Study Title: COAPS: Co-Use of Opioid Medications and Alcohol Prevention Study

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Co-Use of Opioid Medications and Alcohol Prevention Study (COAPS)

SPECIFIC AIMS

Co-use of alcohol and opioid medications can result in serious individual harm. Given alcohol and opioids act on μ-opioid receptors,[1] coinciding consumption potentiates their analgesic effects—producing severe respiratory depression, sedation[2-6] and heightened overdose risk.[7,8] Co-use of alcohol and opioids persists in the US notwithstanding these serious health/safety hazards. Although limited information is available within peer-reviewed literature,[9] large-scale system and clinical research have demonstrated 24-38% of those with alcohol use disorders also have an opioid use disorder,[10,11] with rates of past 30 day opioid medication misuse among those seeking alcohol treatment as high as 68%.[12] Also, half of those with binge alcohol use have past 30 day opioid medication misuse.[13] Our 3 recent studies in community pharmacies with patients receiving opioid medications provide further insight into co-use of alcohol and opioids. Community pharmacy is rapidly becoming recognized as a valuable setting to address opioid medication-related risk[14] given a multi-decade shift with pharmacists integrated into team-based care leading medication management.[15-22] In our first study, we screened 344 pharmacy patients receiving opioid prescriptions in 4 pharmacies (71% consent rate)—22.4% reported current risk drinking.[23] Our second study was a small-scale-clinical trial testing the *Brief Intervention-Medication Therapy Management* (BI-MTM) intervention among pharmacy patients with opioid medication misuse in 2 community pharmacies (N=32; 74% consent rate). BI-MTM showed significant improvements for mitigating opioid medication misuse, depression, and pain compared to control patients (Standard Medication Counseling [SMC]).[24] In this study—19% of participants reported current risk drinking at enrollment.[24] Finally, our third, recently completed study, screened patients in 19 community pharmacies at point-of-opioid-dispensing (94% consent rate).[25] Of the 1,523 patients screened—31% reported current risk drinking.[26] Given these patterns of co-use of alcohol and opioids medications—particularly in community pharmacy—we propose to adapt, manualize, and test the acceptability, feasibility, and preliminary efficacy of an *Alcohol-targeted* Brief Intervention-Medication Therapy Management (ABI-MTM) intervention with community pharmacy patients. ABI-MTM will be a pharmacy-based medication management intervention[27] combined with Screening, Brief Intervention, and Referral to Treatment[28-31] delivered as 1 session at point-of-dispensing with a 7-day telephone-based booster session. ABI-MTM will target: (1) alcohol use elimination during opioid treatment *OR* (2) non-opioid pain management substitution (in consultation with the prescriber). This study will accomplish 3 Specific Aims (SA):

SA1: Adapt/manualize an *Alcohol-targeted* Brief Intervention-Medication Therapy Management intervention. *Rationale*: BI-MTM was developed to address opioid medication misuse and comorbid health conditions (e.g., pain, mental health); yet, it was not designed for universal delivery to patients with active opioid prescriptions and concurrent alcohol use. *Approach*: We will utilize the ADAPT-ITT (Assessment, Decision, Administration, Production, Topical Experts, Integration, Training, and Testing)[32] framework to modify/manualize BI-MTM for delivery to community pharmacy patients with co-use of alcohol (both risk level and non-risk level alcohol use) and opioid medications (i.e., an *Alcohol-targeted* Brief Intervention-Medication Therapy Management or *ABI-MTM*). *Outcome*: Completion of SA1 will result in a manualized protocol for clinical trial evaluation.

SA2: Test the Feasibility, Acceptability, and Preliminary Efficacy of ABI-MTM for Community Pharmacy Patients with Concomitant Alcohol and Opioid Medication Use. *Rationale*: The extent to which ABI-MTM: is acceptable to patients, can be feasibly delivered in community pharmacy settings, and can mitigate co-use of alcohol and opioid medications is unknown. *Approach*: We will conduct a small-scale trial in 3 community pharmacies and enroll those with/without risk drinking, with a stratified randomization to ABI-MTM (1:1 ratio; risk use n=10; non-risk use n=10) or standard medication counseling (SMC; risk use n=10; non-risk use n=10). *Outcome 1*: Feasibility will be established through delivery of both ABI-MTM components to 85% of ABI-MTM recipients. *Outcome 2*: Acceptability will be demonstrated through qualitative interviews, patient satisfaction,[33,34] and participant retention (85%) at study completion. *Outcome 3*: Intent-to-treat analyses will show greater proportions of ABI-MTM recipients will eliminate co-use of alcohol (risk and non-risk alcohol use) and opioid medications compared to SMC assessed by Timeline Follow-Back and urine toxicology.[35-37] *Product*: Accomplishing SA2 demonstrates ABI-MTM is positioned for a subsequent fully-powered multisite randomized trial.

SA3: Identify Pharmacy System/Practice-Level Barriers and Facilitators for Universal Alcohol Screening/Intervention among Opioid Recipients. *Rationale:* The barriers/facilitators that may promote/impede adoption of universal alcohol screening/intervention at point of opioid medication dispensing are not known. *Approach*: Employing the Consolidated Framework for Implementation Research (CFIR)[38,39] and Organizational Readiness to Change Assessment (ORCA),[40] we will develop a mixed methods assessment guide to interview

pharmacy technicians (N=20), pharmacists (N=20), and corporate leaders (N=20).[41,42] Interviews will assess perceptions towards screening/intervention, internal organizational challenges, and processes related to ABI-MTM implementation for large-scale research/practice.[39] *Outcome*: Results will provide critical insights into strategies for executing a subsequent powered trial and possible future system/practice-level implementation.

RESEARCH STRATEGY

SIGNIFICANCE

Opioids, Co-Use with Alcohol, and How Much is Too Much

Notwithstanding important declines in opioid prescribing in recent years,[43] enough opioids were dispensed in 2018 to supply 51.4 prescriptions per 100 Americans, and 11% of US counties dispensed enough medication to supply every person with an opioid prescription.[44] This continued widespread use has perpetuated trends in opioid-related adverse events. Among the most severe repercussions of the continued epidemic include overdose, which in 2018, nearly 70% of the more than 67,000 fatal drug overdoses involved an opioid[45]—with emerging reports indicating spikes in opioid overdose in the face of the COVID-19 pandemic.[46] Among the significant risks for overdose that persist among those prescribed opioid medications is co-use of alcohol. This serious risk is based in both alcohol and opioids acting on μ-opioid receptors[1]—potentiating analgesic effects of these substances and producing possible severe respiratory depression, sedation,[2-6] and heightened overdose risk.[7,8] Previous research has documented more than 1 in 5 individuals with alcohol use disorders also have opioid use disorder (OUD)—with some studies showing as high as 2 in 5 having OUD.[10,11] Further, among those individuals seeking alcohol treatment, nearly 70% reported opioid medication misuse in the month before treatment initiation,[12] and half of those with binge alcohol use also report opioid medication misuse in the last month.[13] Combined use of alcohol and opioid medications is not only found among those with alcohol use disorder and aberrant opioid use patterns, such as misuse and OUD. Our research among community pharmacy patients has demonstrated co-use of alcohol and opioid medications is widespread, showing among patients filling opioid medications—approximately 20-30% have current high risk drinking.[24,25,47]

A most critical question is how much can a person drink while taking opioids and not face possible harmful effects. In working to answer this question, our team has not identified any empirical report, article, textbook, guideline, consensus statement, or other literature that indicates how much alcohol can be safely consumed by an individual while taking opioid medications for acute or chronic pain management. In contrast, our team found extensive literature to the *contrary*. Human lab studies clearly document respiratory and sedative effects alcohol and opioid medications,[48,49] with resultant overdose risk, as well as heightened abuse liability for co-use compared to alcohol or opioids used alone.[50] Labeling by the Food and Drug Administration of marketed formulations of opioid medications contain strong warnings advising against concomitant use of opioids and any other central nervous system depressants, *specifically citing alcohol*.[4-6,51] The Centers for Disease Control and Prevention clearly concludes: "*The risk of harm increases with the amount of alcohol consumed, but* ***there is no safe level of alcohol use for people using opioids***."[52] NIAAA's updated, *Helping Patients Who Drink Too Much, A Clinicians Guide*,[53] recommends for patients taking prescriptions that interact with alcohol, that these individuals abstain from alcohol or consume amounts of alcohol less than maximum daily/weekly limits compared to the general population. However, the Clinician's Guide does not *provide actual suggested quantity limits*. Taken collectively, these data underscore a marked need for interventions to address co-use of alcohol and opioids—particularly among community pharmacy patients—to prevent negative outcomes including overdose and use disorders. Thus, we seek to develop and test an intervention that targets overlapping use of alcohol (risk level use and non-risk level use) and opioid medications for delivery in community pharmacies.

