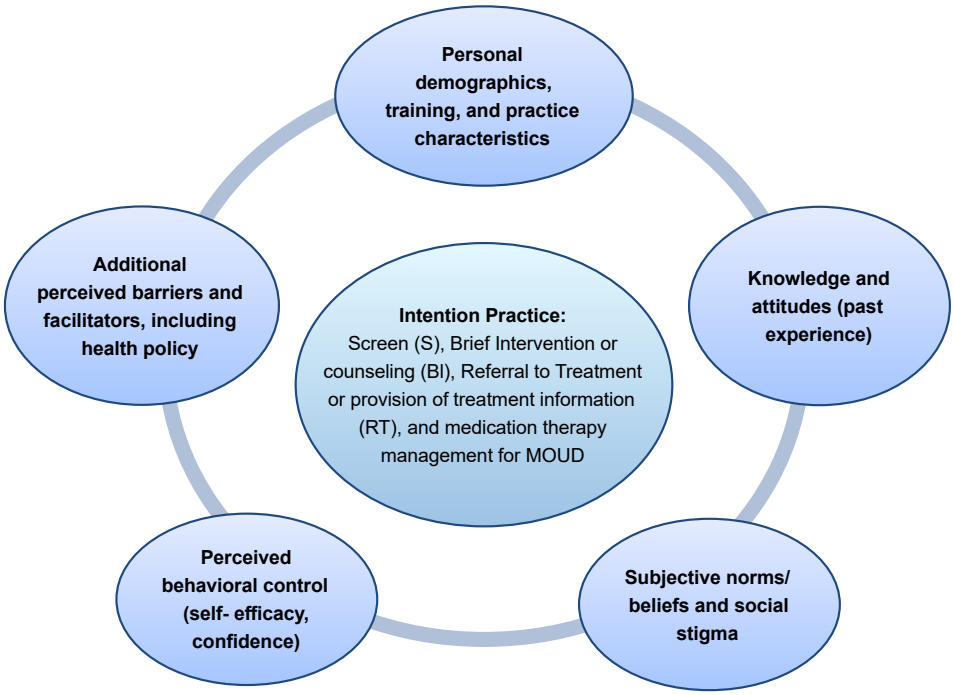
Figure 1. Theory of Planned Behavior:
A health belief model of studying knowledge, attitudes, and practice



While the Theory of Planned Behavior provides a useful framework for understanding the cognitive relationship among the three key constructs (attitudes, subjective norms, and perceived behavioral control/ self-efficacy) and behavioral intentions, it does not consider an individual's past experience, knowledge, and larger environmental factors (e.g., stigma, policy). In addition, the temporal link between the intention to practice and the actual behavioral action has not been addressed by the theory.

To address the limitations of the Theory of Planned Behavior model, we will use an integrated model for studying barriers and facilitators related to pharmacist-provided SRT and MOUD services (**Figure 2**), which also considers pharmacists' training, knowledge, past experience with SRT and/or MOUD, perceived stigma associated with substance misuse, and additional perceived barriers and facilitators (e.g., health policy, environmental factors) that may influence pharmacists' intention to engage in provision of SRT, drug overdose prevention, or MOUD care activities (Ajzen, 2011; APhA, 2014; Kelly et al. 2012; Palamar et al., 2013; SAMHSA, 2018). The integrated model considers multifaceted cognitive and contextual factors that may interact with one another in influencing pharmacists' intentions to practice or practice behaviors within the variable context of healthcare reform and the drug overdose epidemic (Ajzen, 2011; APhA, 2014; Hedegaard et al., 2019).

Figure 2. An integrated model for studying barriers and facilitators related to pharmacist-provided SRT and MOUD services



6.3 Duration of the study

The pre-implementation phase will include: (a) obtaining the IRB approval (i.e., a waiver of documentation of consent) for the study protocol and related study materials, (b) developing case report forms (CRFs) and the electronic database capture (EDC) system, (c) completing the interview guide and manual of operating procedures (MOP),and completing the study training. Once these tasks are completed, data collection will be initiated.

The data collection time is estimated to be about 9-14 months.

- Pilot the survey for feasibility issues: approximately 2-4 months, including the time for CTN DSC to modify the electronic data capture system to address logistical or technical issues.
- Survey: approximately 5-7 months.
- Qualitative interview of survey participants from Aim 1: approximately 2-3 months, including the time for CTN DSC to produce a list of potential participants with demographic information (sex, race, ethnicity) from Aim 1 for recruitment.

After the completion of the survey and the qualitative interview, it will take up to 2 months for completing the database lock by the CTN DSC. After the database lock, the CTN DSC will initiate the data analysis of the survey data for the final study report. The investigative team will complete the Final Study Report in collaboration with the CTN DSC within 4 months after the database lock. Following the submission of the Final Study Report, the investigative team will prepare research manuscripts and conduct data analyses for publication.

7.0 STUDY POPULATION

7.1 Target Sample

Pilot test: The target population of the pilot test of the survey includes licensed community pharmacists from the CPESN. CPESN is a nationwide network of community-based pharmacies, which currently includes over 2900 pharmacy locations from 45 states and Washington D.C.

Survey: The target population of the main survey includes licensed community pharmacists from the CPESN. Participants may also be recruited from other related community pharmacist networks as needed to reach the recruitment goal.

Qualitative interview after the survey: The questionnaire of Aim 1 will include a question at the end of the survey questionnaire to ask the participant whether he/she is willing to be contacted to participate in an interview study of implementing patient care services for patients with SUD in a pharmacy setting. Among those who endorse ”yes” to the interview study, up to 50 survey participants will be recruited to participate in the interview study.

7.2 Recruitment Strategies

Recruitment strategies to achieve a diverse sample of pharmacists

- We will use oversampling strategies as needed to increase the recruitment for women and non- white minorities to participate in the survey and to increase the number of participants from multiple states (Anderssen & Malterud, 2017; Singh et al., 1994). **We plan to distribute survey invites to members of the CPESN, and members of other related community pharmacist networks as needed.** We will review/monitor the daily recruitment report (e.g., distribution of enrollment by sex, race, ethnicity, and state of participants) to track the progress of recruitment by distribution of sex, race, ethnicity, and state. Based on recruitment rates by state/D.C., we will modify our study invitations to increase recruitment efforts to target states with a low enrollment rate in order to meet the goal of enrolling approximately 24 participants from each state and D.C.

- Similarly, we will track the progress of recruitment by distribution of participants' sex, race and ethnicity. Approximately 65% of active licensed pharmacists are female (AACP, 2020). We plan to enroll at least 531 females (50% of 1062 participants) to ensure the analysis of sex differences. Approximately 22% of active licensed pharmacists are non-white (AACP, 2020). We plan to enroll at least 350 non-whites (33% of 1062 participants) to allow the analysis of racial/ethnic differences. Based on recruitment rates by sex, race, and ethnicity, we will modify our study invitations, as needed, to increase recruitment efforts to target demographic groups with a low enrollment rate in order to meet the enrollment goal by sex and racial/ethnic distributions. The survey invites will be distributed continuously (and as needed) to potential participants until the study reaches the final recruitment goal. Given that study participation is voluntary, we will monitor the daily recruitment report closely and modify strategies, as needed, to ensure an adequate number of women and minorities will be recruited.

Recruitment strategies to achieve a high response rate

Multiple strategies will be used to achieve a high response rate.

- First, we plan to leverage the leadership support of the CPESN to achieve a high response rate (e.g., 60%). We will develop IRB-approved study materials that may be distributed by the office of the CPESN to the network's members in order to help describe the value of participating in the survey and reach out to all members of the CPESN. We will monitor the daily recruitment report and have regular communications (e.g., weekly or biweekly) with the CPESN office to identify

- effective strategies for increasing the response rate and address issues affecting the response rate immediately.

- Second, we will apply the principles of the Dillman's total design survey method by using mixed- mode survey options (as needed), including web-based or electronic survey, paper survey (return via self-addressed stamped envelope or secure FAX), and phone/virtual interview to increase the response rate (Dillman et al., 2014; Hoddinott & Bass, 1986; Kroth et al., 2009).

- Third, email and text messaging (with the embedded link to the web-based or electronic survey) invitations to potential participants may be used (as needed) to facilitate the use of eConsent with a waiver of documentation of consent to complete the electronic survey.

- Fourth, for the electronic survey option, participants also will be given the option to fax their completed survey to a study FAX number (as needed). Research staff then will work with DSC complete the data entry into the EDC.

- Fifth, participant compensation will be provided to properly compensate for participants' time to participate in the survey.

Recruitment strategies to identify survey participants in the follow-up qualitative interview

The main survey questionnaire of Aim 1 will include a question at the end of the survey questionnaire to ask the participant whether he/she is willing to be contacted to participate in an interview study of implementing patient care services for patients with SUD in a pharmacy setting. Among those who endorse "yes" to the interview study, up to 50 survey participants (range: 20-50 participants) will be recruited to participate in the interview study. The general guideline for identifying potential participants for the qualitative interview will be based on a sequential explanatory design for mixed methods research (Creswell & Clark, 2017).

- First, after participants complete the main survey, we will work with the DSC to use the survey results mentioned below to identify participants for the qualitative interview.

- Second, we will use the results of the Drug and Drug Problems Perceptions Questionnaire (DDPPQ) to identify potential participants for the qualitative interview. DDPPQ is a valid and reliable tool for assessing healthcare professionals' perceived behavioral control, therapeutic commitment, and readiness for working with individuals with drug use problems (Watson et al., 2007). Low scores indicate positive attitudes, whereas high scores denote negative views and attitudes. We will use the scores of the DDPPQ to define 4 mutually exclusive groups (i.e., quartile) of survey participants. We will recruit and enroll 6 participants from each of the 4 groups to reach a sample size of up to 50 participants for the qualitative interview. By using the scores of the DDPPQ, we will be able to identify pharmacists with a wide range of scores in their perceived behavioral control, therapeutic commitment, and readiness for working with individuals with drug use problems to participate in the interview.

- Third, to enroll a diverse sample of participants, we also will use pharmacists' self-reported information on sex, race, and ethnicity from the survey data to conduct tailored recruitment activities and send study invitations by outreaching to each racial/ethnic group, women, and men. Once an enrollment goal is met for a given group (e.g., approximately an equal number of women and men; approximately an equal number of whites, blacks, Hispanics, and pharmacists of other races), the recruitment will stop for that group, or until saturation of themes for different demographic groups is considered adequate. The process will be continued to meet the planned recruitment goal.

7.3 Subject Recruitment and Sample Size

Pilot test: A total of 10 licensed community pharmacists will be recruited from the CPESN (a) to pilot test the on-line survey in order to identify potential feasibility issues for improvement (e.g., clarity of survey questions, technical issues of navigating the electronic data capture system for completing the survey electronically), and (b) to participate in a virtual meeting following the on- line survey to discuss with the investigative team the feasibility issues and suggestions for improvement

Recruitment: Potential community pharmacist participants will be recruited from the CPESN by email, phone call, and/or postal mail. Potential participants will be currently licensed pharmacists working in a community pharmacy setting.

Survey: Approximately 1062 licensed community pharmacists will be enrolled and complete the survey (i.e., survey completers). Survey completers include participants who complete all sections of the survey questionnaire to the end of the survey (e.g., regardless of the number of questions skipped).

Recruitment: Potential community pharmacist participants will be recruited from the CPESN. Survey invites will be distributed to potential participants who are members of the CPESN (currently with over 2900 pharmacies from 45 states and Washington D.C.). Multiple strategies (email with a link to study information, text messaging with a link to study information and the invitation letter, phone call, and postal mail) will be used (as needed) to increase the recruitment for participation. Participants may also be recruited from other related community pharmacist networks as needed to reach the recruitment goal.

Potential participants will be currently licensed pharmacists working in a community-based pharmacy practice setting during the past year (e.g., retail chain or independent pharmacies, supermarket pharmacies, mass merchandiser pharmacies).

Qualitative interview after the survey: The sample size will be up to 50 licensed pharmacists who will be identified from survey completers (Aim 1 survey).

Recruitment: The questionnaire of Aim 1 will include a question at the end of the survey questionnaire to ask the participant whether he/she is willing to be contacted to participate in an interview study of implementing patient care services for patients with SUD in a pharmacy setting. Among those who endorse “yes” to the interview study, up to 50 survey participants (range: 20-50 participants) will be recruited to participate in the interview study.

7.4 Strategies for Retention

Because this study is a cross-sectional survey (no follow-up assessment), retention in the follow-up phase is not applicable. Here, we are focused on the use of systematic follow-up strategies for increasing the response rates (Dillman et al., 2014; Kroth et al., 2009; Scott et al., 2011). Guided by the principles of the Dillman’s total design method and survey research, we plan to use a study introduction letter, reminders (e.g., emails, text messaging, phone calls, postcards), replacement surveys, and last chance reminders to increase the survey response (Dillman et al., 2014; Kroth et al., 2009; Scott et al., 2011). All the proposed approaches will be reviewed and approved by the IRB before implementation.

7.5 Special Populations to Consider

We will recruit participants of both genders and different racial/ethnic backgrounds and training/years in practice. A minimal number of inclusion criteria are used to increase the diversity of the target population and the generalizability of study findings.

7.6 Site Selection and Rationale – Generalizability

8.0 The main purpose of this study is to survey community pharmacists' knowledge of, attitudes about, and intention to provide patient care and services for SRT for SUDs and MOUD. To increase the generalizability of the study findings, potential participants will be identified from the CPESN that currently includes over 2900 community-based pharmacies from 45 states and Washington D.C. to enhance the geographic diversity of study participants.

8.0 STUDY PROCEDURES

8.1 Informed Consent Procedures

Pilot test: A waiver of documentation of consent will be requested from the IRB for the pilot test based on its minimal risk nature. An electronic online survey (via URL links embedded in an email's text or text messaging) with an electronic consent (e-consent) process will be implemented in the survey tool where the respondent acknowledges that he/she has (1) read, understood and had the opportunity to ask questions about the study (e.g., investigative team's contact phone number and email are included within the consent information) if needed, and that by completing the survey he/she is (2) consenting to participate.

Participants of the pilot survey will also agree to participate in a virtual meeting with the investigative team to give feedback about the feasibility of this on-line survey and suggestions for addressing any issues identified by the participant. Following the survey, an **IRB-approved Script** will be used by research staff to obtain each participant's consent over the phone or virtually for participating in the virtual meeting with the investigative team.

Survey: A waiver of documentation of consent will be requested from the IRB for the main survey based on its minimal risk (i.e., a survey of knowledge, attitudes, beliefs, and practice/intention to practice). An electronic online survey (via URL links embedded in an email's text or text messaging) with an electronic consent (e-consent) process will be implemented in the survey tool where the respondent acknowledges that he/she has (1) read, understood and had the opportunity to ask questions about the study (e.g., investigative team's contact phone number and email are included within the consent information), and that by completing the survey he/she is (2) consenting to participate. **The respondent will also be able to receive a copy of the electronic consent for his/her files.** A cover letter with the link to the online survey that explains the purpose of the study will be e-mailed to potential participants. In addition, potential participants may receive a brief text message as a survey invitation, which allows potential participants to use the URL link embedded in the text messaging to read the study cover letter and make the decision to participate in the survey electronically. **Reminder e-mails with the URL link to the online survey, reminder text messaging with the URL link to the online survey, or phone calls will be used to encourage all non-respondents to complete the survey**. Based on the IRB approval, multiple reminders (e.g., emails, phone calls, text messaging) and mailed surveys will also be used (as needed) to maximize response rates.