Community Pharmacy to Address Co-Use of Alcohol and Opioid Medications

Community pharmacy is an underutilized resource and setting for identification and intervention to address co-use of alcohol and opioid medications. With prescribers reporting high levels of burden and burnout from the myriad of clinical duties,[54] the well-documented multiple physical/behavioral health problems among patients with pain/opioid misuse,[55-63] and the continued nationwide misuse of prescribed opioid medications (>9 million individuals annually)[64]— collaborating with auxiliary health care professionals to support opioid prescribing and patient management is *paramount.* As the last healthcare professional encountered before opioid dispensation, the pharmacist is critical in addressing risks of co-use of alcohol and opioids. Moreover, while pharmacists may benefit from training in psychotherapeutic or motivational approaches for alcohol treatment (as is provided in this project), they have unmatched training in drug-drug interactions, medication safety, and counseling in the safe/effective use of medications.[65] This study leverages and expands upon this specialized training to prevent a harmful medication interaction by providing needed prescriber support with a time critical intervention before opioid dispensation.

Community pharmacy locations; which include supermarket, chain, and independent settings; are primary locations where patients legally fill opioid prescriptions that are often taken concurrently with alcohol[24,25,47] or are misused by patients.[66,67] Community pharmacies are abundant nationally,[68] providing easy access for patients—including those in rural areas—creating a platform for population-level impact. Previous research has

shown patients are willing to receive behavioral health information from these professionals,[69] and *pharmacists are ranked among the top 2 most trusted professionals in the US*.[70] While some question if lack of private space to interact with patients may be a barrier to pharmacist engagement in behavioral health care with patients, m*ore than 40% of community pharmacies have been documented to have private counseling rooms (often used for counseling or vaccination administration) where pharmacists can discretely provide care and maintain confidentiality.*[71] Thus, these specialized service settings and professionals are positioned to make an unparalleled impact in identifying patients currently engaged in co-use of alcohol and opioid medications and aid them to eliminate alcohol consumption during opioid treatment OR substitute their opioid pain treatment (in consultation with their prescriber) with a non-opioid alternative. Yet, limitations for services to address co-use of alcohol and opioids is largely rooted in the lack of empirical evidence supporting interventions delivered in this setting as well as identifying pathways implementation.

INNOVATION

The primary innovation of this proposed study is that it establishes needed data for building a viable community pharmacy-based response to preventing opioid overdose and related adverse events through mitigating co-use of alcohol and opioid medications. To our knowledge, a pharmacist-led intervention does not exist to specifically target co-use of alcohol and opioid medications. This innovation precisely aligns with the *Pilot and Feasibility Studies in Preparation for Drug and Alcohol Abuse Prevention Trials* program announcement *(R34: PA-18-775)*:

> "*Both NIDA and NIAAA are interested in research on prevention strategies to address … alcohol use simultaneous with marijuana, prescription drug and opioid use, and illicit substances…This FOA encourages pilot and feasibility research on the following and related topics: Feasibility and pilot testing of screening and universal brief intervention models to prevent alcohol and drug use and misuse (including opioid misuse and opioid use disorder) for delivery in medical settings and the broader healthcare system (e.g., primary care, obstetrics and gynecology, pediatrics, adolescent medicine, pain and rehabilitation settings, and emergency departments).*"

We include community pharmacy among these vital health care settings. In addition to the topical alignment of addressing co-use of opioids and alcohol within the novel health care setting of community pharmacy, this study likewise brings a critical innovation of adapting a research-based prevention intervention targeting possible future system-level implementation. This innovation is also a key focus of PA-18-775*:*

> "*An important emphasis of NIDA's and NIAAA's prevention research programs is prevention services research, which includes questions pertaining to system- and organizational-level processes and mechanisms associated with … adaptation …[and]… implementation of empirically validated prevention interventions in community, practice and service systems. In preparation for large-scale prevention services and systems research projects, pilot studies often are needed to: empirically test and establish evidence for the feasibility and acceptability of intervention protocols…and implementation strategies…*"

APPROACH

Preliminary Studies

Given the important potential to address co-use of alcohol and opioid medications in community pharmacies, the currently proposed study builds upon critical preliminary data our team has previously established. These preliminary data support this work and answer 4 important questions posed as possible barriers. *Note to reviewers:* Please be aware that we will use two similar acronyms in this application: (1) *BI-MTM,* which represents Brief Intervention Medication Therapy Management and (2) *ABI-MTM,* which represents *Alcohol-targeted* Brief Intervention-Medication Therapy Management intervention. BI-MTM will be discussed in reference to our *previously tested* intervention that primarily targets misuse of opioid medications. ABI-MTM refers to the intervention that *will be brought forward* in this study that specifically targets the co-use of alcohol and prescription opioid medications.

- **Question 1:** An often questioned barrier to pharmacists engaging patients in behavioral health services is: "*Do pharmacists care about intervening with patients with risky opioid medication use behaviors*? We conducted a web-based survey of pharmacists in two states about routinely screening and possibly intervening with patients engaged in opioid medication misuse behaviors, which results are reported in 2 peer reviewed papers.[72,73] Of the 739 respondents, most (89.7%) wanted to help patients engaged in opioid medication misuse and related behaviors but reported needing training (81.1%) and resources (79.8%) to competently/effectively do so.[72,73]
- **Question 2:** Another questioned barrier to pharmacist engagement of patients regarding behavioral health is: *Is it feasible to identify patients at point-of-dispensing using opioid prescriptions and currently engaged in concomitant alcohol use?* Mentioned above, our team has conducted 3 studies in the previous 5 years with community pharmacy patients filling opioid medications, which results have been published in 8 peer reviewed papers,[23,24,74-79] with a number under review. In these studies, we collectively screened approximately

1,900 pharmacy patients filling opioid medications. Results showed approximately 20-30% of these patients reported current risk or binge drinking.[24,25,47]

Specifically, Table 1 shows the results for studies 1 and 2, which took place in southwestern Pennsylvania. In the first study, we collected Alcohol Use Disorders Identification Test-C (AUDIT-C) data from patients filling opioid medications in 4 community pharmacies, which showed 22.4% of 344 participants reported current risk alcohol use.[23] Furthermore, in study 2 (our small-scale RCT testing the BI-MTM intervention, detailed below in Questions 3 and 4) based on the AUDIT-C, 19% of 32 participants reported current risk drinking at baseline. Summarizing item level data across these two projects, 17.4% of participants reported drinking ≥2-3 times per week; 25.8% of participants reporting ≥3-4 standard drinks on their typical drinking days, and 17.2% reported binge drinking ≥monthly. Altogether, these results demonstrate participants in these studies engaged in regular, and often, risky drinking.

Table 1. Percentages of Patients Filling Opioid Medications in Study 1 (N=344) and 2 (N=32) with Drinking Behaviors

	Item	Study #	Never	<Monthly	2-4 times/ month	2-3 times/ week	>4 times/ week
AUDIT-C	How often drink alcohol	1	52.2	29.9	10.0	5.9	2.1
		2	46.9	28.1	15.6	9.4	0.0
	Standard drinks typical day		1-2	3-4	5-6	7-9	>10
		1	86.8	9.6	2.9	0.7	0.0
		2	37.5	6.3	6.3	0.0	0.0
	≥6 drinks on one occasion		Never	<Monthly	Monthly	Weekly	Daily/ almost daily
		1	61.4	24.5	9.2	3.7	1.2
		2	75.0	21.9	3.1	0.0	0.0

In our third study in Ohio and Indiana (recently completed), 31% of 1,523 participants filling opioid medications in community pharmacy reported current risk drinking on the Tobacco, Alcohol, Prescription medication, and other Substance use (TAPS) Tool.[26] Examining specific survey items, Table 2 shows 87.1% reported use of alcohol in the past 3-months, and 67.7% of males and 50.2% of females reported binge use in the last 3-months. Roughly 8-9% of participants had others express concern about their drinking or unsuccessfully had tried to stop/cut down in the last 3-months.

— **Questions 3 and 4:** An additional suggested barrier to pharmacist engagement of patients in behavioral health services is: *Can a pharmacy-centered intervention be adapted to address behavioral health issues among pharmacy patients and be implemented in community pharmacies AND would such an intervention successfully impact opioid-related risk behaviors?* Our research team held a 1-day session in which pharmacy and addiction experts strategized the adaptation of Screening, Brief Intervention, and Referral to Treatment (SBIRT) for opioid medication misuse among pharmacy patients, which results were reported in a peer-reviewed article.[80] Our expert panel advised that the pharmacist deliver SBIRT in conjunction with the evidence-based practice of Medication Therapy Management (MTM), targeting medication adherence/misuse. The expert panel also suggested enriching the pharmacist delivered SBIRT/MTM intervention with a Patient Navigation adjunctive intervention to activate patients in self-management of health conditions that elevate risk for misuse—this intervention was named: *BI-MTM*.

Table 2. Percentages of Patients Filling Opioid Medications in Study 3 (N=1523) with Drinking Behaviors

TAPS Tool	Past 3 mo use	87.1
	Past 3 mo male ≥5 drinks in a day	67.7
	Past 3 mo female ≥4 drinks in a day	50.2
	Past 3 mo others concered about use	8.3
	Past 3 mo tried/failed to control, cut down or stop use	9.3

We subsequently implemented the BI-MTM in a small-scale randomized clinical trial (RCT, PI: Cochran, NIDA: R21DA043735) that compared BI-MTM (n=15) to Standard Medication Counseling (SMC; n=17). We published our findings, which demonstrated feasibility with a 74% recruitment rate and >93% retention at the final assessment (3-months).[24] BI-MTM feasibility was demonstrated by delivery of all pharmacist-led sessions and an average of 7 of 8 patient navigation sessions. BI-MTM acceptability was exhibited by high participant satisfaction ratings for pharmacist and patient navigation sessions. Study results at the final 3-month assessment showed preliminary BI-MTM efficacy for positive improvements in opioid misuse, depression, and pain compared to SMC (all $p<0.05$)—with strong trends for reductions in opiate toxicology ($p=0.05$).[24]

We acknowledge only this pilot study for BI-MTM has been completed—with strong preliminary data cited above. Nevertheless, this current application is the product of urgency in the field, documented by 3 clinical studies from our research team (also cited above) conducted in 3 separate states across 5 years. These preliminary studies each has shown similar high rates of risky drinking among patients receiving opioid medications. Considering this exigency combined with the robust premise of our research program in community pharmacy addressing opioid misuse, our team has brought forth this application as a strong candidate to address this serious risk behavior of co-use of alcohol and opioids.

Overall, these preliminary studies show pharmacists are interested in engaging patients with opioid related-risk behaviors; patients with co-use of alcohol and opioid medications are prevalent and can be identified

at point-of-dispensing; and an intervention can be adapted/implemented and possesses preliminary evidence for patient benefit. *The currently proposed study will advance the field by (1) adapting/manualizing an Alcohol-targeted Brief Intervention-Medication Therapy Management intervention, i.e., ABI-MTM, (2) testing ABI-MTM feasibility/acceptability and examining preliminary efficacy for eliminating concomitant alcohol use during opioid treatment, and (3) identifying facilitators and barriers for large-scale research and practice implementation.*

Project Investigators

Principal Investigator: *Gerald Cochran, MSW, PhD*, is an Associate Professor of Internal Medicine and Psychiatry at the University of Utah. Dr. Cochran is an expert in evaluation of evidence-based practices for addressing behavioral health conditions and outcomes. He has published more than 80 peer-reviewed articles, with the majority related to monitoring/treatment of opioid and other substance misuse/use disorders—including risk/binge alcohol use. He has extensive knowledge of brief alcohol interventions delivered in health care settings and extensive experience in analysis thereof. He is the Multiple PI of the NIDA Clinical Trials Network Greater Intermountain Node and has extensive experience in the management/conduct of multisite trials. He was PI on the above discussed preliminary studies (and related grants) and is first author on the related publications. Dr. Cochran will be responsible for all aspects of this project. *Multiple Principal Investigator*: *Alina Cernasev, PharmD, PhD*, is an Assistant Professor of Pharmacy at University of Tennessee. Dr. Cernasev possesses doctorate degrees in clinical pharmacy and social and administrative pharmacy, with *specialization in qualitative methodology*. Dr. Cernasev will work closely with Dr. Cochran in day-to-day management of Tennessee study staff, training, data collection, intervention delivery, session fidelity, and reporting. Dr. Cernasev will also be charged with leading SA3, in collaboration with Drs. Cochran and Ken Hohmeier (coinvestigator, see below).

Coinvestigators: Adam Gordon, MD, MPH, is a Professor of Medicine at the University of Utah School of Medicine and the Section Chief of Addiction Medicine at the Salt Lake VA Healthcare System. Dr. Gordon is the PI of the NIDA Clinical Trials Network Greater Intermountain Node. He is *board-certified in internal medicine and addiction medicine* and is an *expert in implementation science*. Dr. Gordon will provide expertise in high risk opioid use, implementation science, and will assist in interpretation of findings and publications. *Dr. Ken Hohmeier, PharmD* is an Associate Professor and Director of Community Affairs for Clinical Pharmacy at University of Tennessee. Dr. Hohmeier's *expertise is in pharmacy management/operations, medication therapy management (a critical component of the ABI-MTM intervention), and pharmacist training/education*. As Director of Community Affairs, he manages relationships with 90 community pharmacy practice locations in state. In this study, Dr. Hohmeier will provide community pharmacy practice expertise, aid in management of the clinical pharmacy sites, and session fidelity review. He will also aid in the intervention protocol manualization. *Ralph Tarter, PhD* is psychologist and Professor of Pharmacy, Psychiatry, and Clinical & Translational Sciences at the University of Pittsburgh. Dr. Tarter has a long history of NIH funded substance use research—including center grants, large-scale investigator-initiated awards, and career development. Dr. Tarter has been a long-time coinvestigator with Dr. Cochran on the above-mentioned preliminary studies (~10 years). Dr. Tarter is an *expert in measurement of substance use and related behaviors* and will continue work with Dr. Cochran on outcome assessment and data analysis/interpretation. *Craig Field, PhD* is an Associate Professor at the University of Texas, El Paso and a clinical psychologist. Dr. Field is an *expert* in *SBIRT for alcohol use* and has been PI and Co-PI on a number of NIH funded large-scale studies testing these interventions. He is the director of the Latino Alcohol & Health Disparities Research Center. He has been coinvestigator with Drs. Cochran, Gordon, and Tarter on several of the studies preliminary to the current application. He will provide extensive expertise to the team regarding brief alcohol interventions. *It is important to note, Dr. Cochran has a number of current and past collaborations with the investigators from this team, which require(d) regular/frequent team meetings and communication. Dr. Cochran has published with Drs. Tarter, Gordon, Field, or Hohmeier more than 40 articles combined and with Drs. Tarter and Gordon has received more than a dozen foundation or federally funded research grants.* Dr. Cochran had recently began a close collaboration with Dr. Cernasev, which since September 2020 they have coauthored two papers (along with Dr. Hohmeier)[81,82] and have submitted 1 grant (not including the current application) regarding opioid harm reduction in community pharmacy.

SA1: Adapt and manualize an *Alcohol-targeted* Brief Intervention-Medication Therapy Management intervention.

Rationale. While the BI-MTM intervention, as cited above, has demonstrated promising outcomes for mitigating opioid medication misuse, depression, and pain; it was not specially tooled for targeting co-use of alcohol and opioids. We will thus systematically adapt BI-MTM to eliminate alcohol use during opioid treatment OR to facilitate non-opioid substitution for pain treatment by creating an *Alcohol-targeted Brief Intervention-Medication Therapy Management intervention (ABI-MTM)*, which will leverage and expand upon the unique expertise of the community pharmacist in preventing harmful medication interactions. To do so, we will employ the ADAPT-ITT framework (Assessment, Decision, Administration, Production, Topical Experts, Integration, Training, and Testing).[32] ADAPT-ITT is a framework originally designed for adapting evidence-based HIV interventions. Given the epidemiological nature and health concerns associated with the opioid epidemic and risks associated with co-use of alcohol, ADAPT-ITT is a highly appropriate framework to guide the modification of this intervention.