For non-respondents and those without an email, mailed surveys (postal mail) and phone (or web-based) interviews will be implemented (as needed) to increase the response rate. An **IRB-approved Script** for the survey will be used by research staff to obtain the participant's consent for participating in the survey over the phone, WebEx, or Zoom where the participant acknowledges that he/she has (1) understood and had the opportunity to ask questions about the study, and that he/she is (2) consenting to participate in the survey. The participant will also be able to obtain a copy of the IRB-approved script (via email or postal mail) for his/her records.

Qualitative interview after the survey: Because of the minimal risk nature of the qualitative interview, a waiver of documentation of consent for telephone, WebEx, or Zoom consent will be requested from the IRB. An **IRB-approved Script** for the qualitative interview will be used by research staff to obtain each participant's consent for participating in the interview over the phone, WebEx, or Zoom where the participant acknowledges that he/she has (a) understood and had the opportunity to ask questions about the study, and that by completing the survey he/she is (b) consenting to participate. The participant will also be able to obtain a copy of the IRB-approved Script (via email or postal mail) for his/her records.

8.2 Data collection method:

Pilot test: Participants will receive emails including study information and instructing about how to access the electronic database capture (EDC) system to complete the survey electronically. After the participant completes the survey electronically, research staff will schedule a virtual meeting with the participant to discuss any feasibility issues and suggestions for improving the survey questionnaire, technical issues with the EDC, or other study related logistical concerns for completing the survey.

Survey: Following the informed consent process, participants who accept the study invitation electronically will have access to the EDC system to complete the survey electronically. In addition, participants may complete the survey via a Telephone, WebEx, or Zoom interview with research staff or complete it on the paper survey and then either mail it back to the study's research office or fax it to a secure FAX number.

Qualitative interview after the survey: A qualitative Telephone, WebEx, or Zoom interview will be conducted by trained research staff based on an **IRB-approved Interview Guide**. The interview may take up to 1.5 hours. Participants' responses will be documented by research staff electronically or on the paper interview question form. All telephone, WebEx, or Zoom interviews will be **recorded** by an IRB-approved device or method. The interview notes and digital recordings will be reviewed and summarized in a report.

8.3 Participant Discontinuation

Participants may discontinue at any time, which will be specified in the informed consent document. If a participant withdraws from the study, a new potential participant will be identified for recruitment to participate in the study in order to meet target sample sizes. **Lead node will work with DSC to specify the definition of a completer.**

8.4 Participant Compensation

Study compensation will be based on study aim.

Each participant of the pilot test will receive $300 as compensation for their time, which may take approximately 1.5 hours.

Each participant of the survey will receive $150 as compensation for their time, which may take up to 1 hour.

Each participant of the qualitative interview will receive $250 as compensation for their time, which may take up to 1.5 hours.

9.0 SURVEY MEASURES

9.1 Primary Measures

This study involves a survey for a new, under-researched area. All study variables will be examined and analyzed. As noted in the earlier section by the Theory of Planned Behavior and the Knowledge, Attitudes, and Practice framework (**Figure 2)**, pharmacists' knowledge, attitudes, beliefs, and practice (or intent to practice) are interconnected to one another.

Primary measures (variables) of key interests include the following domains:

- Knowledge and attitudes
- Subjective norms/beliefs
- Perceived social stigma
- Perceived behavioral control
- Current practice and intention to practice MOUD care.

Details of all measures are included in **Section 10 (SURVEY ASSESSMENTS and Table 2).**

9.2 Secondary Measures

Secondary measures (variables) are personal demographics, training, and practice characteristics, as well as macro factors, such as health policy and the potential impact of the Novel Coronavirus (COVID-19) pandemic.

Personal demographics, training, and practice characteristics are included to (a) better characterize their associations with variables of primary measures (knowledge and attitudes, subjective norms/beliefs, perceived social stigma, perceived behavioral control, and current practices/intention to practice); and (b) quantify the study results based on sex, age group, and racial/ethnic differences.

In addition, we include "questions of pharmacists' training need assessment for conducting SRT services" and "questions of policy support for pharmacist-provided MOUD" to identify current training needs and gaps for informing the development of training materials for future Continuing Pharmacy Education courses and for identifying health policy barriers and facilitators of engaging community pharmacists in addiction prevention and treatment efforts.

Finally, we include questions to assess the potential impact of the COVID-19 pandemic on providing care to patients with addiction (e.g., barriers to dispensing medications to patients with SUD and providing patient care due to staff shortages or medication shortages). The COVID-19 infection attacks the respiratory track and lungs. People with SUD frequently use multiple substances (tobacco, marijuana, and/or other drugs) and have comorbid chronic diseases, which could increase the vulnerability to the COVID-19 infection and the mortality (John et al., 2018; Volkow, 2020; Wu et al., 2018). Moreover, social distancing measures for preventing the spread of the COVID-19 infections can limit patients' access to both medical and behavioral health care (Volkow, 2020). Therefore, we also include questions to explore pharmacists' opinions about whether legislative changes may enable community pharmacists to help patients and the pharmacy operation during the COVID-19 crisis (e.g., allowing licensed pharmacists to test COVID-19 and provide treatment linkage, to dispense medications and provide counseling remotely, to permit mail and home delivery of medications, to permit substituting drugs without doctor authorization in order to address drug shortages).

10.0 SURVEY ASSESSMENTS

10.1 Overview of Assessments

Guided by the model presented in **Figure 2**, the following areas of assessments are considered for the survey:

1) Personal background information (e.g., demographic, training, and practice characteristics)
2) Knowledge and attitudes/perception (including past experience or practice)
3) Subjective norms/beliefs (e.g., the perceived social pressure to perform or not to perform the behavior)
4) Perceived social stigma related to substance misuse
5) Perceived behavioral control (e.g., self-efficacy, confidence, controllability of behaviors)
6) Perceived barriers to and facilitators of addressing opioid misuse/OUD
7) Current practice or intention to practice MOUD care
8) Health policy and macro factors (the COVID-19 pandemic).

10.2 Protocol Specific Assessments

This section presents measures for the eight areas that are considered for inclusion in the survey. Protocol amendments will be made, as needed, to document the modifications for the IRB review and approval.

1) <u>Personal background information (demographic, training, and practice location)</u>

Locator Form: A locator form is used to obtain information to assist in finding participants for the survey, sending the survey invitation and reminders, as well as for paying study compensation. This form collects the participant's contact information (e.g., current address, email address, and phone numbers). In order to facilitate locating participants if direct contact efforts are unsuccessful, addresses, phone numbers, or emails of family/friends who may know how to reach the participant are collected, as well as additional participant information, such as social security number, driver's license number and other information, to aid in searches of public records. This information will be collected at screening and will be updated as needed. The information from this form will not be used in the data analysis.

Demographic characteristics:

CTN's demographic form will be used to collect participants' demographic information (e.g., age, sex, race, ethnicity, education).

Pharmacist's education and practice characteristics:

The following pharmacist's education, practice, and setting information may be collected (Burstein et al., 2020; McCaig et al., 2011):

(a) Pharmacist's terminal degree level
(b) Practice state
(c) County of the pharmacy/rurality status (United States Department of Agriculture [USDA], 2019)
(d) Type of pharmacy/current practice setting (e.g., chain, independent, mass merchandiser, supermarket)
(e) Years in practice
(f) Pharmacist's role(s) at the pharmacy
(g) Number of licensed pharmacists at the pharmacy (number of hours/week)
(h) Number of pharmacy technicians at the pharmacy (number of hours/week)

(i) Number of prescriptions for controlled substances filled per week.

2) <u>Knowledge and attitudes/perceptions (including past practice or experience)</u>

Opioid overdose knowledge:

Pharmacists' opioid overdose knowledge will be assessed by the Opioid Overdose Knowledge Scale (OOKS) (Williams et al., 2013; Wagner et al., 2016). The OOKS (14 questions with 45 items) assesses four subscales of opioid overdose (risks, signs, actions, and naloxone use). The OOKS was internally reliable (Cronbach's alpha = 0.83); retest was completed by 33 participants after 14 (SD 7) days (OOKS, ICC = 0.90) with sub-scale item sets from each measure falling within the fair-to-excellent range(ICC = 0.53–0.92) (Williams et al., 2013). In addition, professionals reported significantly higher scores than family members.

Past personal experience with opioid misuse and overdose prevention:

Assessments of pharmacists' personal experience with opioid misuse and overdose prevention may include the questions that assess "Ever witnessed a drug overdose event" and "Had a family member or close friend with opioid misuse/OUD" (Kennedy-Hendricks et al., 2017).

Concerns about patients' drug use problems:

Assessments of pharmacists' concerns about patients' drug use problems may include the questions that assess "the number of patients causing the concern" and "the reasons for the concerns" (Kahan et al., 2011). The reasons for the concerns may include the following:

- Patient comes before opioid prescription is due.
- Patient appears intoxicated or drowsy.
- Patient tries to get a replacement for "lost" medication.
- Patient alters prescription.
- Patient pays cash for the prescription.
- Multiple prescribers of opioids for the same patient.
- You suspect the patient is selling or buying drugs near the pharmacy
- Other.

Concerns about opioid prescribers' opioid prescribing practices:

The question assessing pharmacists' concerns about physicians' opioid prescribing practices may include the following responses (Kahan et al., 2011):

- Prescribing benzodiazepines along with opioids.
- Prescribing opioids to patients you suspect of opioid misuse.
- Prescribing opioids to patients who, in your opinion, probably do not need them.
- Prescribing high opioid doses (in your opinion).
- Increasing opioid doses too quickly.
- Prescribing injectable opioids for chronic non-cancer pain.
- Other.

Knowledge about the availability of screening tools and past experience with delivering SRT: Questions assessing pharmacists' personal experience or practice behaviors with Screening (S) and Referral to Treatment (RT) may include questions related to:

(a) personal experience of ever delivering smoking cessation intervention (Brown et al., 2016; CARE, 2000),
(b) personal experience of ever delivering S and RT for unhealthy alcohol use (McCaig et al., 2011; Jin, 2018; USPSTF, 2019),
(c) knowledge about the availability of screening tools (e.g., Opioid Risk Tool [ORT]) for prescription opioid misuse or risk for opioid/substance misuse,
(d) personal experience ever delivering S and RT for prescription opioid misuse, and

(e) knowledge about the availability of screening tools for other prescription drug misuse and illicit drug use, and
(f) personal experience of ever delivering S and RT for other prescription drug misuse and illicit drug use.

3) Subjective norms/beliefs

Pharmacists' attitudes/beliefs regarding drug use problems (opioids and non-opioid drugs) in the pharmacy practice setting:

Questions assessing pharmacists' attitudes/beliefs regarding prescription drug misuse and illicit drug use may be adapted from the questions used in the previous research (Hagemeier et al., 2014; Irwin et al., 2020):

(a) Opioid misuse is a problem in my community practice setting.
(b) Improving pharmacist–patient communication would deter opioid misuse.
(c) Improving prescriber–patient communication would deter opioid misuse.
(d) Improving pharmacist–prescriber communication would deter opioid misuse.
(e) Other non-opioid prescription drug misuse and illicit drug use is a problem in my community practice setting.
(f) Improving pharmacist–patient communication would deter non-opioid prescription drug misuse and illicit drug use.
(g) Improving prescriber–patient communication would deter non-opioid prescription drug misuse and illicit drug use.
(h) Improving pharmacist–prescriber communication would deter non-opioid prescription drug misuse and illicit drug use
(i) I received adequate training regarding opioid misuse when I was in pharmacy school.
(j) I received adequate training regarding non-opioid prescription drug misuse and illicit drug use when I was in pharmacy school.

4) Perceived social stigma

Perceived social stigma toward individuals with opioid use problems:

Questions assessing pharmacists' perceived social stigma towards individuals with opioid use problems may include questions adapted from the study by Kennedy-Hendricks et al. (2017):

- perceived *affected social groups* of opioid misusers and
- perceived social stigma toward individuals with OUD.

Specifically, questions about perceived social stigma toward individuals with OUD may include the following items:

(a) Would you be willing to have a person with an addiction to opioids start working closely with you on a job?
(b) Would you be willing to have a person with an addiction to opioids marry into your family?
(c) People addicted to opioids are more dangerous than the general population.
(d) Employers should be allowed to deny employment to a person addicted to opioids.
(e) Landlords should be allowed to deny housing to a person addicted to opioids.
(f) Would you be concerned about the safety of other costumers if patients with opioid use disorders come to your pharmacy for medication dispensing?

5) Perceived behavioral control

Pharmacists' perceived behavioral control (self-efficacy, confidence) towards providing care to individuals with drug use problems:

Pharmacists' perceived behavioral control (e.g., self-efficacy, confidence, motivation, satisfaction) towards

working with individuals with drug use related problems will be assessed with the Drug and Drug Problems Perception Questionnaire (DDPPQ) (Cartwright et al., 1980; Watson et al., 2007). DDPPQ is used to assess healthcare professionals' perceived behavioral control or therapeutic commitment and readiness of health professionals for working with individuals with drug use problems (Watson et al., 2007). DDPPQ is a reliable and valid 20-item scale that includes 5 subscales related to role adequacy, role support, job satisfaction, role-specific self-esteem and role legitimacy (Watson et al., 2007):

1) I feel I have a working knowledge of drugs and drug related problems.
2) I feel I know enough about the causes of drug problems to carry out my role when working with drug users.
3) I feel I know enough about the physical effects of drug use to carry out my role when working with drug users.
4) I feel I know enough about the psychological effects of drugs to carry out my role when working with drug users
5) I feel I know enough about the factors which put people at risk of developing drug problems to carry out my role when working with drug users.
6) I feel I know how to counsel drug users over the long-term.
7) I feel I can appropriately advise my patients/clients about drugs and their effects.
8) I feel I have the right to ask patients/clients questions about their drug use when necessary.
9) I feel I have the right to ask a patient for any information that is relevant to their drug problems.
10) If I felt the need when working with drug users I could easily find someone with whom I could discuss any personal difficulties that I might encounter.
11) If I felt the need when working with drug users I could easily find someone who would help me clarify my professional responsibilities.
12) If I felt the need I could easily find someone who would be able to help me formulate the best approach to a drug user.
13) I feel that there is little I can do to help drug users.
14) I feel I am able to work with drug users as well as other client groups.
15) All in all I am inclined to feel I am a failure with drug users.
16) In general, I have less respect for drug users than for most other patients/clients I work with.
17) I often feel uncomfortable when working with drug users.
18) In general, one can get satisfaction from working with drug users.
19) In general, it is rewarding to work with drug users.
20) In general, I feel I can understand drug users.

Perceived self-efficacy to address opioid use problems:

Questions related to pharmacists' perceived self-efficacy to address opioid use problems may be adapted from the prior research and may include the following (Irwin et al., 2020):

(a) I feel I have a working knowledge of prescription opioid misuse.
(b) I feel I have a clear idea of my responsibilities in helping patients who misuse prescription opioids.
(c) I feel I have the right to ask patients about their use of prescription opioids.
(d) I feel awkward asking patients about their possible misuse of prescription opioids.

Perceived confidence to address opioid use problems/OUD:

Questions related to pharmacists' perceived confidence in addressing opioid misuse/OUD may be adapted from the prior research and may include the following (Hagemeier et al., 2014; Irwin et al., 2020):

(a) I am confident in my ability to detect patient opioid misuse issues in my practice setting.
(b) I am confident in my ability to counsel patients regarding perceived opioid addiction-related issues.
(c) I am confident in my ability to discuss treatment facility options with potential opioid misusers.
(d) I feel comfortable questioning prescribers regarding the legitimacy of opioid prescriptions.
(e) I fear that I may damage prescriber-pharmacist relationships if I question opioid-prescribing behaviors.

(f) I fear that I may face disciplinary action from my employer if I question the legitimacy of an opioid prescription.