Drs. Cochran (project PI), Tarter, and Gordon (project coinvestigators) have successfully employed the ADAPT-ITT model in previous collaborations for adapting evidence based interventions,[80,83] which interventions have been successfully funded for testing in separate clinical trials on which Dr. Cochran was PI and Drs. Tarter and Gordon were coinvestigators (NIDA: R21DA043735; CDC: R01CE002996).

Methods. The following points outline how we will adapt the BI-MTM model to address co-use of alcohol and opioid medications using the ADAP-ITT framework.

- *Assessment*: Dr. Cochran will provide written materials on the etiology, epidemiology, pharmacology, and ways to address co-use of alcohol and opioids to the project expert panel and project investigators with the assignment to read and mark up the materials. The expert panel will consist of 4 individuals, including:
  - Michael Moss, MD, Assistant Professor and Medical Director of the Utah Poison Control Center. He is also a practicing emergency physician, Data 2000 waivered, and active care provider in the U of U emergency department opioid use disorder bridge clinic. Expertise: Pharmacology/toxicology of opioids.
  - Katie Witkiewitz, PhD, Professor and Director of the University of New Mexico Addictive Behaviors and Quantitative Research Lab. She is a licensed clinical psychologist in New Mexico. Expertise: Co-use of alcohol and opioid medications.
  - Kenneth E. Leonard, PhD, Professor and Director of the University of Buffalo Clinical and Research Institute on Addictions. Expertise: Co-use of alcohol and opioid medications.
  - Maureen Reynolds, PhD, Research Assistant Professor of Pharmaceutical Sciences at the University of Pittsburgh. Expertise: Pharmacist delivery of screening, brief intervention, and referral to treatment.

Completing materials review, the panel and project investigators will attend a full-day (6 hrs.) recorded web-conference where: (1) Dr. Moss will present on critical aspects of human pharmacology of alcohol and opioid medication use; (2) Dr. Cochran (project PI) will present on clinical characteristics of those who misuse opioids and previous research on the BI-MTM intervention; and (3) Dr. Witkiewitz will present on epidemiology and clinical implications of co-use of alcohol and opioid medications. The assessment phase of the meeting will also involve panel members and project investigators providing brief verbal summaries of their assigned reading materials to one another within the group.

- *Decision*: Following the presentation and summaries, the web-conference will involve Dr. Cochran facilitating a roundtable discussion, eliciting comments and dialog regarding needed intervention modification, and components needed for inclusion. This portion will specifically plan how pharmacists will facilitate referral for high needs patients (e.g., substance use or mental health disorders). Dr. Cochran will also provide information from his previous work regarding warm handoff for high needs patients. A rich literature shows warm-handoff is an evidence-based method for connecting individuals with substance use needs, including opioid use, to treatment.[84-88]
- *Administration*: Dr. Cochran will instruct the meeting participants to provide specific recommendations on how to incorporate the identified components into the intervention that will result in an alcohol targeted intervention for pharmacy patients with co-use of alcohol and opioid medications.
- *Production*: Concluding the web conference, Dr. Cochran will request handwritten notes and comments recorded during the Decision phase. Once received, Dr. Cochran will incorporate the identified components into the intervention materials/manual.
- *Topical Experts*: The adapted intervention manual will be circulated to the project coinvestigators and expert panel for review and comment.
- *Integration*: Comments and edits from the review will be returned to Dr. Cochran for finalization and incorporation into the intervention materials/manual.
- *Training*: Dr. Cochran will work with Dr. Hohmeier, coinvestigator, (given Dr. Hohmeier's expertise in training/education of pharmacists, see investigator section) to author training/instructions for delivery of the adapted intervention.
- *Testing*: The alcohol adapted intervention will be included within the pilot RCT materials, and co-use of alcohol and opioid medications outcomes will be assessed at baseline, 2, and 3 months post-delivery (see SA2).

Product: Completion of SA1 will result in an adapted/manualized protocol ready for trial evaluation.

SA2: Test the Feasibility, Acceptability, and Preliminary Efficacy of ABI-MTM for Community Pharmacy Patients with Concomitant Alcohol and Opioid Medication Use.

SA2 Rationale. Possessing the manualized ABI-MTM intervention, it is paramount to assess ABI-MTM's feasibility for delivery in community pharmacy; whether patients will find the intervention acceptable, and if it will produce a preliminary clinical effect resulting in elimination of co-use of alcohol. Such a preparatory step is critical to demonstrate if ABI-MTM is adequately prepared for subsequent testing within a larger multi-site framework and possible eventual system-wide implementation.

SA2 design and participant identification. We will conduct a small-scale single-blinded 2-group RCT (staff administering data collection will be blinded to intervention condition) within 3 Kroger community pharmacy locations in the greater Nashville area (2 in metro areas and 1 in a rural location; see Kroger letter of support). The rationale for RCT implementation in this location was based on its high rate of opioid overdose rates, high

prescribing rates,[89] and high alcohol consumption compared to other states, which alcohol consumption results in the state's status among the top 15 in the US for alcohol related drunk driving deaths[90] and the state being among the top alcohol-attributable death states in the US.[91]

The Kroger pharmacies selected provide a full complement of pharmacy services that attract a highly diverse patient population within local communities. Study pharmacists or technicians trained in the screening protocol will approach patients dropping off/picking up opioid prescriptions at the counter and ask if they are interested in taking a brief confidential electronic tablet-based health screening (<5 minutes), with the opportunity of compensation up to $240 if they qualify and enroll in the study. In our small-scale study of BI-MTM, we successfully engaged 81% of patients at point of service who presented at the community pharmacies picking up medications as well as health plan members who received a study advertisement and came to the pharmacy. Patients approached will be asked on a tablet to verify they are English speaking, ≥18 years, and not receiving cancer treatment.

Patients fitting these criteria will move on to being screened for eligibility for receiving ABI-MTM. As stated above, given that no scenarios exist where co-use of alcohol and opioids would be advisably safe, we will target delivery of the intervention to all patients with overlapping use—both those with risk and non-risk alcohol use. Risk drinking will be operationalized by a score of ≥4 or in men and ≥3 or more in women using the valid/reliable the AUDIT-C.[37,92] Screening will include administration of 5 questions: the 3 items from the AUDIT-C, 1 item inquiring when the patient last consumed alcohol, and 1 item inquiring days supply and refills available. Self-reported alcohol consumption patterns rather than biochemical testing was selected given biochemical testing of alcohol use currently has a limited window of detection that could unnecessarily exclude patients who would be eligible for intervention receipt.

The decision flow diagram depicted in Figure 1 will be used to determine ABI-MTM eligibility. The first question will be from the AUDIT-C, item 1: "*How often do you have a drink containing alcohol?*" Responses of ≥2-4 times per month indicate eligibility for ABI-MTM—given participants drinking patterns will likely overlap with any opioid medication regimen prescribed to them. A response of ≤monthly drinking will trigger the second question: "*When was your last drink?*" Alcohol consumption ≥7 days ago indicates eligibility for ABI-MTM—given that participants' regular drinking pattern could overlap with the current opioid medication. Alcohol consumption of <7 days will trigger the third question: "*How many days of supply and numbers of refills do you have of your current opioid medication*? We will use this question instead of relying on the Kroger medication record given the patient may have prescriptions outside of Kroger. Reponses of ≥7 days current supply indicate eligibility for ABI-MTM given that patients' regular drinking patterns in the month and their medication supply will likely overlap.

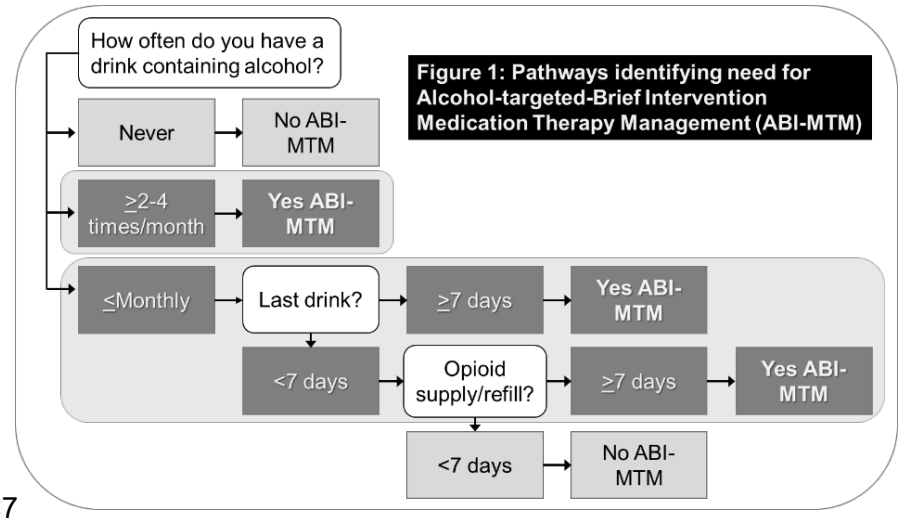

Figure 1: Pathways identifying need for Alcohol-targeted-Brief Intervention Medication Therapy Management (ABI-MTM)

***SA2 inclusion/exclusion criteria*.** Patients eligible for ABI-MTM aged ≥18 will be offered the opportunity to learn about the study. Patients will be excluded if they: (1) are pregnant (given potential complications associated with pre-natal opioid use[93-97] and/or alcohol use[98]), (2) cannot provide collateral contact information for ≥2 persons (to ensure consistent contact/follow up), (3) do not have a reliable landline or mobile phone to be contacted by study staff, (4) are filling *only* buprenorphine (given some formulations are not indicated for pain), (5) plan to leave the area for an extended period of time in the next 3-months, or (6) have experienced a psychotic and/or manic episode in the last 30 days (before consent, patients will be asked to screen for psychosis [psychosis subscale from the reliable/valid Behavior and Symptom Identification Scale[99]] and mania [from the reliable/valid Altman Self-Rating Mania Scale[100]]). We will *not* exclude patients with severe substance use problems given ABI-MTM will possess the capacity to refer and follow up on patient engagement in substance use treatment. Patients excluded will be given educational information about co-use of alcohol and opioid medications, and research assistants will aid them to seek additional care if desired. Patients not interested or not co-use positive will be rescreened on subsequent visits. Patients positive for co-use, who are interested/eligible, will be asked to provide written informed consent to participate.

SA2 recruitment feasibility, randomization, sample size, and justification. It is important to note, in order to enroll an equal number of participants engaged in risk drinking (n=20) and non-risk drinking (n=20), we will sample those with risk and non-risk drinking at a ratio of 1:1. Noted above, our previous research has shown that approximately 20-30% of pharmacy patients filling opioid medications have risk use or binge drinking. To ensure risk and non-risk drinking status is not strongly collinear with enrollment time, enrollment during the study for the larger sample size group may be periodically/temporarily held until the smaller sample size group achieves an equal sample size, which would occur if the larger group has a sample size of more than 2 greater than the smaller sample size group. Once the 1:1 enrollment is met, full enrollment will proceed, with this process repeating until recruitment ends. Randomization will be stratified to ensure equal distribution of those with risk and non-risk drinking into treatment and control groups. Randomization will be generated via SAS PROC PLAN, with limited runs of 4 to condition assignment.

Table 3: Recruitment Projections	n [a]
Total needed to approach	338
Interested in screening (81%)	373
Screening eligible after anticipated exclusion (50%)	137
Not risk drinking (~ 80%)	110
Risk drinking (~ 20%)	27
Consented and randomized (74% of those with risk drinking + those with non-risk drinking)	40

[a] Rate estimates based on pilot study consort chart numbers.

Sample size will not be based on a power estimate. Rather, our sample size is based on our experience of how many patients can be screened and consented within the study timeframe.[101] Using consort chart data from our BI-MTM small scale study,[102] we present Table 3 that demonstrates our estimates of how many patients we anticipate needing to approach/screen to meet our recruitment target within our study time-line. Based on these data, we will need to approach 338 patients during the study recruitment phase. Of these, we anticipate 81% will be interested/available for screening, of whom approximately 50% will meet eligibility criteria (most patients will be ineligible because they will not have co-use of alcohol and opioid medications). From among the eligible patients who are positive for co-use of alcohol and opioid medications, we anticipate 27 will be positive for risk drinking, and 110 will be positive for non-risk drinking. We anticipate consenting 74% of those interested in participation and *eligible*—including consideration of our procedure mentioned above of 1:1 recruitment of individuals with risk/non-risk use—which will result in our final population to be randomized: N=40 (ABI-MTM: risk use n=10; non-risk use n=10; SMC: risk use n=10; non-risk use n=10). Randomization will be stratified by pharmacy site.

In terms of needed time to recruit our targeted patient population, based on our data from our recently completed research study (mentioned above) at 19 Kroger sites and based on our previous screening study and small scale study, we expect to approach 9 patients for recruitment monthly at each of our pharmacy locations.[23,25,102] With this rate and based on our procedure mentioned above of 1:1 recruitment of individuals with risk/non-risk alcohol use, study recruitment will require approximately 13-months to complete. We have chosen to focus recruitment at a limited number of sites (N=3) during feasibility/acceptability/preliminary efficacy testing to ensure internal validity of our procedures, limiting possible site variation, and limiting multisite challenges. During screening, we will capture sex, insurance status, and age for all eligible patients to assess basic demographic differences among those who participate versus those that do not.

While definitive estimation and hypothesis testing are not the aim of this study, the target sample size will allow estimation of odds ratios via 95% confidence intervals comparing outcome rates in the intervention and control arms, while accounting for within site clustering, with lower bounds differing from the odds ratio estimate by a factor of 1/3 to 1/2 and upper bounds differing from the odds ratio estimate by a factor of 2 to 3 for a broad range of overall rates, true odds ratios, and magnitude of site-to-site effects. In particular, this study will allow detection of strong signals of preliminary benefit and provide suggestions of benefit for more subtle signals.

SA2 treatment-as-usual and intervention conditions. *Standard Medication Counseling (SMC)* will be the treatment as usual condition in this study and was chosen/developed following Gold et al.'s guide for selecting control conditions in behavioral intervention studies.[103] For the first component, all SMC participants will receive a single 5-10 minute medication information/counseling session delivered by a Kroger pharmacist, other than the study pharmacist, that possesses a similar level of education and professional licensing. The content of this session follows federal and state pharmacy requirements[104,105] requiring pharmacists to: (1) offer counseling, (2) document counseling was offered, (3) offer a counseling process for patients not present (not applicable to this study given all patients must screen in person), and (4) discuss generic substitution.[104,106] Following this session, in the second SMC component, participants will be emailed/mailed (according to participant preference) safety information about co-use of alcohol and opioids. Pharmacists delivering SMC will be provided information quarterly to remind of practice standards for SMC service delivery by Dr. Hohmeir. SMC is specifically yoked in duration with ABI-MTM, totaling 2 participant contacts to control for attention bias in outcome assessment. It is important to note all study participants will receive SMC given state and federal requirements.

Alcohol Brief Intervention-Medication Therapy Management (ABI-MTM) will be the intervention condition adapted and prepared for utilization in this study. ABI-MTM sessions will be *set by appointment* between the pharmacist and the participant. The study pharmacist will possess a PharmD degree and be licensed. Study

pharmacist training will be led by Drs. Cochran, Cernasev, and Hohmeier. Training entails: the pharmacist pre-reading/studying the protocol followed by 2-days of motivational interviewing training *tailored* to the protocol, including lecture, group discussion, and observed role-plays (motivational interviewing training will provided in Nashville by Kali Worley, PhD, MA; a Nashville-based Motivational Interviewing Network of Trainers [MINT], trainer; see letter of support). Following in-person training, mock sessions are conducted/recorded and assessed using fidelity checklists. Drs. Cochran, Cernasev, Worley, and Hohmeier will adapt and prepare fidelity checklists, including a protocol adherence checklist and motivational interviewing scoring sheet, which will be modified from BI-MTM materials employed in the small-scale study cited above. The protocol adherence checklist will be reviewed and scored by Drs. Cochran, Cernasev, and Hohmeier, with the study pharmacist required to demonstrate ≥80% proficiency on the protocol checklist to be permitted to interact with study participants (80% being an acceptable level based on Dr. Cochran's previous experience training staff in similar interventions). For initial Motivational interviewing proficiency, Dr. Worley will code training sessions using the Motivational Interviewing Treatment Integrity Code (MITI 4)[107,108] and will ensure fair/basic competency on technical and relational global scores as well as complex reflections and ratio of reflections to questions.[107,108] Ongoing session fidelity will be monitored by review of session recordings (all pharmacist sessions will be audio recorded to ensure delivery and for fidelity review). With these recordings, each month, investigators and staff will (including Dr. Worley): (1) review randomly selected recorded sessions using the protocol checklist and MITI 4, (2) provide verbal/written feedback, and (3) participate in a group discussion.