6) <u>Perceived barriers to and facilitators of addressing opioid use problems</u>

Perceived barriers to addressing opioid use problems:

Questions related to pharmacists' perceived barriers to addressing opioid use problems may be adapted from the prior research and may include the following (Irwin et al., 2020):

(a) I possess too little training in helping patients who misuse opioids.
(b) I have insufficient access to screening tools to assess opioid misuse.
(c) I know too little about how to identify patients who misuse opioids when they do not have obvious symptoms of opioid misuse.
(d) I have too little self-help or few educational pamphlets available for opioid misuse.
(e) I know too little about where to refer patients with opioid misuse problems for help.
(f) I have insufficient training to screen opioid misuse for potential patient safety issues.
(g) I have insufficient training to discuss opioid misuse factors with prescribers.

Provision of addiction treatment facility information to patients:

Pharmacists will be asked to list potential barriers of and facilitators for providing addiction treatment facility information to patients and making referrals to treatment for SUD (Bratberg, 2019; Hagemeier et al., 2015).

Training need assessment for conducting SRT related services:

Questions assessing pharmacists' training needs for conducting SRT services, including barriers to SRT training opportunities, may be adapted from substance misuse prevention training literature and may include the following (Hall et al., 2000):

(a) During your professional training, about how many lecture/seminar hours (including Continuing Pharmacy Education) were devoted to Screening for substance misuse and Referral to Treatment for substance use disorders? [*Substance use disorders include tobacco, alcohol, prescription drug, and illicit drug use disorders.]*
(b) In the past year, how many lecture/seminar hours (including Continuing Pharmacy Education) have you attended on SRT for substance misuse (alcohol, opioid, and non-opioid drug use problems)?
(c) In the past year, how many lecture/seminar hours (including Continuing Pharmacy Education) have you attended on SRT for opioid misuse?
(d) In the past year, how many lecture/seminar hours (including Continuing Pharmacy Education) have you attended on the use of assessment tools for OUD or other SUDs?
(e) Please choose the responses that best describe your current clinical practice of counseling adult patients about their **opioid use**:
    - What percentage of your adult patients do you ask about their opioid misuse?
    - Of your adult patients who may misuse opioids, what percentage do you discuss with or advise to change their opioid use?
    - Of your adult patients who may misuse opioids, what percentage do you make any kind of referral for opioid use disorder treatment?

7) <u>Practice and intentions to practice</u>

Pharmacists' experience of dispensing medication treatment for OUD:

The following different forms of medication treatment for OUD may be assessed (Burstein et al., 2020; Raisch et al., 2005):

(a) Previous experience in dispensing **buprenorphine (e.g., Suboxone®, Subutex®, other dosage forms)** for OUD treatment.

(b) Total number of **buprenorphine** (e.g., Suboxone®, Subutex®) and other dosage forms prescriptions dispensed for OUD in a typical week at the pharmacy.
(c) Previous experience in dispensing **naltrexone (ReVia®)** for OUD treatment.
(d) Total number of **naltrexone (ReVia®)** prescriptions dispensed for OUD in a typical week at the pharmacy.
(e) Previous experience in administering **njectable depot naltrexone (Vivitrol®)** for OUD.
(f) Total number of **naloxone** prescriptions dispensed for overdose prevention in a typical week at the pharmacy.

Pharmacists' perceptions of effectiveness of OUD treatment options:
Pharmacists' perceptions of effectiveness of OUD treatment options may be assessed based on questions used in the literature (Kennedy-Hendricks et al., 2016).

Opinions about MOUD and intention to practice:
Opinions About Medication Assisted Treatment (OAMAT) measures healthcare professional's knowledge, perceptions, and intentions regarding the use of pharmacotherapy for the treatment of opioid use disorder (Friedmann et al., 2015). Items were derived from several different surveys about attitudes toward medication-assisted treatment (MAT), and the resulting measure consists of Likert-type items (1=Strongly Disagree, 5=Strongly Agree), with higher scores indicating more favorable attitudes toward MAT (Friedmann et al., 2015).

Questions assessing pharmacists' opinions about MOUD and intention to practice may be adapted from the following 4 subscales of OAMAT (Friedmann et al., 2015):
(a) Methadone for opioid dependence (6 items)
(b) Buprenorphine (Suboxone®/Subutex®) for opioid dependence (6 items)
(c) Naltrexone (ReVia®) for opioid dependence (6 items)
(d) Injectable depot Naltrexone (Vivitrol®) for opioid dependence (6 items)
Each subscale includes 6 questions about familiarity with the medication, receipt of training, knowledge of referral sources, perceptions of its helpfulness to clients, and likelihood of referring clients to this type of treatment both now and in the future (Friedmann et al., 2015).

Pharmacists' perceived benefits and barriers of utilizing a physician-community pharmacist collaborative care model approach to manage maintenance care for MOUD:
Questions about pharmacists' perceived benefits and barriers of utilizing a physician and community pharmacist collaborative care approach to managing MOUD may be adapted from the questions used in the CTN-0075 study (Wu et al., 2021). *A physician and community pharmacist collaborative care model approach to managing MOUD* refers to the use of Collaborative Practice Agreements (CPAs) to create a formal practice relationship between a community pharmacist and a prescriber (physician/practitioner) to allow for expanded services the pharmacist can provide to patients and the healthcare team (CDC, 2017). The agreement specifies what functions—in addition to the pharmacist's typical scope of practice—are delegated to the community pharmacist by the collaborating prescriber (CDC, 2017). Under such a physician and pharmacist collaborative model for MOUD using buprenorphine, pharmacists would dispense buprenorphine, conduct monthly follow-up care and medication use monitoring, provide medication education, conduct urine drug screens (as needed) under the supervision of the buprenorphine prescriber. The buprenorphine prescriber would continue to prescribe buprenorphine and adjust the dosing (as needed) for the patient through monthly remote/virtual communication with the pharmacist, and the medically stable patients would not need to see the buprenorphine prescriber monthly. This model would free-up some of the buprenorphine prescriber's time for other clinical priorities.

Pharmacists may be asked to provide responses for the following areas:
(a) Perceived benefits of a physician and community pharmacist collaborative care approach to MOUD using buprenorphine (Suboxone®/Subutex®).

(b) Perceived barriers of a physician and community pharmacist collaborative care approach to MOUD using buprenorphine (Suboxone®/Subutex®).
(c) Solutions that would address barriers of supporting a physician and community pharmacist collaborative care approach to MOUD using buprenorphine (Suboxone®/Subutex®).

8) Health policy and macro factors

Legislative changes and policy support for pharmacist-provided SRT and patient care for MOUD:

Pharmacists may be asked to indicate their opinions about the following areas:
(a) Community pharmacists should be authorized to be Drug Addiction Treatment Act of 2000 ("DATA")-waived providers by including as qualified practitioners.
(b) Community pharmacists should be reimbursed for providing treatment services for OUD (e.g., monitoring and adjusting buprenorphine doses under a Collaborative Practice Agreement, conducting urinalyses).
(c) Community pharmacists should be reimbursed for administering injectable depot naltrexone (Vivitrol®) for OUD.
(d) Community pharmacists should be allowed to administer and dispense methadone for OUD at the community pharmacy setting.
(e) Community pharmacists should be reimbursed for delivering screening for opioid misuse and other drug misuse.
(f) Community pharmacists should be reimbursed for delivering behavioral interventions (e.g., motivational interviewing, smoking cessation counseling, drug misuse counseling).

Potential impact of the COVID-19 pandemic crisis on providing care to patients with addiction:
Pharmacists may be asked to indicate their opinions about the following areas during the COVID-19 pandemic:
(a) Personal experience with the COVID-19 testing and treatment.
(b) Barriers to dispending medications to patients with SUD and providing patient care (e.g., staff shortages, drug shortages).
(c) Facilitators to dispending medications to patients with SUD and providing patient care.
(d) Legislative changes that will enable community pharmacists to help patients and the pharmacy operation during the COVID-19 crisis (e.g., allowing licensed pharmacists to test COVID-19 and provide treatment linkage, to dispense medications and provide counseling/education remotely, to permit mail and home delivery of medications, to permit substituting drugs without doctor authorization in order to address drug shortages).

10.3 Table 2: Summary of Protocol Specific Assessments

Table 2 summarizes the survey assessments. Specific questions may be modified for clarity based on the findings from the pilot test.

Table 2: Summary of Study Assessments/Measures
(The number of questions and wording may be modified to improve clarity and feasibility.)

Forms/Assessments	Completed by
Recruitment and Enrollment	
Recruitment Log	Research staff
Informed Consent (A waiver of documentation of consent)	
Master Enrollment Log	Research staff
Locator Form (for reminders and study compensation payment)	Research staff
Study Assessments	
1. Personal background information	
Demographics Form (age, sex, race, ethnicity, education) (CTN demographic form)	Participants
Pharmacist's education and practice characteristics	Participants
2. Knowledge and attitudes/perceptions	
Opioid Overdose Knowledge Scale (OOKS)	Participants
Past personal experience with opioid misuse and overdose prevention	Participants
Concerns about patients' drug misuse problems	Participants
Concerns about opioid prescribers' opioid prescribing practices	Participants
Knowledge about the availability of screening tools and past experience with delivering SRT	Participants
3. Subjective norms/beliefs	
Pharmacists' attitudes/beliefs regarding drug misuse (opioids and non-opioid drugs) in the pharmacy practice setting	Participants
4. Perceived social stigma	
Perceived social stigma toward individuals with opioid misuse problems	Participants
5. Perceived behavioral control	
Pharmacists' perceived behavioral control (self-efficacy, confidence) towards providing care to individuals with drug use problems - Drug and Drug Problems Perception Questionnaire (DDPPQ)	Participants
Perceived self-efficacy to address opioid misuse	Participants
Perceived confidence to address opioid misuse/opioid use disorder	Participants
6. Perceived barriers and facilitators	
Perceived barriers to addressing opioid misuse/opioid use disorder	Participants
Perceived barriers of providing addiction treatment facility information to patients	Participants
Training need assessment for conducting SRT related services	Participants
7. Practice and intentions to practice medication therapy management for medication treatment for opioid use disorder	
Pharmacists' experience of dispensing medication treatment for opioid use disorder	Participants
Pharmacists' perceptions of effectiveness of opioid use disorder treatment options	Participants
Opinions about medication treatment for opioid use disorder and intention to practice	Participants
Perceived benefits and barriers of utilizing a physician-community pharmacist collaborative care approach to managing medication treatment for opioid use disorder	Participants
8. Health policy and macro factors	
Policy support for pharmacist-provided SRT services and patient care for medication treatment for opioid use disorder	Participants
Potential impact of the COVID-19 crisis (Novel Coronavirus) on providing care to patients with addiction	Participants

10.4 CTN Substance Use Related Measures

Substance use related measures or questionnaire (including mental health measures) used in SUD research or clinical settings will be identified from CTN studies, CTN Dissemination Library (http://ctndisseminationlibrary.org/), and the PhenX (consensus measures for **Phen**otypes and e**X**posures) Toolkit (https://www.phenxtoolkit.org/index.php) as needed. Measures or questionnaire identified from this study will be compared with this list and summarized in the study reports.

10.5 Qualitative Interview Questions

a. Demographic and practice characteristics:

The qualitative interview will include two sections. Section one will collect **demographic information** (e.g., state of residence, zip code for a rurality indicator, age, sex, race, ethnicity, and education) and practice characteristics.

The following **practice characteristics** may be collected:

- How many years have you been in pharmacy practice (after residency)?
- What is your current pharmacy practice setting?
- What is your current role at your pharmacy practice setting?
- On average, how many hours per week do you work as a licensed pharmacist?

b. Interview questions:

The qualitative interview will obtain additional information about pharmacists' knowledge of, perception towards, or interest in providing preventive care and medication therapy management services for patients with substance misuse or SUD. Although the current U.S. Preventive Services Task Force (USPSTF) recommendations for screening and intervention for unhealthy drug use has not recommended brief intervention (USPSTF, 2020), the use of a Screening (S), Brief Intervention (BI), and Referral to Treatment (RT) (SBIRT) approach for substance use disorders has been widely promoted by the SAMHSA (SAMHSA, 2017). SBIRT has been defined by the SAMHSA as a comprehensive, integrated, public health approach to the delivery of early intervention for individuals with risky alcohol and drug use, and the timely referral to more intensive substance abuse treatment for those who have SUDs (SAMHSA, 2011).

In addition, "*Screen for substance misuse and SUDs in the patient or family and offer brief interventions to patients with hazardous and harmful substance use in all pharmacy practice settings using SBIRT*" has been included by the Association for Multidisciplinary Education and Research in Substance Use and Addiction (AMERSA) as a required skill of the core competencies for the U.S. pharmacists to address substance use in the 21st century (Bratberg, 2019). Therefore, the qualitative interview will be focused on exploring pharmacists' knowledge of, perception towards, or interest in providing preventive care (i.e., SBIRT) and medication therapy management services (i.e., MOUD) for patients with substance misuse or SUD.

Section two of the qualitative interview may include the following questions:

1) Please tell me what you know about the Screening (S), Brief Intervention (BI), and Referral to Treatment (RT) (SBIRT) approach for substance use disorders.
2) Please describe any SBIRT related education or training courses (e.g., Continuing Education courses) that you have completed.

3) There are several ways that community pharmacists could engage in screening patients for substance misuse (such as tobacco use, unhealthy alcohol use, opioid misuse, or non-opioid drug use/misuse) and making referrals to treatment for substance use disorders.
    - Please describe why and how you engaged in screening for any substance misuse (such as tobacco use, unhealthy alcohol use, opioid misuse, or non-opioid drug use/misuse), conducting patient education, and/or made a referral to treatment for substance use disorders for your patients.

4) If you were to initiate or increase SBIRT at your pharmacy, what substance(s) would you prefer to focus on and practice the S, BI, and/or RT? What resources, tools, financial support, and infrastructure would you need to be successful?
5) What are your thoughts about current barriers to practicing SBIRT by pharmacists in a community pharmacy setting?
6) Please describe potential advantages and benefits of delivering SBIRT services in a community pharmacy setting
7) Do you plan to practice SBIRT in the coming year to help combat the US drug overdose crisis?
8) Please describe your experience administering and/or dispensing Medication treatment for Opioid Use Disorder, such as Buprenorphine, Naltrexone, and Extended-Release Injectable Naltrexone (Vivitrol), at your practice setting?
9) If buprenorphine prescribers and community pharmacists were to use collaborative practice agreements to expand pharmacist-provided care for managing medically stable patients receiving Buprenorphine for opioid use disorder treatment, what would be potential advantages and benefits of doing so? [Note: Under such a physician and pharmacist collaborative care model, pharmacists would dispense buprenorphine, conduct monthly follow-up care and medication use monitoring, provide medication education, conduct urine drug screens (as needed) under the supervision of a buprenorphine prescriber. The buprenorphine prescriber would continue to prescribe buprenorphine and adjust the dosing (as needed) for the patient through monthly communication with the pharmacist, and the medically stable patients would not need to see the buprenorphine prescriber monthly. This model would free-up some of the buprenorphine prescriber's time for other clinical priorities.]
10) What are your thoughts about current barriers to implementing such a physician and pharmacist collaborative care model that utilizes the pharmacist's Medication Therapy Management approach for Medication treatment for Opioid Use Disorder in a community pharmacy setting?
11) What are your thoughts about the role community pharmacists can play in the prevention and treatment of opioid use disorder and other drug use disorders (such as cannabis, cocaine, methamphetamine, and other prescription use disorders), such as using an SBIRT approach or a physician and pharmacist collaborative care model?
12) What important issues and questions about engaging community pharmacists in addiction prevention and treatment have not been mentioned in this interview?
13) Finally, do you have any closing thoughts about the role of community pharmacists can play in addiction prevention and treatment and potential solutions for addressing the barriers to practicing SBIRT or a physician and pharmacist collaborative care model in a community pharmacy setting?