While details regarding the various components, specific language, and materials of the intervention and its manual for delivery will be determined and produced as the primary outcome of SA1, the framework of the ABI-MTM intervention (similar to BI-MTM) will be based in MTM (i.e., medication therapy management) and SBIRT (i.e., screening brief intervention, and referral to treatment). *MTM* is an evidence-based intervention delivered in community pharmacy involving a brief session where medications are reviewed, and patients are assisted to resolve barriers to adherence. MTM has been documented to improve medication adherence.[27] While lack of payment has been cited as a possible barrier for many services in community pharmacy settings, *MTM is reimbursable by Medicare and several commercial insurance plans*.[109] A core goal of MTM is to empower patients in active medication self-management.[110,111] MTM in the current study will be based on the American Pharmacists Association and National Association of Chain Drug Stores Foundation service model, which includes 5 core elements.[112] A common duration for medication counseling in outpatient pharmacies a single 30-45 minute session;[113] we anticipate ABI-MTM session duration to be similar. Session 1 will be in-person; however, if in-person visits are not possible (e.g., COVID-19 restrictions), both sessions may occur telephonically.

- *Element 1* is a medication review. In this element, the pharmacist collects patient specific information related to the medication regimen and their health and prioritizes any identified problems.
- *Element 2* develops a personal medication record. In this element, the pharmacist and the patient develop a list of the medications the patient is taking. This list also documents patient and health care provider contact information, problematic interactions, allergies, review date, and medication details.
- *Element 3* produces a medication action plan. This plan includes steps the patient must take to improve medication self-management and their health.
- *Element 4* is the intervention and/or referral. This is where the pharmacist would employ SBIRT to work with the participant to either choose (1) to eliminate alcohol use during opioid therapy OR (2) to facilitate communication with the prescriber to select a non-opioid pain management alternative. SBIRT is an evidence-based practice for improving alcohol problems,[28-31] with demonstrated evidence from pharmacists and other providers for medication adherence improvement[114-118] and reductions in *problematic prescription opioid use*.[24,119-121] It is highly important to note that in the current application context, SBIRT targeting elimination of co-use of alcohol and opioids (i.e., alcohol use elimination during opioid treatment OR non-opioid pain management substitution) is designed to prevent related sequelae, i.e., possible overdose risk and use disorders. We do recognize, however, some participants may not choose the non-opioid pain treatment option and also be ambivalent about elimination of alcohol use. These participants will be encouraged to reduce alcohol use.
- *Element 5* includes documentation and follow up. Documentation includes the pharmacist recording notes/action items related to elements 1-4. The follow-up (booster session) portion includes scheduling a telephonic session 7 days following the initial visit, during which the pharmacist reviews commitments made during the initial session, works to resolve barriers, and provides additional referrals/resources.

SA2 assessment, follow up, and retention. Participants will be assessed at baseline, 2-months, and 3-months post-randomization at the Kroger community pharmacy settings or other appropriate locations. Participants will be compensated $40 for the baseline assessment, $50 for the 2-month, and $75 for the 3-month—with a $75 completion bonus for those completing all assessments. Research assistants will aid participants to complete self-administered portions of the questionnaires as necessary to prevent missing data and ensure accurate/completed assessments. Research assistants will also be trained to administer urine toxicology assessments to participants. Efforts to ensure continued participant contact include collecting locator information and at least 2 collateral contacts as well as sending letters and cards, electronic messages, and making phone

calls. Noted above, these retention methods were successful in the BI-MTM study, resulting in >93% retention at the final study follow up.[102]

SA2 intervention feasibility and acceptability outcome measurement. Achievement of *feasibility* of delivery of all intervention components to 85% of ABI-MTM recipients will be captured by the pharmacist logging completed intervention components. Achievement of ABI-MTM *acceptability* will be assessed at month 3 and will be captured by intensive qualitative interview following a semi-structured interview guide focusing on participant opinions/experience with ABI-MTM. Acceptability will also be captured at month 3 by assessing patient satisfaction using the Patient Satisfaction Survey for Comprehensive Medication Management (PSSCMM),[33] a reliable and content/factorially valid 10-item self-report instrument[33] that will assess patient satisfaction with intervention. Last, acceptability will also be assessed by intervention recipient retention (85%) at study completion.

SA2 preliminary efficacy outcome measurement. This aim postulates that intent-to-treat analyses will show greater proportions of ABI-MTM recipients will report elimination of co-use of alcohol and opioid medications compared to SMC.[35,36] Our primary assessments will include:

- *Timeline Follow Back* (TLFB) assesses quantity/frequency of alcohol and opioid medication use, which is a measure that is reliable and is content, criterion, and construct valid.[35,36] Also note, we will capture any illicit drug use with the TLFB.
- *14 panel drug urinalysis* will be collected in private restrooms of the pharmacies or other appropriate locations, which will capture opiates, oxycodone, methadone, cannabis, cocaine, PCP, amphetamine, MDMA, methamphetamine, barbiturates, benzodiazepines, buprenorphine, tricyclic antidepressants, and propoxyphene. Participants are considered co-use free if self-report and urine assessments coincide.

In addition to our primary outcome measures, we will also capture concomitant conditions as covariates at each time point. Each of these conditions are well known correlates of opioid related risk, substance use, and health behavior change:

Opioid Use Behaviors[122,123]

- *Prescription Opioid Misuse Index (POMI),* a 6-item criterion valid and reliable measure that assesses prescription opioid misuse behaviors and opioid medication misuse.[124]
- *Opioid Compliance Checklist (OCC),* an 8-item, a test/retest reliable and criterion valid tool[125-127] that assesses adherence/misuse to the prescribed opioid regimen.
- *Diagnostic Statistical Manual-5 Checklist for Opioid Use Disorder*, is an 11-item reliable and valid assessment that identifies mild, moderate, and severe opioid use disorder. [128,129]

Pain and Physical Health[130-133]

- *Brief Pain Inventory*, is a well-validated and reliable assessment, which consists of a 4-item pain intensity subscale and a 7-item pain interference subscale.[134]
- *Pain Catastrophizing Scale*, a 13-item factorially/concurrent/discriminant valid and reliable assessment[135] that measures rumination, magnification, and helplessness aspects of pain catastrophizing.
- *Short Form-36 (SF-36)* will assess physical health and is a 36-item content, criterion, and construct valid measure with demonstrated reliability.[136] This measure assesses physical functioning, role functioning, bodily pain, general health, vitality, social functioning, emotional functioning, and mental health.

Mental Health and Risk Alcohol Use[47,122,123]

- *Patient Health Questionnaire* (PHQ) will assess mental health and is an 11-item criterion valid mental health assessment with demonstrated reliability.[137-140] The PHQ assesses depression, anxiety, somatoform, eating, and alcohol use disorders. This assessment will also be used to monitor suicidal ideation across time.
- *Primary Care-Posttraumatic Stress Disorder* assessment will measure post-traumatic stress disorder, which is a 5-item criterion valid and test-retest reliable instrument.[141-144]
- *Alcohol Use Disorders Identification Test-C* (AUDIT-C) is a 3-tem abbreviated version of the AUDIT-10, which has demonstrated internal consistency and test-retest reliability and construct and criterion validity.[37,92] The AUDIT-C has highly similar performance as the full version[37,92] and assesses frequency, quantity, and binge drinking (note, the AUDIT-C will be administered at screening [not baseline], 2-, and 3-months assessments).
- *WHO Alcohol, Smoking, and Substance Involvement Screening Test* alcohol subscale will be used to assess lifetime and recent alcohol use. This 7-item measure has demonstrated reliability as well as criterion, construct, concurrent, discriminant validity.[145]

Engagement in Physical Health and Psychosocial Services

- *Treatment Services Review (TSR)-6* will assess engagement in services for: substance abuse, medical/mental health, family issues, financial/housing needs, and legal concerns. The TSR-6 also captures medication use; which we will use to capture type, dose, and frequency of opioid consumption and other medications. The TSR contains 56-items and is criterion and construct valid and reliable.[146-149] The TSR will be used, in particular, to identify length of the written opioid prescription, which will allow for examination of elimination of co-use ***during*** the opioid treatment. This will also allow for monitoring of natural cessation of opioid use during the course of treatment

Readiness to Change[150,151]

- The Readiness to Change Questionnaire is a 12-item assessment of individual readiness to change drinking behaviors that evaluates three of the stages of change: pre-contemplation, contemplation, and action. This assessment has content, criterion, and construct validity—with test-retest reliability.[152-155]

Social Desirability

- The Marlowe-Crowne Social Desirability Scale and short Form contains 13 items and is criterion valid[156,157] and reliable. This measure will assess the participants' degree of social desirability at each time point.

SA2 acceptability and feasibility analysis plan. Successful delivery of all intervention components will be analyzed by calculating the total number recipients that received both ABI-MTM sessions divided by the total number of participants randomized to this condition. Intensive qualitative interviews of ABI-MTM acceptability will be analyzed following methods recommended by Braun and Clarke that capture associations between categories, extract, and conceptualize themes.[158] Our team will independently review the interview data and code inductively and deductively. Codes will be clustered based on their similarities into categories. The research team will meet multiple times to discuss the emergent themes.[158] Patient satisfaction with the intervention reported on the PSSCMM will be analyzed by calculating frequencies of responses, measures of central tendency, and proportions. Treatment retention of 85% of ABI-MTM recipients at study completion will be analyzed by calculating number of recipients retained at 3-months divided by number of consented recipients.

SA2 preliminary efficacy analysis plan. This aim compares the preliminary efficacy of the intervention (ABI-MTM vs. SMC) on the primary binary co-use outcome (i.e., co-use vs. no co-use of alcohol and opioid medications). Mentioned above, successful elimination of co-use can be in the form of (1) participants eliminating their alcohol consumption while they are receiving opioid therapy, which will be measured by the TLFB, OR (2) by choosing an alternative non-opioid pain management strategy (not altering their alcohol consumption) by recommendation of the pharmacist and in collaboration with their prescriber, which will be measured by agreement of urine toxicology and TLFB.

We will first provide descriptive summaries of each variable measured at baseline, 2-, and 3-months overall, by risk/non-risk alcohol use, as well as by intervention group (note that all included participants are positive for co-use at baseline). Within an intent-to-treat framework, we will fit 3-level generalized linear mixed models (GLMM) to relate repeated assessments across time of the primary outcome measured (i.e. elimination of co-use) to the intervention. Additional analyses within the 3-level GLMM framework will also be conducted to assess the overall impact of the intervention on reducing percent days alcohol use among patients during the prescribed opioid treatment period. All analyses will be adjusted for covariates likely to be associated with the outcome. Specifically, this will include baseline measures such as opioid use, mental health, substance use, pain/physical function, social services utilization, and readiness to change in addition to and demographic covariates including (but not be limited to) age, sex, race, socioeconomic status, and rural/urban living.[159] Social desirability[156,157] will also be included as a time varying covariate to account for the degree to which participant response bias may impact study outcomes. Random intercepts will be used to account for correlations on the patient level and pharmacy site level. We will also test risk/non-risk alcohol use as an effect modifier to determine whether the intervention has a differential impact on individuals with distinct levels of drinking; we recognize, however, the sample study sample size may limit the power of the analysis to detect changes at a probability of <0.05. Thus, it is important to note our above discussed analysis focus on 95% confidence intervals comparing outcome rates in the intervention and control arms in order to detect subtle trends in relation to intervention efficacy. Model parameters, including treatment effects at each follow-up, will be estimated using restricted maximum likelihood.[160] An advantage of this approach is treatment effect estimates remain consistent and approximately unbiased if missing data follow a missing-at-random pattern (MAR; data values are independent of the missingness mechanism conditional on the observed data[161]), the most general data-centric missing data assumption.

As biological sex is an important factor among individuals with pain and opioid/alcohol use,[162,163] we will explore differences by intervention group and biological sex for SA2. Based on our previously published research in this population, we anticipate recruiting ~57% females/~43% males[24,164] in this study. We will first examine descriptive demographic differences at baseline, 2-, and 3-months within the ABI-MTM and SMC conditions by sex. Next, to explore the potential role of sex as an effect modifier for ABI-MTM on co-use, we will test interaction terms between the intervention group and sex to explore possible heterogeneity of treatment effects and to characterize if sex subgroups might benefit more from the intervention. As discussed above with reference to the risk/non-risk alcohol use as an effect modifier analyses, sex subgroup analyses will likewise focus on 95% confidence intervals comparing outcome rates in the intervention and control arms in order to detect subtle trends in relation to intervention efficacy.

SA2 product. By successfully accomplishing SA2, this will establish the necessary feasibility, acceptability, and preliminary efficacy data to demonstrate ABI-MTM is ready for a subsequent fully powered multisite randomized trial.

SA3: Identify Pharmacy System/Practice-Level Barriers and Facilitators for Universal Alcohol Screening/Intervention among Patients with Opioid Medications.

SA3 rationale. We have discussed above a number of barriers to pharmacists engaging patients regarding behavioral health. While our previous research has worked to address these barriers, the process of applying evidence-based services into real world health care settings is a paramount aspect of evidence-based implementation science and involves rigorous planning, monitoring, and evaluation[165-167] and indeed requires thoughtful preparation. Therefore, SA3 focuses on implementation planning to identify what *barriers* exist for implementing universal alcohol screening/intervention for those using opioid medications for a subsequent large-scale multi-site efficacy trial as well as eventual integration into system-level commercial pharmacy chain workflow. Likewise, this step will also identify *facilitators* to scaling alcohol screening/intervention for those who use opioid medications for a large-scale multisite trial and pharmacy system wide. To establish this information, we will employ tools from the Consolidated Framework for Implementation Research (CFIR)[38] and organizational behavior and management. The CFIR is a multidimensional framework comprised of constructs for drawing out information related to implementing research into practice,[168] ranging from pre-implementation activities to post-implementation outcome analyses.[169-171] The CFIR has been employed within a variety of clinical and administrative areas, including healthcare delivery and processes redesign, quality improvement, health promotion, and disease management as well as in clinical areas including mental health, obesity, and high blood pressure.[168]

SA3 design and participant identification. We will implement cross-sectional one-time mixed methods key informant interviews to capture data that will inform our understanding of pharmacy system/practice-level barriers and facilitators for universal alcohol screening/intervention among patients with opioid medications. Interview participants will be identified through a purposive/snowball sampling approach. Relying on both on Dr. Hohmeier (project coinvestigator) and Dr. Stacey Frede's (project consultant) professional networks at the Kroger corporate and Nashville regional levels, our team will reach out and offer interview participation to individuals in each category of key informant (technicians, pharmacists, and corporate leaders). Dr. Frede is the national Manager of Clinical Program Development with the Kroger Health Corporate office who has been a close collaborator with Dr. Cochran over the past 3 years in his NIDA CTN funded research project (CTN-0093; see letter of support). Identified interviewees will be contacted via email and/or by telephone. Interviews will take place in a location and time that is convenient and selected by the participants. The interviews will be conducted by a research assistant trained in qualitative interviewing and are anticipated to last up to 1 hour. At the close of these interviews, the research assistant will request from the participant suggestions of other individuals who would represent the specific perspective of pharmacy corporate leaders, pharmacists, and technicians. Completing the interview, participants will be provided with a $75 gift card.

SA3 assessment. Prior to meeting in-person for the qualitative interview, the first step in our mixed methods assessment will involve the quantitative data collection. We will administer, via a web-based survey platform, the internally consistent reliable and factorially valid Organizational Readiness to Change Assessment (ORCA).[40] This 77 item instrument assesses organizational readiness for implementing evidence-based practices in clinical settings. Primary domains assessed by the instrument include respondents' perceptions of strengths of evidence for the change and ability of the organization to support the change.[40]

For the in-person portion of the interview, we will administer open-ended questions drawn and adapted from the CFIR interview guide for qualitative research. Items will be selected by the research team in collaboration with Dr. Frede. Items from the constructs set forth in Table 4 will be employed[39] and include Intervention Characteristics, Inner Setting, Characteristics of Individuals, and Process. Our team has previously employed CFIR constructs along with the CFIR interview guide to develop an open-ended survey schedule for administration to health care professionals regarding substance use care within health care settings,[172,173] which interview results were used for system-level and community-wide intervention/ implementation planning. Also mentioned above, Dr. Gordon is an expert in implementation science and has more than 20 years of experience in this area.