11.0 TRAINING REQUIREMENTS

All investigators and research staff of this study are required to complete Human Subjects Protection (HSP) and Good Clinical Practice (GCP) training as well as protocol-specific training before participating in the study recruitment and data collection activities. The protocol-specific training (e.g., reading protocol and MOP, practicing mock interviews and survey) will be based on the role and responsibilities of the research personnel member. Completion of the required training will be documented in the Training Document Forms (TDFs) and approved by the Lead Investigator.

12.0 STATISTICAL ANALYSIS

12.1 General Design

This study seeks to collect new information about potential barriers and facilitators in engaging community pharmacists in the drug misuse prevention efforts and medication treatment for SUD. Given a new research direction for NIDA CTN, a mixed methods design is used to improve the study design and its generalizability of results to community pharmacists.

The analysis will examine the distribution of all study variables, including proportion estimates for variables with categorical responses and mean scores for variables of each scale and subscales. The analysis will also examine demographic and practice differences in knowledge and attitudes, subjective norms/beliefs, perceived social stigma, perceived behavioral control, barriers and facilitators, current practice, and intention to practice. Sex, age group, racial/ethnic differences in primary variables will be analyzed and reported.

12.2 Study Hypothesis

This is a survey study of new research areas that are focused on the understudied population for addiction research. It seeks to identify research gaps and directions for further research and generating new insight about barriers and facilitators of implementing pharmacist-provided care for SUDs. The latter will be useful to informing the development of actionable strategies for improving addiction care at the community pharmacy setting. Given the nature of the descriptive study for understudied areas, it is important to analyze all study variables and describe their overall patterns and associations. Thus, this is not a strict hypothesis-testing study like a clinical trial.

Nonetheless, the Theory of Planned Behavior is used to guide the content of survey questions and analysis of the proposed study of pharmacists' knowledge, attitudes, and practices about SRT for SUDs, drug misuse prevention, and MOUD (Ajzen, 2011; Kelly et al. 2012; Fleming et al. 2018; Talbot et al. 2015).

The following hypotheses provide a general guidance about the hypothesized associations that will be explored for the survey data:

(a) Pharmacists' past training and experience with opioid misuse/overdose prevention will be associated with better knowledge about opioid overdose, lower scores in social stigma towards persons with drug misuse problems, and higher scores in self-efficacy/confidence towards providing patient care to persons with drug misuse problems, respectively.

(b) Pharmacists' past experience with or positive attitudes/perceptions towards SRT will be associated with higher scores in self-efficacy/confidence towards providing patient care to persons with drug misuse problems.

(c) Pharmacists' past training and experience with opioid misuse or overdose prevention, or SRT services will be associated with lower scores in the perceived barriers to providing patient care to persons with drug misuse problems.

(d) Pharmacists' past experience with delivering SRT or providing care to persons with OUD will be associated with higher scores in pharmacists' intention to provide care to persons with OUD.

(e) Pharmacists' past experience with opioid misuse/overdose prevention or positive attitudes/perceptions towards SRT will be associated with more support for health policies that promotes pharmacist-provided SRT and patient care for OUD, respectively.

12.3 Projected Number of Sites

The intention of this study is to conduct a nationwide survey of licensed community pharmacists.

12.4 Projected Number of Study Sample Size

The sample size for each aim is included in **Table 3**.

Table 3: The projected number of the study sample size

Study aim	Sample size
Pilot test for feasibility	N=10
Survey	N=1062
Qualitative interview after the survey	N= up to 50 (range: 20-50)

12.5 Primary and Secondary Survey Measures

In general, the objectives of this study are descriptive, and all measures will be considered. However, the following are considered primary: knowledge and attitudes, subjective norms/beliefs, perceived social stigma, perceived behavioral control, as well as current practices and intention to practice MOUD care.

Additional regression analysis will also explore whether knowledge and attitudes/perceptions, subjective norms/beliefs, perceived social stigma, perceived behavioral control, and barriers and facilitators will be associated with intention to practice variables. Pharmacists' sex, age group, race, ethnicity, pharmacy type, and pharmacy location (rural, suburban, urban) will be included as covariates in these analysis in order to inform future training and intervention needs for population subgroups of community pharmacists.

12.6 Statistical Methods for Primary and Secondary Analyses

As a descriptive study, the primary outcome measures will be summarized using descriptive statistics. Continuous measures, such as score variables, will be summarized using means, standard deviations, confidence intervals, and relevant percentiles. Binary variables will be summarized using frequencies and percentages. Categorical variables, such as the 5-point Likert scale will also be summarized using frequencies and percentages. To capture the potential correlation between survey responses of participants practicing in the same state, linear mixed models may be used to analyze the continuous outcomes via PROC MIXED in SAS, and binary or categorical outcomes will be analyzed using generalized linear mixed models via PROC GLIMMIX in SAS (SAS Institute Inc. 2013). The state variable would enter the models as a random effect and no independent variables should be included in the analyses since the objectives are descriptive. By using random effects, point estimates, including confidence intervals, will appropriately adjust for the clustering of survey respondents within states. Nonetheless, if the variance of the random effect is not statistically different from zero, the random effect will be dropped.

The primary outcome measures of interest are the key study domains: knowledge and attitudes/perceptions, subjective norms/beliefs, perceived social stigma, perceived behavioral control, barriers and facilitators, and intention to practice. Separate mixed effects models may be used to analyze the associations between the

listed outcome measures and the pharmacists' characteristics where fixed effects will be included capturing the characteristics, and a random effect is included to adjust for the correlation of pharmacists from the same state. During analysis, a formal test of whether the variance of the random effect is different from zero, and if appropriate, the random effect may be dropped from modelling. These analyses will be used to determine the strength of associations for the five main hypotheses mentioned previously.

In terms of secondary analyses, descriptive analysis will be conducted to describe the pattern of findings for perceived barriers and facilitators (regarding SRT training, health policy, potential impact of COVID-19 on providing patient care) by pharmacists' personal background and practice characteristics, including pharmacists' sex, age, race, ethnicity, pharmacy type, and pharmacy location (rural, suburban, urban). Separate mixed effects models may be used to analyze the associations of pharmacists' personal background and practice characteristics with these perceived barriers and facilitators.

Finally, additional analyses stratified by sex and by race/ethnicity will be conducted for both primary and secondary measures. Results will be presented by sex and by race/ethnicity.

12.7 Rationale for the Sample Size

Pilot test: The power analysis is not relevant for the pilot test of the survey for understanding feasibility issues of the on-line survey. Data from the pilot testing of the 10 participants will not be included in the analysis of the survey data.

Survey: The power and precision analyses are considered for the sample size of the survey. Assuming a population size of 190,000 employed community pharmacists, a sample size of 1062 pharmacists would have 95% confidence in results with 3% margin of error (HRSA, 2018). The sample size of 1062 licensed pharmacists will be adequate for logistic regression of between-group differences under different assumptions (Hsieh, 1989). In addition, for observational studies with large population size that involve logistic regression in the analysis, a minimum sample size of 500 participants is recommended to derive the statistics that represent the parameters (Bujang et al., 2018). Since the study is largely descriptive in nature, precision analyses were conducted to assess the adequacy of the sample size of 1062 in estimating mean outcomes for the survey. Since it is unknown at this point what the various survey items will be that contribute to the various outcomes, we considered three different types of outcome measures: continuous, binary and categorical (corresponding to the 5-point Likert scale). Interest also lies in evaluating which pharmacist characteristics are associated with the various outcome measures, therefore we also conducted power analyses for these three types of outcome measures. Since it is also unknown at this point exactly which covariates will be used to estimate mean outcomes, all power analyses utilize no/yes binary covariate to represent the primary concept being explored – pharmacist's experience with a given treatment service.

Qualitative interview: The sample size of existing qualitative interview studies varies greatly, and it is influenced by multiple factors, such as the sample size guideline in the literature, saturation, richness and volume of the data, characteristics of the target study sample (homogeneity of the sample), nature of a study, key stratifiers of study topics (e.g., concept, demographics), and pragmatic considerations (e.g., available budget and resources) (Dworkin, 2012; Vasileiou et al., 2018). The concept of saturation appears to be a key factor for deciding the sample size; however, reviews of prior studies have found that various definitions of "saturation" used in the literature tend to be subtle and nonobjective as the claims of saturation are rarely substantiated in relation to procedures conducted in the study itself (Vasileiou et al., 2018). The definition of saturation has been described as "no new data," "no new themes," or "no new codes" can be further obtained from the data collection process (Vasileiou et al., 2018). Pragmatic considerations and study-specific characteristics are other key factors for justifying a sample size (Dworkin, 2012; Vasileiou et al., 2018). Therefore, there is no single and explicit gold standard available to decide a sample size of a qualitative interview study.

We will recruit pharmacists for participating in the qualitative interview until saturation of themes for different

demographic groups (sex, race, ethnicity) is considered adequate. Based on prior studies, we plan to recruit **up to 50 participants** (range of the target sample size: **20 to 50 participants**) for the qualitative interview. A very large number of articles, book chapters, and books indicate that a sample size of 5 to 50 participants is considered adequate for a qualitative interview study (Dworkin, 2012). Hagaman and Wutich (2017) conducted a multisite study to evaluate the number of interviews needed to support a qualitative study. A sample size of 20 to 40 interviews were found to be needed to reach data saturation, and the required sample size was reduced when the sample of participants was homogeneous (Hagaman & Wutich, 2017). Thus, our sample size is within the range of an adequate sample size for a qualitative interview study in the literature. In addition, this study uses an explanatory sequential mixed methods design that involves the collection of quantitative data (i.e., a survey) followed by qualitative interviews of the survey participants in order to use results from qualitative interviews to help explain in more detail the quantitative results from survey responses (Creswell & Creswell, 2009; Ivankova et al., 2006). In addition, we plan to enroll participants from each of four racial/ethnic groups (white, black, Hispanic, and other race) to enhance the diversity of participants of the qualitative interview, which is important for improving our understanding of survey results from perspectives of licensed pharmacists with diverse racial/ethnic backgrounds.

Taken together, a sample size of up to 50 participants (range: 20 to 50 participants) will be adequate for the qualitative interview, which will allow a thorough exploration of survey results relevant to pharmacist-provided SRT and patient care for MOUD to distinguish conceptual categories of interest (e.g., screening, communicating with physicians, providing patient education or counseling, making referrals to addiction treatment, conducting medication therapy management for MOUD in collaboration with physicians), and identify variations in the knowledge of and attitudes toward pharmacist-provided SRT and patient care for MOUD.

12.8 Precision and Power Analyses

To determine the level of precision expected, while estimating continuous, binary, and ordinal outcomes, as well as the detectable effect size of a given binary variable for pharmacist experience, regression coefficient for each outcome type, precision and power analyses were conducted, respectively. Using PROC MIXED and PROC GLIMMIX in SAS, several simulations were conducted for the assumed parameters in Table 4.

Table 4. Parameters Used in Simulations for Precision Analyses

State ICC values	Continuous outcomes true mean values	Binary outcomes proportion endorsing Yes	Ordinal outcomes proportion endorsing category 1-5, respectively
State ICC values	**Continuous outcomes true mean values**	**Binary outcomes proportion endorsing Yes**	**Ordinal outcomes proportion endorsing category 1-5, respectively**
0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.09, 0.10	1, 2, 4, 8, 16, 32, 64, 128	0.1, 0.3, 0.5	p_1=0.08, p_2=0.14, p_3=0.20, p_4=0.26, p_5=0.32 and p_1=0.32, p_2=0.26, p_3=0.20, p_4=0.14, p_5=0.08

Table 5. Parameters Used in Simulations for Power Analyses

State ICC values	Continuous outcomes true mean values	Binary outcomes proportion endorsing Yes	Ordinal outcomes proportion endorsing category 1-5, respectively	Fixed effect of pharmacist experience on continuous outcome	Fixed effect of pharmacist experience on binary outcome	Fixed effect of pharmacist experience on ordinal outcome
0.01, 0.10, 0.30	1, 4, 16, 64	0.1, 0.3, 0.5	p1=0.08, p2=0.14, p3=0.20, p4=0.26, p5=0.32 and p1=0.32, p2=0.26, p3=0.20, p4=0.14, p5=0.08	0.16, 0.17, 0.18, 0.19, 0.20, 0.21, 0.22, 0.23, 0.24, 0.25	1.49, 1.65, 1.82, 2.01	1.35, 1.49, 1.65

Our expected sample size is N = 1062 pharmacists, with 46 groups for the states and D.C., averaging approximately 23.09 pharmacists per group. To simulate the plausible scenario in which an unequal number of pharmacists participate within each state, group sizes were randomly selected from a uniform distribution of integers. The N = 1062 can be expressed as (42*23) + (4*24). Alternatively, this can be thought of as such: across 1000 iterations, there are 23 pharmacists per group for 42/46 of the iterations (0.913, or 913/1000, rounding down), and 24 pharmacists per group for 4/46 of the iterations (0.087, or 87/1000, rounding up). Summarizing the sample sizes for each iteration results in a precise overall approximation of the target sample size. For 913 iterations, between 1 and 45 pharmacists were assigned to 46 states (uniform mean: (1+45)/2=23); for 87 iterations, between 1 and 47 pharmacists were assigned (uniform mean: (1+47)/2=24). Mean total sample size and 95% confidence intervals were calculated for the 1000 iterations. As shown in Table 6 below, for all simulations, the target sample size of 1062 was within the 95% confidence intervals. Thus, we were able to consistently estimate the target size while allowing for a realistic degree of variability in the number of pharmacists per state/D.C. For comparability across parameter values, the same seeds were used to synthesize subjects for each outcome type. See Table 6 below for the overall mean sample sizes with 95% confidence intervals for precision and power analyses.

Table 6. Sample Sizes for Precision and Power Analyses

Outcome	Lower 95% CI	Mean	Upper 95% CI
Continuous	1059.080	1064.512	1069.944
Binary	1055.854	1061.434	1067.014
Ordinal	1056.902	1062.363	1067.824

12.9 Precision Analyses

12.9.1 Approach

We investigated the distribution of the widths of the 95% confidence intervals for the mean responses (continuous outcomes), proportion of survey respondents endorsing the “Yes” category (binary outcomes), and the proportion (cumulative probabilities) of survey respondents endorsing category 1, categories (1 and 2), categories (1, 2 and 3), and categories (1, 2, 3, and 4) for the ordinal outcomes. The simulations were based on 1000 iterations under various scenarios for the assumed true values of the state intraclass correlation (ICC), mean responses and proportions. There were 80 (10*8=80) scenarios for the continuous outcomes, 30 (10*3=30) scenarios for the binary outcomes, and 20 (10*2=20) for the ordinal outcomes. For each scenario, we ran 1000 iterations (See Table 4 for the parameter values used in the simulations).

12.9.2 Simulation Results

Below we present the 90th percentile of the distribution of the 95% confidence interval width for the pharmacist survey outcomes estimates (Figures 4 through 7).

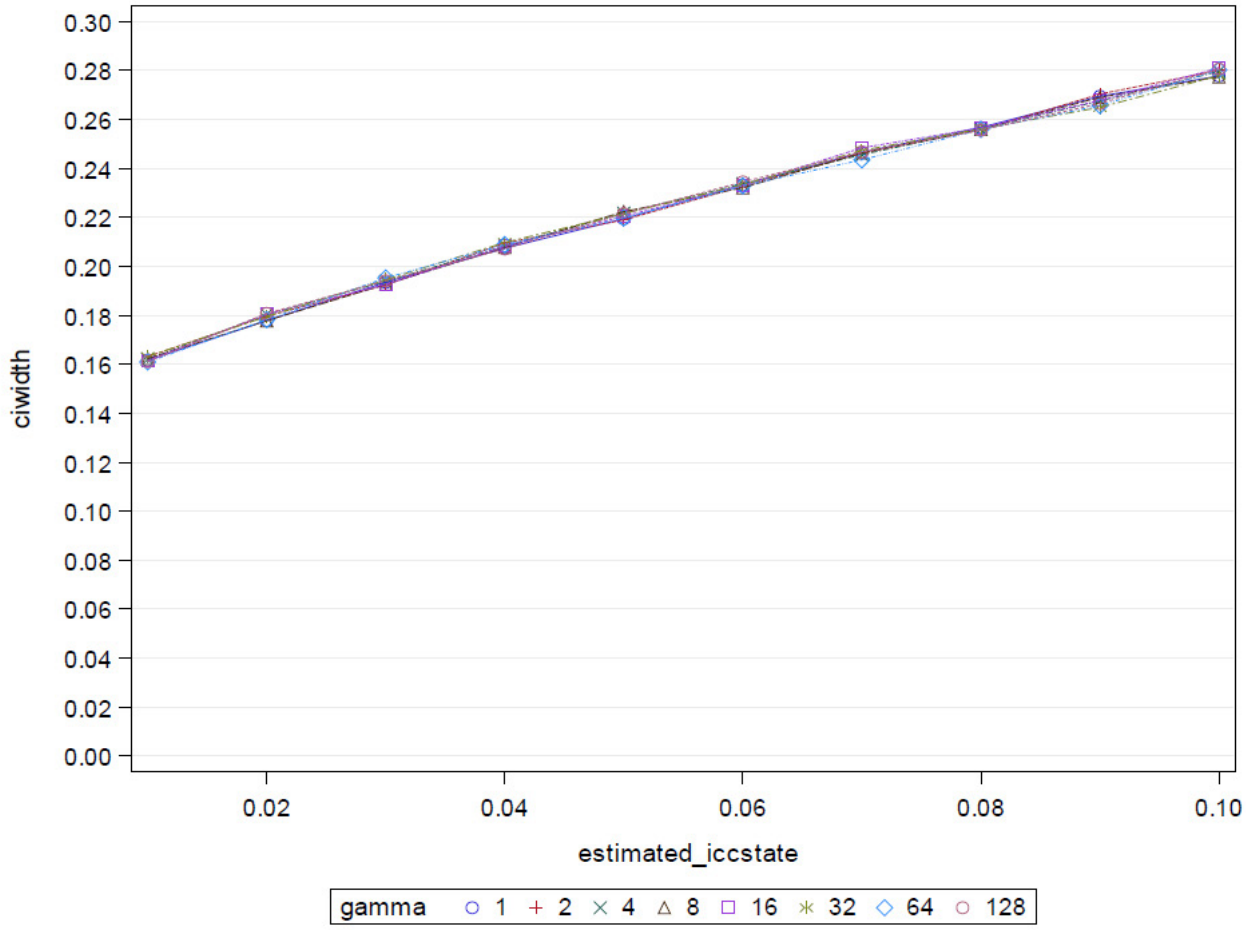


Figure 4. Pharmacist *continuous* outcomes. 90th percentile for the 95% confidence interval width of the mean as a function of the true mean (gamma) for given values of state ICCs (estimated_iccstate). The y-axis shows the confidence interval width (ciwidth) and the x-axis shows different values of state ICC.

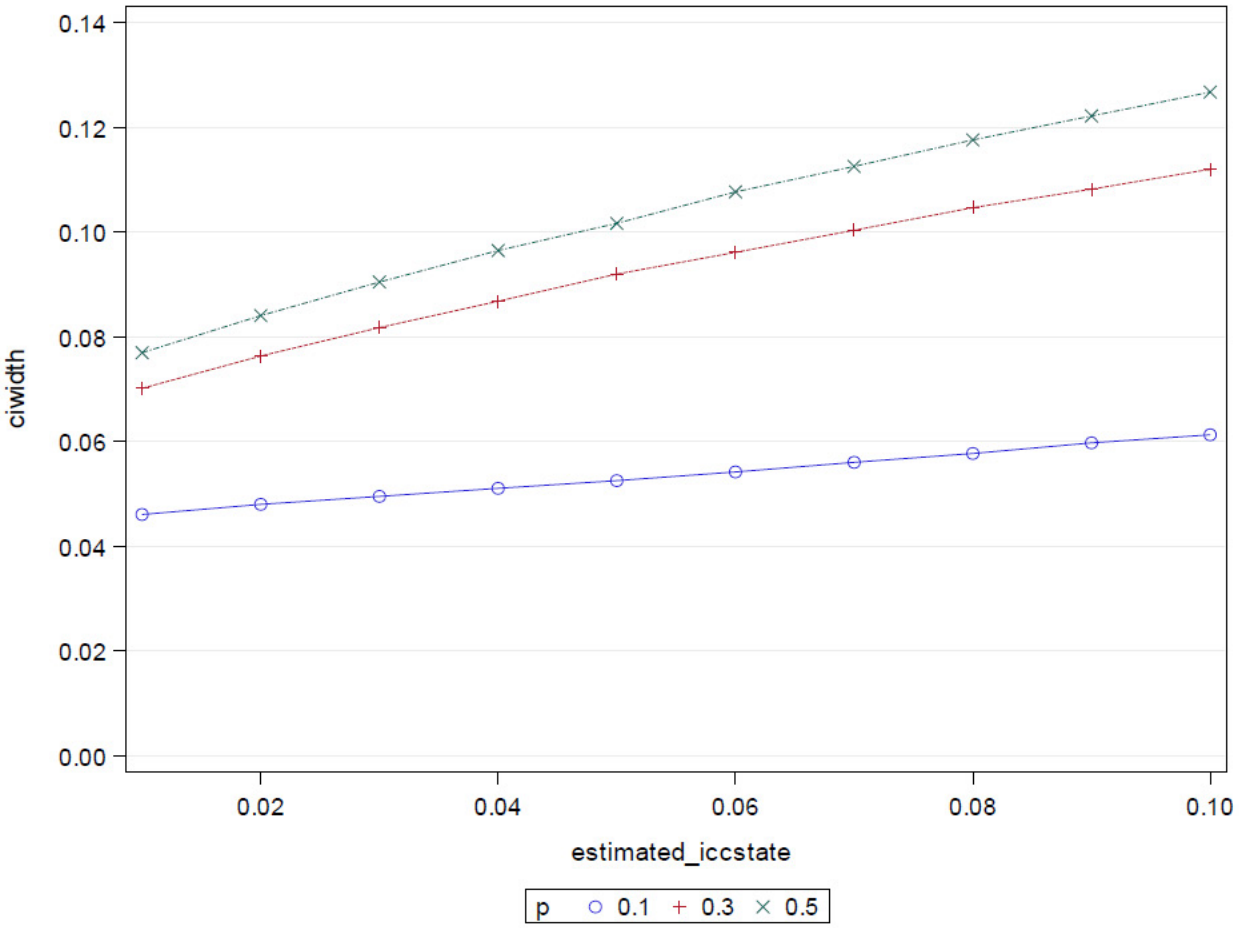


Figure 5. Pharmacist *binary* outcomes. 90th percentile for the 95% confidence interval width of the proportion estimate as a function of the true proportion (p) for given values of state ICCs (estimated_iccstate). The y-axis shows the confidence interval width (ciwidth) and the x-axis shows different values of state ICC.

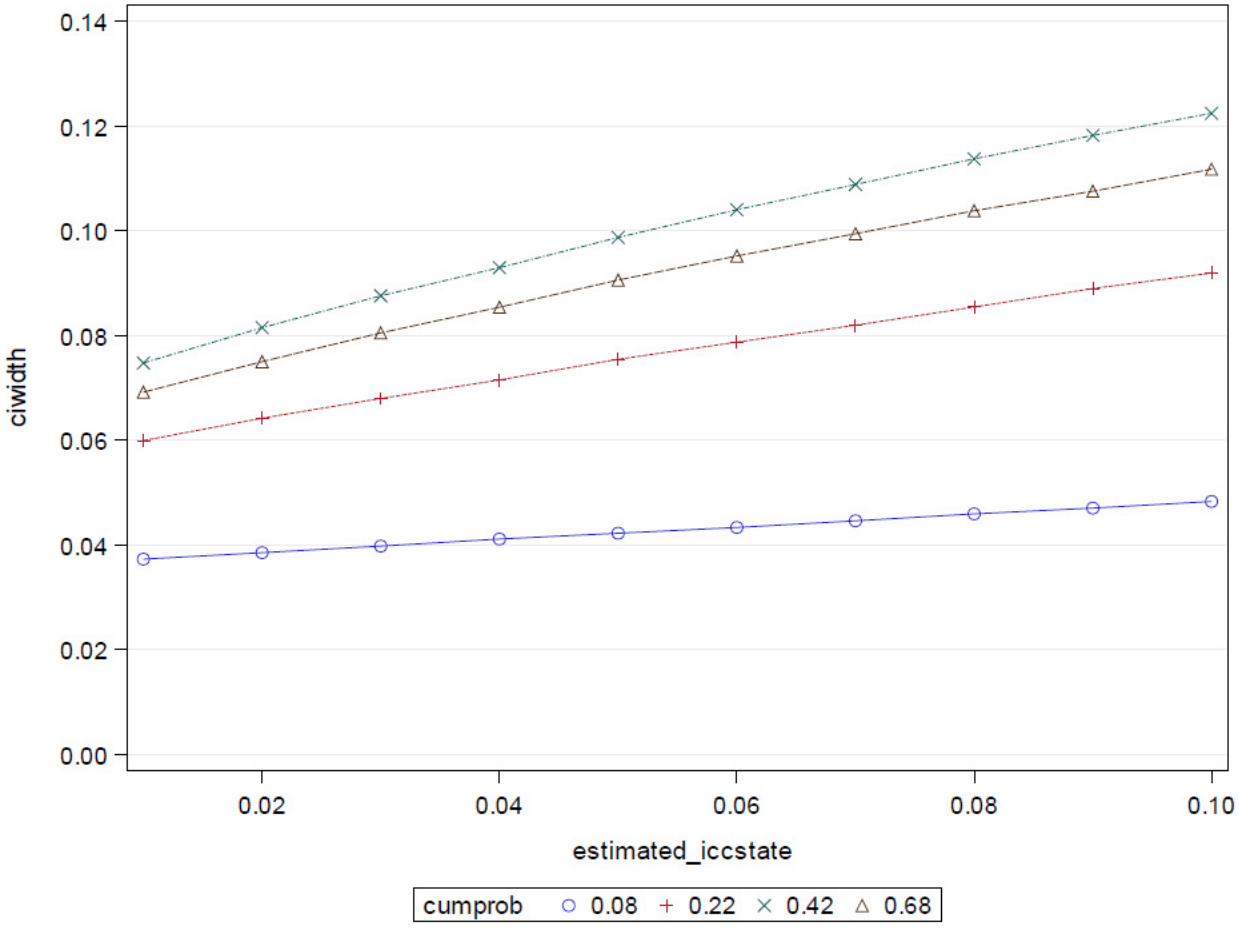


Figure 6. Pharmacist *ordinal* outcomes with p_1=0.08, p_2=0.14, p_3=0.20, p_4=0.26, p_5=0.32. 90th percentile for the 95% confidence interval width of the cumulative probability estimates as a function of the true cumulative probabilities (cumprob) for given values of state ICCs (estimated_iccstate). The y-axis shows the confidence interval width (ciwidth) and the x-axis shows different values of state ICC.

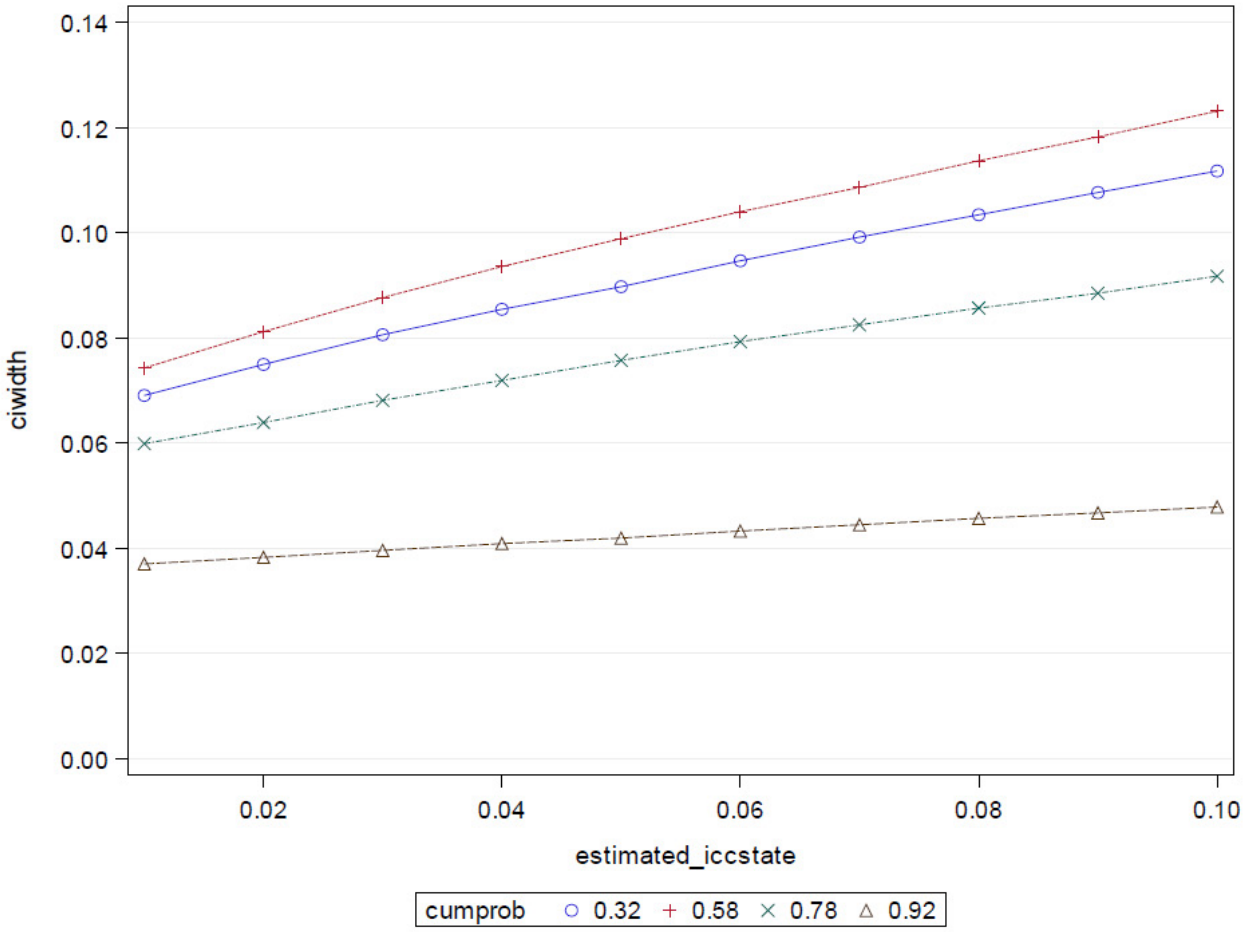


Figure 7. Pharmacist *ordinal* outcomes with p_1=0.32, p_2=0.26, p_3=0.20, p_4=0.14, p_5=0.08. 90th percentile for the 95% confidence interval width of the cumulative probability estimates as a function of the true cumulative probabilities (cumprob) for given values of state ICCs (estimated_iccstate). The y-axis shows the confidence interval width (ciwidth) and the x-axis shows different values of state ICC.

12.9.3 Summary of Precision Analyses

For all the simulation scenarios of pharmacist outcomes, the 90th percentile of the 95% confidence interval widths are below 0.28 for continuous outcomes and below 0.13 for binary and ordinal outcomes. In summary, it is highly unlikely to see confidence interval widths greater than 0.28 for the mean responses for the continuous outcomes, or widths greater than 0.13 for the proportion of survey respondents endorsing a given response category for the categorical outcomes.

12.10 Power Analyses

12.10.1 Approach

We investigated the statistical power curves for the mean responses (continuous outcomes), proportion of survey respondents endorsing the “Yes” category (binary outcomes), and the proportion (cumulative probabilities) of survey respondents endorsing category 1, categories (1 and 2), categories (1, 2 and 3), and categories (1, 2, 3, and 4) for the ordinal outcomes. The simulations were based on 1000 iterations under various scenarios for the assumed true values of the state ICC and assumed effect of pharmacist experience with respect to outcome variables. There were 120 (3*4*10=120) scenarios for the continuous outcomes, 36 (3*3*4=36) scenarios for the binary outcomes, and 18 scenarios (3*2*3=18) ordinal outcomes. For each scenario, we ran 1000 iterations. See Table 5 for the parameter values used in the simulations.

12.10.2 Simulation Results

Below we present the power curves for the pharmacist survey outcomes estimates (Figures 8 through 11).

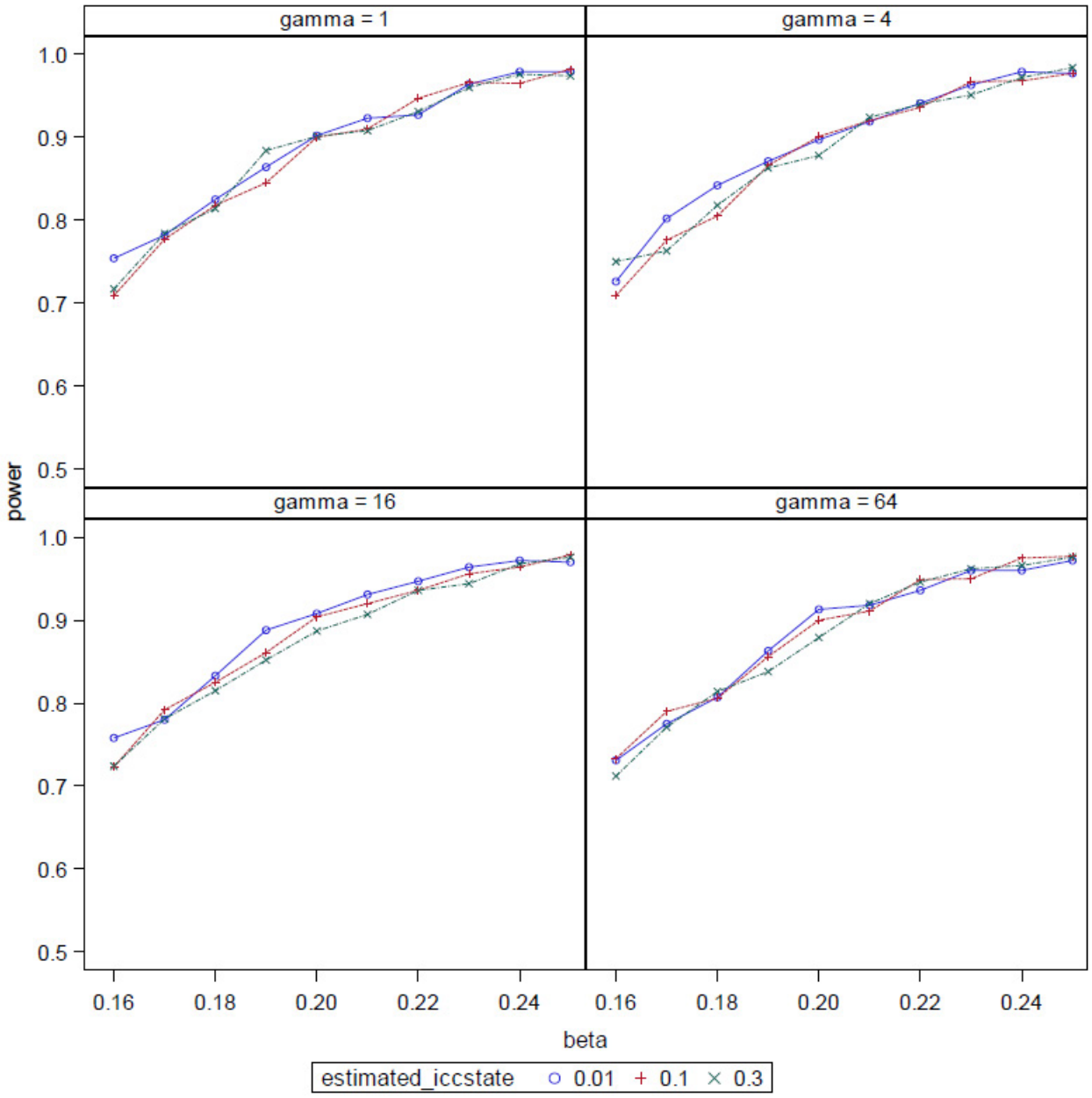


Figure 8. Pharmacist *continuous* outcomes. Statistical power for given values of binary indicator fixed effect coefficient (beta) as a function of the given values of state ICCs (estimated_iccstate). The panels show different values of the true mean (gamma). The y-axis shows the statistical power and the x-axis shows different values of beta.

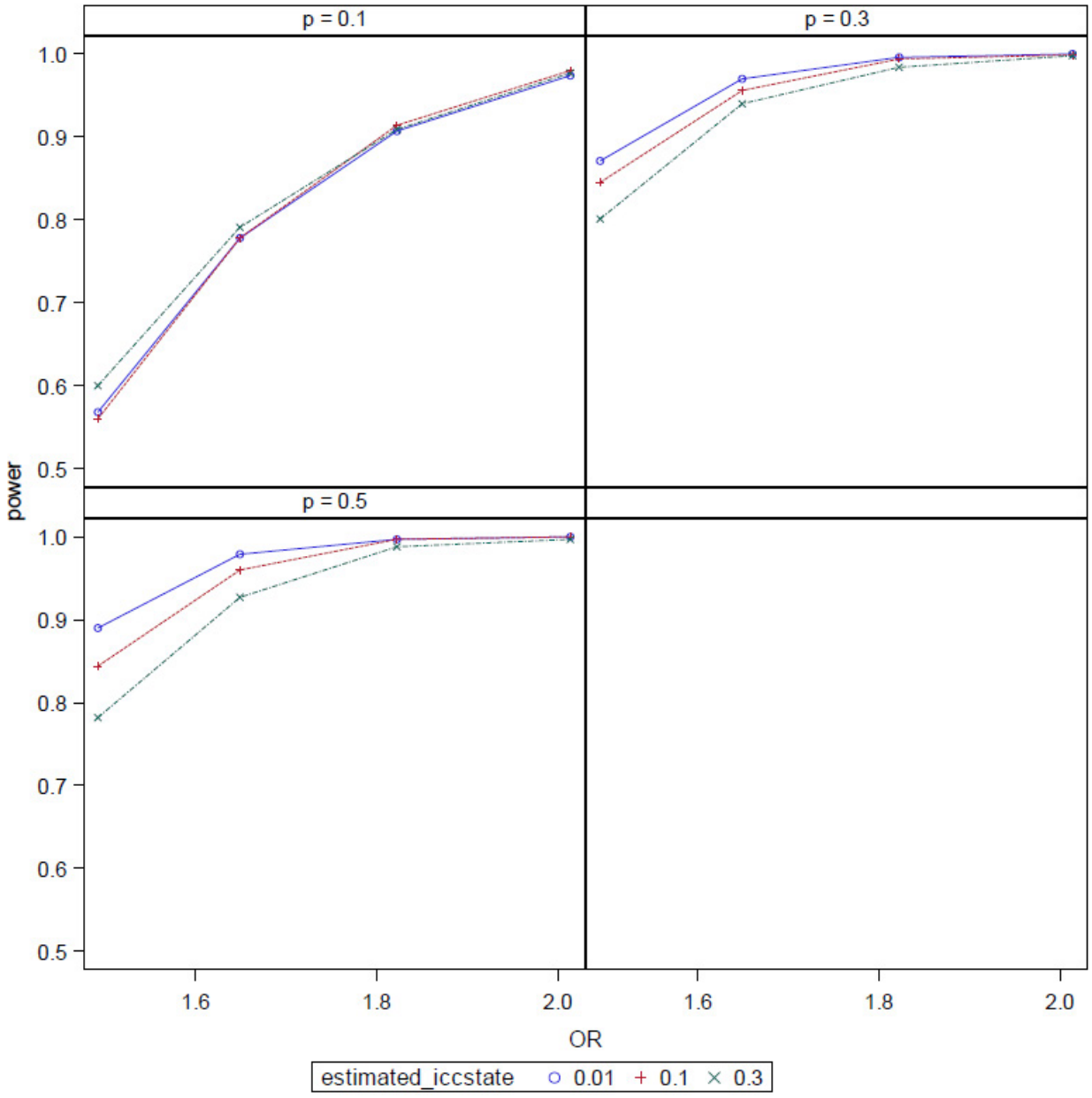


Figure 9. Pharmacist *binary* outcomes. Statistical power for given values of binary indicator odds ratio (OR) as a function of the given values of state ICCs (estimated_iccstate). The panels show different values of the true proportion (p). The y-axis shows the statistical power and the x-axis shows different values of OR.

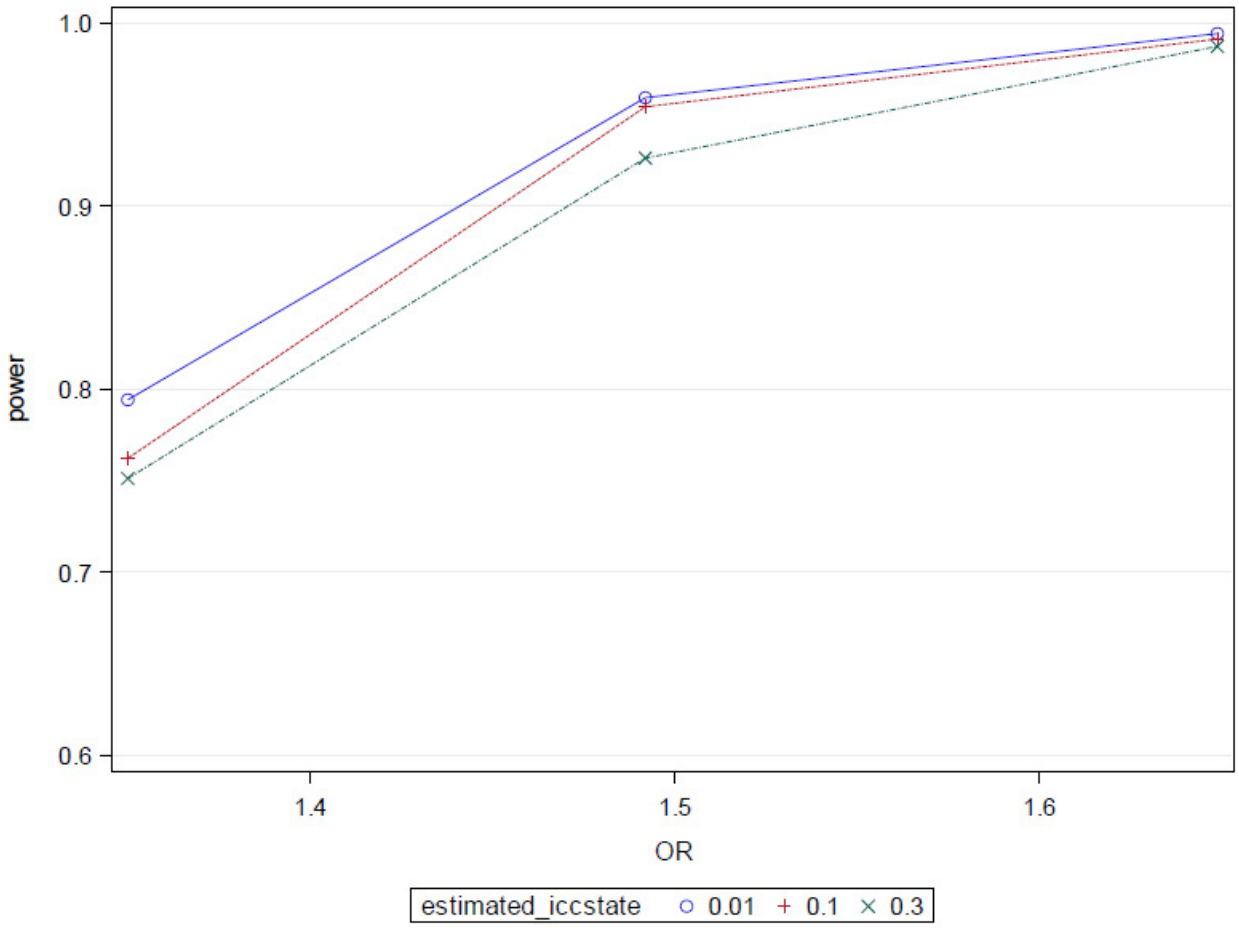


Figure 10. Pharmacist *ordinal* outcomes with p_1=0.08, p_2=0.14, p_3=0.20, p_4=0.26, p_5=0.32. Statistical power of the cumulative probability estimates, for given values of binary indicator odds ratio (OR) and as a function of the given values of state ICCs (estimated_iccstate). The panels show different values of the true cumulative probability (cumprob). The y-axis shows the statistical power and the x-axis shows different values of OR.

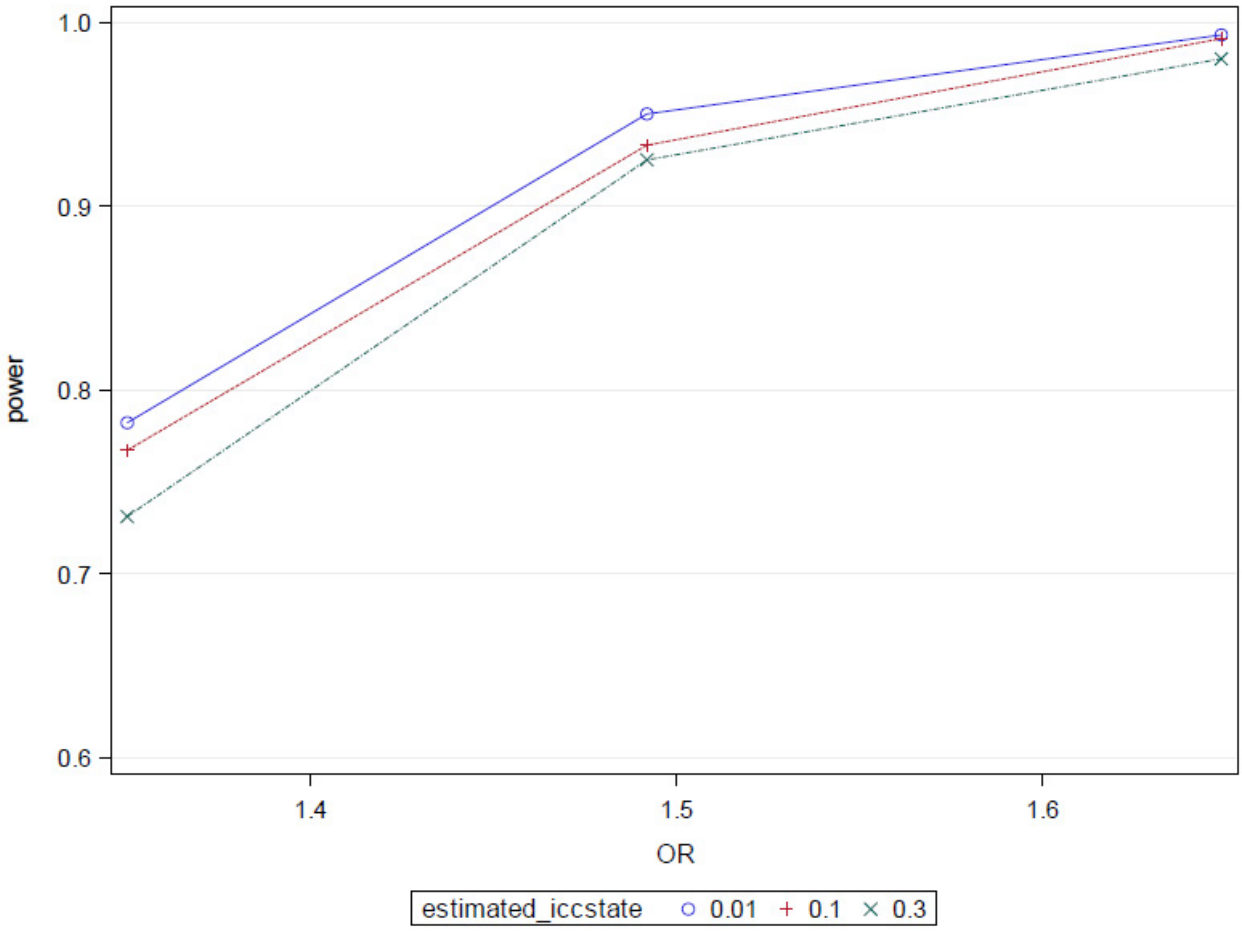


Figure 11. Pharmacist *ordinal* outcomes with p_1=0.32, p_2=0.26, p_3=0.20, p_4=0.14, p_4=0.08. Statistical power of the cumulative probability estimates, for given values of binary indicator odds ratio (OR) and as a function of the given values of state ICCs (estimated_iccstate). The panels show different values of the true cumulative probability (cumprob). The y-axis shows the statistical power and the x-axis shows different values of OR.

12.10.3 Summary of Power Analyses

For all the simulation scenarios of pharmacist outcomes, 90% power can be achieved with a coefficient at or above 0.22 for continuous outcomes; an odds ratio at or above 1.82 for binary outcomes; odds ratio at or above 1.49 for ordinal outcomes with p_1= 0.08, p_2= 0.14, p_3= 0.20, p_4= 0.26, p_5= 0.32; and odds ratio at or above 1.49 for ordinal outcomes with p_1= 0.32, p_2= 0.26, p_3= 0.20, p_4= 0.14, p_4= 0.08. In summary, it is highly unlikely to achieve statistical power below 90% when looking for an experience fixed effect of at least 0.22 for the mean responses for the continuous outcomes; odds ratio 1.82 for the proportion of survey respondents endorsing a given response category for the categorical outcomes (binary); odds ratio 1.49 for the proportion of survey respondents endorsing a given response category for the categorical outcomes (ordinal; p_1= 0.08, p_2= 0.14, p_3= 0.20, p_4= 0.26, p_5= 0.32); or 1.49 for the proportion of survey respondents endorsing a given response category for the categorical outcomes (ordinal; p_1= 0.32, p_2= 0.26, p_3= 0.20, p_4= 0.14, p_4= 0.08).

12.11 Synthesis of Results

The precision analyses show that with a sample size of approximately 1062, regardless of the type of outcome variable, the confidence interval width is likely to be less than 0.28, which indicates sufficient precision for the descriptive nature of this study. The power calculations also show that, regardless of the type of outcome variable, with an approximate sample size of 1062, we will have at least 90% to detect an OR less than 1.82 or a change in mean of 0.22.

12.12 Exploratory Analyses

To inform the measure development for assessing community pharmacists' barriers and facilitators in the provision of SRT, drug overdose prevention and MOUD, item response theory (IRT) analysis will be conducted to identify a smaller subset of more relevant, precise items for assessing each of various measures for knowledge and attitudes, subjective norms/beliefs, perceived social stigma, perceived behavioral control, barriers and facilitators, and intention to practice (Fries et al., 2005; Fries et al., 2006; Wu et al., 2013). IRT has been used by the NIH roadmap Patient-Reported Outcome Measurement Information System (PROMIS) initiative to improve assessment of patient-reported outcome measures by producing more relevant, lower-cost tools or measures with more precise and fewer/efficient items for measures of patient-reported outcome assessments (Fries et al., 2005; Fries et al., 2006).

12.13 Significance Testing

While this study is not designed to test the impact of study interventions, mixed effects models will be implemented to determine the associations between variables of interest. Since this testing is not of primary interest, there will be no adjustment for multiple comparisons, and all two-sided tests will be conducted at the 5% significance level.

12.14 Missing Data and Dropouts

The extent and frequency of missing data and the number of cases with missing data may be examined to determine whether the data were missing at random. A multiple imputation approach to the missing data may be considered. The imputed data can be used in the analysis comparing with results based on complete data. The survey is a cross-sectional survey. There is no concern about study dropouts.

12.15 Interim analyses

No interim looks at primary or secondary outcomes are planned for this study.

12.16 Demographic and Baseline Characteristics

Demographic and pharmacy (facility) characteristics will be collected for all aims. Participants' baseline demographics and characteristics will be presented using summary statistics. Descriptive summaries of the distribution of continuous variables will be presented with mean and standard deviation. Categorical variables will be summarized in terms of frequencies/counts and percentages. Sex, race and ethnicity, per NIH requirements, will be explored regarding their impact on the various outcomes.

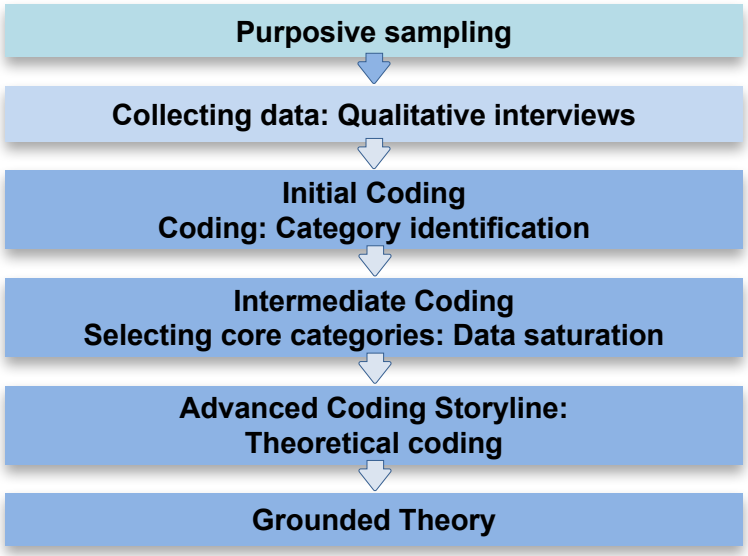
12.17 Safety Analysis

Not applicable.

12.18 Qualitative Data Analysis

Each semi-structured qualitative interview will be audio-recorded, transcribed verbatim, and reviewed for accuracy (e.g., transcription errors) before conducting the analysis. A computer-assisted qualitative data analysis software (e.g., NVivo) will be used to facilitate the qualitative data analysis (Leech & Onwuegbuzie, 2011; Wong, 2008: Woods et al., 2016). We will use the grounded theory as a framework to guide the coding of the data for the identification of key themes of barriers and facilitators of pharmacist- provided patient care for SRT and MOUD (Chun Tie et al., 2019; Saldaña, 2013). The grounded theory can be considered a method of conducting qualitative research that focuses on creating conceptual frameworks or theories through building inductive analysis from the data (Charmaz, 2005) as well as a process by which theory is generated from the analysis of data (Birks and Mills, 2015). **Figure 3** summarizes the grounded theory framework for the qualitative data analysis (Chun Tie et al., 2019).

Figure 3. The grounded theory framework for the qualitative data analysis



The analysis will consist of several steps. First, two research team members (coders) will independently evaluate the transcripts to identify emerging codes and themes based on our conceptual model of the Theory of Planned Behavior and relevant studies used to help understand pharmacist-provided patient care and services for SRT and MOUD (see Section 6.2). The processes of coding will follow the principles described by the coding manual for qualitative researchers (Chun Tie et al., 2019; Ryan & Bernard 2003; Saldaña, 2013). Second, coders will review the coding and add child codes (subthemes) to provide more detailed explanations for each of the codes (constructs) identified from the initial coding to further understand the

meaning of each of these codes (constructs) within the context of this study. Coders will review and discuss coding results to resolve discrepancies. Third, another research team member will independently review all codes (including child codes) to determine the suitability of the assigned codes to each of the constructs and identify potential issues and questions for further evaluation. Finally, coders and other investigative team member(s) will review the coding and resultant themes and meet together to iteratively discuss initial coding, refine coding categories, resolve discrepancies, and reach consensus (i.e., themes are all appropriately coded and in line with the constructs) (Saldaña, 2013).

13.0 REGULATORY COMPLIANCE AND SAFETY

13.1 Regulatory Compliance

This study will be conducted in accordance with the current version of the protocol, in full conformity with the ethical principles outlined in the Declaration of Helsinki, the Regulations for the Protection of Human Subjects codified in the International Council for Harmonization Good Clinical Practice (GCP) Guidelines, and all other applicable regulatory requirements. An Operations Manual will be provided as a reference guide and study quality assurance tool.

13.2 Statement of Compliance

This trial will be conducted in compliance with the appropriate protocol, current Good Clinical Practice (GCP), the principles of the Declaration of Helsinki, and all other applicable regulatory requirements. Participating sites must obtain written approval of the study protocol, consent form, other supporting documents, and any advertising for participant recruitment from the Institutional Review Board (IRB) of record in order to participate in the study. Prior to study initiation, the protocol and the informed consent documents will be reviewed and approved by an appropriate Ethics Review Committee (ERC) or IRB. Any amendments to the protocol or consent materials must be approved before they are implemented. Unanticipated problems involving risk to study participants will be promptly reported to and reviewed by the IRB of record, according to its usual procedures.

13.2.1 Health Insurance Portability and Accountability Act (HIPAA)

Not applicable**.** This study will not access or collect participants' personal medical record data. It will assess only self-reported information related mainly to individual perception, attitude, past experience/practice, knowledge, and intention to practice patient care related to SRT and MOUD.

13.2.2 Participant and Data Confidentiality

Confidentiality will be maintained in accordance with all applicable federal regulations and/or state/ Commonwealth law and regulations. By signing the protocol signature page, the investigator affirms that information furnished to the investigator by NIDA will be maintained in confidence and such information will be divulged to the IRB/Privacy Board, Ethical Review Committee, or similar expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees.

To further protect the privacy of study participants, the lead investigator will obtain a federal Certificate of Confidentiality (CoC) from NIH (or the FDA, if the study is operating under the agency's authority), which protects identifiable research information from forced disclosure, and will distribute it to all sites when received. This protects participants against disclosure of sensitive information (e.g., drug use). The CoC allows the investigator and others who have access to research records to permanently refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level, excepting certain circumstances.

By protecting researchers and institutions from being compelled to disclose information that would identify research participants, the Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants. The NIH office that issues the CoC will be advised of changes in the CoC application information. Participating sites will be notified if CoC revision is necessary. Participant records will be held confidential by the use of study codes for identifying participants on CRFs, secure storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data.

13.2.3 Investigator Assurances

Duke University Health System has committed to uphold regulatory and ethical standards through a Federal-Wide Assurance, FWA00009025, issued by the federal Office for Human Research Protections (OHRP). Research covered by these regulations cannot proceed in any manner prior to NIDA receipt of certification that the research has been reviewed and approved by the IRB provided for in the assurance (45 CFR 46.103(b) and (f)). Prior to initiating the study, the principal investigator will sign a protocol signature page, providing assurances that the study will be performed according to the standards stipulated therein.

13.2.4 Financial Disclosure

All investigators will comply with the requirements of 42 CFR Part 50, Subpart F to ensure that the design, conduct, and reporting of the research will not be biased by any conflicting financial interest. Everyone with decision-making responsibilities regarding the protocol will have an up-to-date signed financial disclosure form on file with the sponsor.

13.2.5 Inclusion of Women and Minorities

Women and minorities will be recruited to participate in the stakeholder interviews and the survey study.

13.2.6 Regulatory Files

The regulatory files should contain all required regulatory documents, study-specific documents, and all important communications. Regulatory files will be checked at each participating site for regulatory compliance prior to study initiation, throughout the study, as well as at the study closure. Regulatory files will be maintained at Duke University according to the policies set forth by the Duke Office of Clinical Research (DOCR).

13.2.7 Records Retention and Requirements

Study records will be maintained at Duke University according to the university records retention policy. All records relating to this study will be retained for **6 years** after completion of the research and will fulfill the Duke University Health System IRB's record retention requirements. The 6-year time period begins when the individual institution's engagement in the human subject research activity ends.

13.2.8 Audits

No audits of this work are planned. However, this research is subject to review and oversight by Duke University Health System and the NIDA Center for Clinical Trials Network (CCTN) and may be subject to an audit from these at any time.

The Sponsor has an obligation to ensure that this study is conducted according to good research practice guidelines and may perform quality assurance audits for protocol compliance. The Lead Investigator and authorized staff from the CTN Mid-Southern Node; the National Institute on Drug Abuse Clinical Trials Network (NIDA CTN, the study sponsor); NIDA's contracted agents, monitors or auditors; and other agencies such as the Department of Health and Human Services (HHS), the Office for Human Research Protection (OHRP) and the Institutional Review Board of record may inspect research records for verification of data, compliance with federal guidelines on human participant research, and to assess participant safety."

13.2.9 Reporting to Sponsor

This research is funded by NIDA CCTN and will be regularly reported to NIDA CCTN. In addition, under the Mid-Southern Node Cooperative Agreement, NIDA staff will participate in the conduct of this research.

13.2.10 Informed Consent

A waiver of documentation of consent will be requested for the pilot test, survey, and the qualitative interview. In accordance with applicable federal regulations (45 CFR 46.116(d)), the study IRB is expected to waive the requirement to obtain informed consent for the following reasons:

- The research involves no more than minimal risk to the subjects (i.e., a survey of knowledge, attitudes, beliefs, and practice/intention to practice);
- The waiver or alteration will not adversely affect the rights and welfare of the subjects; and
- Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

This study does not preempt any applicable federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective. It is in conformance with 42 CFR 2.52, which allows for research-related provisions with regard to the disclosure of substance use disorder patient identifying information in the absence of the informed consent process and HIPAA authorization.

For the survey, an electronic online survey (via URL links embedded in an email's text or text messaging) with an electronic consent (**e-Consent**) process will be implemented in the survey tool where the respondent acknowledges that he/she has (1) read, understood and had the opportunity to ask questions about the study, and that by completing the survey he/she is (2) consenting to participate. The respondent will also be able to print a copy of the electronic consent for his/her files. For non-respondents and those without an email or, mailed surveys (postal mail) and phone (or virtual, web-based) interviews will be implemented to increase the response rate. An **IRB-approved Script** for the survey will be used by research staff to obtain the participant's consent for participating in the survey over the phone or web- based call where the participant acknowledges that he/she has (1) understood and had the opportunity to ask questions about the study, and that he/she is (2) consenting to participate in the survey. The participant will also be able to obtain a copy of the IRB-approved Script (via email or postal mail) for his/her records.

13.2.11 Clinical Monitoring

Not applicable. The survey is a one-time, cross-sectional survey. There is no follow-up assessment.

13.2.12 Study Documentation

The conduct of this study will be documented in the Duke University regulatory files. Versions of the data throughout the study including sponsor-investigator correspondence and signed protocol and amendments, IRB correspondence and approved consent form, will be retained and archived by the study team according to university policy.

Each participating site will maintain appropriate study documentation (including research records) for this study, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants. Study documentation includes all case report forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence, and signed protocol and amendments, Ethics Review Committee or Institutional Review Board correspondence and approved consent form and signed participant consent forms. As part of participating in a NIDA- sponsored study, each site will permit authorized representatives from NIDA and regulatory agencies to examine (and when permitted by law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

Source documents include all recordings of observations or notations of research activities and all reports and records necessary for the evaluation and reconstruction of the research study. Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

13.3 Protocol Deviations

Any departure from procedures and requirements outlined in the protocol will be classified as either a major or minor protocol deviation. The difference between a major and minor protocol deviation has to do with the seriousness of the event and the corrective action required. A minor protocol deviation is considered an action (or inaction) that by itself is not likely to affect the scientific soundness of the investigation or seriously affect the safety, rights, or welfare of a study participant. Major protocol deviations are departures that may compromise the participant safety, participant rights, inclusion/exclusion criteria or the integrity of study data and could be cause for corrective actions if not rectified or prevented from re-occurrence. The Lead Node will be responsible for developing corrective action plans for both major and minor deviations as appropriate. Those corrective action plans may be reviewed/approved by the Duke IRB as appropriate. All protocol deviations will be monitored at the study site for (1) significance, (2) frequency, and (3) impact on the study objectives, to ensure that site performance does not compromise the integrity of the study.

All protocol deviations will be recorded by research staff. The DSC and the Lead Investigator must be contacted immediately if an unqualified or ineligible participant is enrolled into the study.

Additionally, the study site is responsible for reviewing the IRB of record's definition of a protocol deviation or violation and understanding which events need to be reported. The study site (Duke University) must recognize that the CTN and IRB definition of a reportable event may differ and act accordingly in following all reporting requirements for both entities."

13.4 Safety Monitoring

Not applicable. The study is a survey of knowledge, attitudes, beliefs, and practice/intention to practice. There is no study intervention. Safety risk, including loss of confidentiality, is minimal. Thus, formal monitoring is not warranted. Efforts for protecting participant and data confidentiality are discussed in section 13.2.2.

13.4.1 Data and Safety Monitoring Board (DSMB)

There will not be a DSMB for this study. This study does not involve any study intervention (i.e., no study intervention related safety and efficacy data).

14.0 DATA MANAGEMENT AND PROCEDURES

14.1 Design and Development

This protocol will utilize a centralized Data and Statistics Center (DSC). The DSC will be responsible for development of the electronic case report forms (eCRFs), development and validation of the clinical study database, ensuring data integrity, and training site and participating node staff on applicable data management procedures. A web-based distributed electronic data capture (EDC) data entry system will be implemented. This system will be developed to ensure that guidelines and regulations surrounding the use of computerized systems used in clinical trials are upheld. The remainder of this section provides an overview of the data management plan associated with this protocol.

14.2 Site Responsibilities

The data management responsibilities of each individual site will be specified by the DSC and outlined in user's guides.

14.3 Data Center Responsibilities

The DSC will 1) develop a data management plan and will conduct data management activities in accordance with that plan, 2) provide final guided source documents and eCRFs for the collection of all data collected by DSC (i.e., the survey), 3) develop data dictionaries for the eCRF, which will comprehensively define each data element, 4) conduct ongoing data monitoring activities on study data,

5) monitor any preliminary analysis data cleaning activities as needed, and 6) monitor final study data cleaning to the extent possible in Qualtrics. Specifically, survey data provided through Qualtrics will only be monitored for completeness.

The study team and DSC will work together to identify or create the interview and survey questions. Validation data quality checks are available for the end-user and include: range checks for date, time and numeric fields; and skip logic that prevents entry of data determined to be not required by the "rules" as defined in the eCRFs. The DSC will program, test and administer the interviews and surveys and collect the data. This includes sending reminders and tracking and reporting of response rates, follow-up with, and eventual replacement of non-responders. The DSC is not involved in data collection for the qualitative interviews.

14.4 Data Collection

The data collection process consists of direct data entry by the participants into the EDC system implemented by the DSC or data entry by research staff (as needed). Data entry by research staff will be implemented when participants complete the interview or survey via phone/WebEx/Zoom interviews by research staff or when paper CRFs are used for the interview or survey. Research staff are responsible for maintaining accurate, complete and up-to-date records, and for ensuring the completion of the eCRFs for each research participant.

14.5 Data Acquisition and Entry

Online survey data will be entered by respondents into the DSC's EDC system. When phone/WebEx/Zoom interviews are conducted by research staff or when paper CRFs are used for data collection, research staff will enter the data into the EDC. Completed forms and electronic data will be entered into the EDC systems in accordance with user's guides and source document completion instructions. Only authorized individuals shall have access to eCRFs.

14.6 Data Editing

Data will be entered directly into the EDC system either by participants or research staff. The DSC will review data for completeness and may replace survey response if warranted.

14.7 Data Transfer/Lock

The Mid-Southern Node team will work collaboratively with the DSC on data analysis and completing the database lock. The DSC will “lock” the study database from further modification after the final survey completion. Data will be transmitted by the DSC to the NIDA central data repository, as requested by NIDA for storage and archive. Following the completion of the database lock, the Lead Investigator will receive a copy of the study data.

15.0 PUBLIC ACCESS AND DATA SHARING

This study will comply with the NIH Data Sharing Policy and Implementation Guidance (https://grants.nih.gov/grants/policy/data_sharing/data_sharing_guidance.htm) and the HEAL Public Access and Data Sharing Policy (https://www.nih.gov/research-training/medical-research-initiatives/heal- initiative/research/heal-public-access-data-sharing-policy). Investigators will also register and report results of the trial in ClinicalTrials.gov, consistent with the requirements of the Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration (https://grants.nih.gov/policy/clinical-trials/reporting/understanding/nih-policy.htm).

De-identified primary data from Aim 1 (main survey) will be available to the public in the NIDA Data Share repository, per NIDA CTN policy. For more details on data sharing please visit https://datashare.nida.nih.gov/.

The primary outcomes publication(s) will be included along with study underlying de-identified primary data in the data share repository, and it will also be deposited in PubMed Central http://www.pubmedcentral.nih.gov/ per NIH Policy (http://publicaccess.nih.gov/).

The planning, preparation, and submission of publications will follow the policies of the Publications Committee of the CTN. Considerations for ensuring confidentiality of any shared data are described in Section 13.

16.0 SIGNATURES

SPONSOR REPRESENTATIVE

Typed Name	Signature	Date

INVESTIGATOR(S)

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol and will only make changes in the protocol after notifying the sponsor except when necessary to protect the safety, rights, or welfare of participants.

I will ensure that the requirements relating to obtaining informed consent and institutional review board (IRB) review and approval in 45 CFR 46 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation, and to provide annual reports and a final report in accordance with 45 CFR 46.

I agree to maintain adequate and accurate records and to make those records available for inspection in accordance with 45 CFR 46.

I will ensure that an IRB that complies with the requirements of 45 CFR 46 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human participants and others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human participants.

I agree to personally conduct or supervise this investigation and to ensure that all associates, colleagues, and employees assisting in the conduct of this study are informed about their obligations in meeting these commitments.

Typed Name	Signature	Date

PRINCIPAL INVESTIGATOR

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APPENDIX: DATA AND SAFETY MONITORING PLAN (DSMP)

1.0 BRIEF STUDY OVERVIEW

This overall goal of this study is to investigate community pharmacists' knowledge of, attitudes about, and intention to provide patient care and services for Screening for substance misuse and referral to Treatment (SRT) for substance use disorders (SUDs) and Medication treatment for Opioid Use Disorders (MOUD). The findings from this study will identify specific barriers and facilitators related to pharmacist-provided services and patient care for SRT and MOUD. The findings will have important clinical and research implications, such as informing pharmacy-based study designs and trials (e.g., recruitment, engagement, implementation strategies, areas of SRT and MOUD services for improving clinical practice and research); providing baseline data for future directions for CTN and non-CTN studies; gauging training and educational needs for community pharmacists; and developing clinical models and strategies to enable effective community pharmacist-physician collaborative care models to enhance patient care and satisfaction, reduce cost, and improve physician well-being (i.e., value-based care).

2.0 OVERSIGHT OF CLINICAL RESPONSIBILITIES

A. *Lead Investigator*

Lead Investigator is responsible for study oversight, including ensuring human research subject protection by designating appropriately qualified, and trained research staff.

B. *CCC Safety Monitor/Medical Monitor*

Not applicable. This study is a one-time survey of pharmacists and involves no or minimal risk to the study participants. There will be no CCC safety/medical monitoring for this study. However, if any safety-related issues among participants arise during the trial, the NIDA CTN Clinical Coordinating Center's (CCC) safety/ medical monitors will be consulted.

Voluntary Regulatory Reporting in non-IND Trials:

Not applicable. This study is not a clinical trial. There is no study intervention.

C. *Data and Safety Monitoring Board (DSMB)*

Not applicable. There will not be a DSMB for this study based on input from the NIDA official. Lead Investigator is responsible for study oversight and ongoing monitoring of research conduct at the study site. Weekly project meetings (e.g., conference calls) will be used to monitor study progress, identify study related issues or challenges, and address any issue or challenge encountered. The Trial Progress Report produced by the DSC will be reviewed regularly at the regular project meeting/call in order to monitor and address issues related to recruitment, data quality, and other regulatory issues (as needed).

D. *Quality Assurance (QA) Monitoring*

The purpose of QA monitoring activities or visits is to assess compliance with the protocol, GCP requirements, and other applicable regulatory requirements, as well as to document the integrity of the study progress.

Quality Assurance (QA) monitoring will include two approaches. First, designated research personnel (project manager, research coordinator, or regulatory coordinator/monitor) will conduct ongoing monitoring activities (e.g., audits) to compare source documents to the data entered on the eCRF and evaluate other regulatory issues. Any discrepancies identified between the source document and the eCRF will be corrected by research staff. Such ongoing monitoring activities (e.g., audits) may take place weekly or biweekly during the data collection phase at Duke University's research office to provide continuous monitoring of the data quality and research ethics. Any data quality or regulatory issue identified will be addressed promptly by the

investigative team and reported to Duke IRB based on the Duke IRB policy and guidance.

Second, Lead Investigator and/or designated research personnel (e.g., project manager) will host QA visits for independent monitor(s) from Duke University's research unit based on the Duke University School of Medicine's research policy. During the QA visit, the investigative team will provide direct access to the research office, source data/documentation, and reports for the purpose of monitoring, auditing, or inspection by the monitors or regulatory authorities. Areas of particular concern will be the review of inclusion/exclusion criteria, participant Informed Consent Forms (if applicable), protocol adherence, IRB reviews and approvals, regulatory documents, participant records, and Lead Investigator supervision and involvement in the study. The monitors will interact with research staff to identify issues and request for additional research training as needed to enhance research quality. Following the visit, QA monitoring reports will be prepared and discussed with Lead Investigator and other research personnel. The investigative team will receive a copy of the final QA report for each visit.

E. *Management of Risks to Participants Confidentiality*

Confidentiality of participant records will be secured by the use of study codes for identifying participants on CRFs, and secure storage of any documents that have participant identifiers, as well as secure computing procedures for entering and transferring electronic data. The documents or logs linking the study codes with the study participant will be kept locked/securely stored separately from the study files. No identifying information will be disclosed in reports, publications, or presentations.

Information That Meets Reporting Requirements

The consent form will specifically state the types of information that are required for reporting and that the information will be reported as required.

Participant Protection

Trained research staff will evaluate all pertinent screening and assessments prior to participant enrollment to ensure that the participant is eligible and safe to enter the study.

Pregnancy

This study is limited to survey research and there is no study intervention (e.g., medication). Pregnancy will not affect inclusion criteria or study participation. No pregnancy data will be collected by this survey.

Study Specific Risks

This study is a one-time survey with no anticipated safety concern. However, there is a potential risk regarding participants' loss of privacy/confidentiality. Every effort will be made to keep the study information confidential. Lead Investigator and designated research staff will monitor the study progress for confidentiality protection and data integrity in collaboration with CTN DSC.

3.0 DATA MANAGEMENT PROCEDURES

This protocol will utilize a centralized Data and Statistics Center (DSC). A web-based distributed data entry model will be implemented. This electronic data capture (EDC) system will be developed to ensure that guidelines and regulations surrounding the use of computerized systems in clinical trials are upheld.

4.0 DATA AND STATISTICS CENTER RESPONSIBILITIES

For Aim 1, the DSC will: (1) develop and apply data management procedures to ensure the collection of accurate and good-quality data, (2) provide source documents and electronic Case Report Forms (eCRFs)

for the collection of all data required by the study, (3) develop data dictionaries for each eCRF that will comprehensively define each data element, (4) prepare instructions for the use of EDC and for the completion of eCRFs, (5) conduct ongoing monitoring activities on study data, and (6) perform minimal data cleaning activities prior to the final study database lock.

5.0 DATA COLLECTION AND ENTRY

Data will be collected for Aim 1 directly from the participant via direct data entry. In the event of using a phone or web-based (virtual) interview to collect data, research staff at the study site will record the data on source documents and enter into eCRFs, or will be collected via direct entry into the eCRF in the EDC. In the event of the participant completing the survey on paper CRFs (e.g., using a postal survey), research staff at the study site will enter the data into the eCRF in the EDC. Data will be entered into the EDC system in accordance with the instructions provided during protocol-specific training and guidelines established by the DSC. Data entry into the eCRFs is performed by authorized individuals. In some situations, data collected on source documents will not be entered into the EDC system, but when it is entered, it will follow the guidelines stated above. Lead Investigator and designated research staff are responsible for maintaining accurate, complete, and up-to-date research records.

6.0 DATA MONITORING, CLEANING AND EDITING

eCRFs will be monitored for completeness throughout the Aim 1 portion of the study. Due to the nature of this study, accuracy of data will not be monitored. Reports listing missing values and missing forms will be made available. These reports will be monitored regularly by the DSC. Designated research personnel from the investigative team at Duke University will conduct regular monitoring activities (e.g., audits) to compare source documents to the data entered on the eCRF and evaluate other regulatory issues. Any discrepancies identified between the source document and the eCRF will be corrected by research staff.

The study progress and data status reports, which provide information on items, such as recruitment, availability of primary outcome, regulatory status, and data quality, will be generated daily and posted to a secure website. These reports are available to Lead Investigator, research staff, DSC, and NIDA CCTN to monitor the study progress.

7.0 DATABASE LOCK AND TRANSFER

Study participant research data for Aim 1, which are for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the DSC. Individual participants and their research data will be identified by a unique study identification number; further, some identifiable data may be collected.

At the conclusion of data collection for the study, the DSC will perform final data cleaning activities and will “lock” the Aim 1 study database from further modification. The final raw datasets will be transferred to the Lead Investigator or designee. These datasets will also be provided to the NIDA CCTN-designated party for storage and archiving. De-identified versions of these datasets will be posted on the NIDA Data Share website.