Sample size. We will recruit pharmacy technicians (N=20), pharmacists (N=20), and corporate leaders (N=20) to complete the SA3 interview.[41,42] Previous research has demonstrated sample sizes of 20 individuals or less can achieve close associations between the researcher and the participants, which will generate rich data needed for elucidating complex relationships.[41] Previous research has also demonstrated samples of approximately 12 interviews can reach saturation of findings.[42] Saturation has been defined as a point beyond which no significantly new information is being obtained. Saturation will be discussed and analyzed by the research team after each interview has been completed. Lincoln and Guba's framework[174] will be used to address and meet criteria for quality and rigor in this study and involve credibility, dependability, confirmability, and transferability.[174]

Table 4. Consolidated Framework for Implementation Research Constructs in SA3 Key Informant Survey Development

Intervention Characteristics	Evidence Strength and Quality	Stakeholders' perceptions of the quality and validity of evidence supporting the belief that the intervention will have desired outcomes.
	Relative Advantage	Stakeholders' perception of the advantage of implementing the intervention versus an alternative solution.
	Trialability	The ability to test the intervention on a small-scale in the organization, and to be able to reverse course (undo implementation) if warranted.
	Complexity	Perceived difficulty of the intervention, reflected by duration, scope, radicalness, disruptiveness, centrality, and intricacy and number of steps required to implement.
Inner Setting	Implementation Climate	The absorptive capacity for change, shared receptivity of involved individuals to an intervention, and the extent to which use of that intervention will be rewarded, supported, and expected within their organization.
	Relative Priority	Individuals' shared perception of the importance of the implementation within the organization.
	Leadership Engagement	Commitment, involvement, and accountability of leaders and managers with the implementation.
	Available Resources	The level of resources dedicated for implementation and on-going operations, including money, training, education, physical space, and time.
Characteristics of Individuals	Knowledge and Beliefs about the Intervention	Individuals' attitudes toward and value placed on the intervention as well as familiarity with facts, truths, and principles related to the intervention.
Process	Engaging	Attracting and involving appropriate individuals in the implementation and use of the intervention through a combined strategy of social marketing, education, role modeling, training, and other similar activities.
	Champions	Individuals who dedicate themselves to supporting, marketing, and 'driving through' an implementation overcoming indifference or resistance that the intervention may provoke in an organization.

SA3 analysis plan. For the quantitative survey items collected based on the ORCA survey, we will employ descriptive analyses as well as conduct chi square and One-Way ANOVA tests to examine differences between interviewed groups (pharmacy technicians, pharmacists, and corporate leaders). For the qualitative data, similar to SA2, the research team will follow methods recommended by Braun and Clarke that will capture associations between categories and extract and conceptualize themes.[158] The researchers will independently review the interview data and code inductively and deductively. Codes will be clustered based on their similarities into categories. The research team will meet multiple times to discuss the emergent themes.[158]

Timeline. Based on our previous work in conducting clinical research with similar populations in community pharmacy settings, we estimate this study will require 3 years to complete (Table 5). Year 1 quarters (Q) 1-3 will involve receiving IRB approval and hiring/training staff. During the same time, we will undertake and complete all activities related to SA1, intervention adaptation and protocol development. Year 1 Q 2-3 will involve finalizing the assessment battery for SA2; Q3 will also involve the initiation of activities related to the small-scale

trial, including patient recruitment, intervention delivery, outcome assessments and data safety monitoring board meetings (DSMB), which will conclude in Year 3 Q1. Beginning in Year 1 Q4, we will initiate our activities related to SA3, including developing our qualitative interview schedule, participant identification, interviewing, and analyses, which will conclude Year 3 Q1. Study papers will be produced Year 1 Q3-4 and Year 3 Q2-4.

Table 5. Project Timeline		Year 1				Year 2				Year 3			
Aim	Activity	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
1-3	IRB approval	x											
	Hire staff	x	x	x									
	Train staff		x	x									
1	Adapt intervention	x	x										
	Adapt/expand protocol	x	x										
	Finalize study protocol		x	x									
2	Finalize assessment battery		x	x									
	Patient recruitment			x	x	x	x	x					
	Intervention delivery			x	x	x	x	x	x				
	Outcome assessments			x	x	x	x	x	x	x			
	DSMB meetings			x	x	x	x	x	x	x			
	Data cleaning/analyses									x	x		
	Protocol paper			x	x								
	Main outcome paper										x	x	x
3	Develop qualitative interview				x	x							
	Identify participants					x	x						
	Administer survey/interview						x	x					
	Data analysis								x	x			
	Main outcome paper										x	x	x
1-3	Submit final report												x

Possible Barriers to Study Success and Resolutions

We anticipate 3 primary barriers to the success of this study and have plans in place for response and/or resolution. First, critics may suggest that providing an intervention to those with non-risky alcohol use who are also taking opioid medications is unnecessary given they are at low probability for negative consequences. It is important to recall, as reviewed/cited above, there is no empirical literature that supports this perspective—rather all-peer reviewed human and animal, governmental, packaging inserts, and professional literature available clearly state that any co-use of alcohol and opioid medications is dangerous and should be not done. Therefore, this study will specifically recruit on a 1:1 ratio those with non-risk as well as those with risky alcohol use and examine outcomes for both subgroups by intervention condition.

Second, some critics may also assert that given the BI-MTM intervention already has been developed and tested in a small-scale clinical trial, that advancing *ABI-MTM* is unnecessary and BI-MTM should be sufficient for co-use of alcohol and opioid medications. Our team deliberated over this question extensively. Opioid medication misuse is a composite set of behaviors including, for instance, using more medication than prescribed, using to get high or to cope with problems, and doctor shopping. Misuse also is frequently accompanied by a variety of concomitant conditions (i.e., mental health, illicit substance use) that together require a resource intense and comprehensive intervention. Our goal with the ABI-MTM intervention is to integrate a very brief and targeted intervention focusing only on the highly specific outcome of co-use elimination (i.e., [1] eliminating alcohol use during opioid treatment or [2] substituting a non-opioid pain therapy). Thus, ABI-MTM will be very different in practice than the BI-MTM—requiring specific adaptation efforts and preliminary testing.

Third, we do not anticipate a change in our ability to recruit participants in SA2 (i.e., pharmacy patients); however, there is a chance recruitment could slow at some point in the study. Given the hundreds of Kroger stores in Tennessee (and thousands across the US) and our close collaboration with corporate and local leaders on this project, should participant recruitment become a challenge, we have the ability to open up recruitment in other stores and/or create Kroger medication system hard stops in the store workflow that would *require* patients to be screened before leaving the stores. Based on our experience, these are highly effective tools that can be used to improve site performance. In the same vein, based on our close collaboration with corporate and local leaders, we are confident that should our sampling approach for SA3 (i.e., staff/leadership key informant interviews) prove to not meet our targets, our local and corporate partners will help assist us to identify additional possible participants who would be available and potentially interested with speaking with us.

CONCLUSION

The opioid epidemic continues to result in serious negative consequences in the US. While some improvements have been observed for reductions in prescribing in recent years; high rates of misuse, subsequent OUD, and overdose persist. Among the most high-risk behaviors for those taking opioid medications is co-use with alcohol. The Centers for Disease Control and Prevention has clearly stated: "…***there is no safe level of alcohol use for people using opioids***."[52] Previous research, including that of our team, shows that a significant portion of those regularly using opioids medications—particularly filling opioids at community pharmacies—are involved in the co-use of alcohol. This study proposes to leverage pharmacists' special training in medication interactions and safety; adapt a previously developed intervention for opioid medication misuse; test its acceptability, feasibility, and preliminary efficacy; and identify barriers/facilitators to large-scale research and system-level implementation. Results will inform a subsequent powered multisite trial examining the impact of the ABI-MTM intervention on reducing co-use of opioid medications and alcohol and improve public health nationally.

REFERENCES

1. Amato L, Minozzi S, Davoli M, Vecchi S. Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification. *The Cochrane database of systematic reviews.* 2011(9):Cd005031.
2. Brands B, Blake J, Marsh DC, Sproule B, Jeyapalan R, Li S. The impact of benzodiazepine use on methadone maintenance treatment outcomes. *J Addict Dis.* 2008;27(3):37-48.
3. Kuerbis A, Sacco P, Blazer DG, Moore AA. Substance abuse among older adults. *Clinics in geriatric medicine.* 2014;30(3):629-654.
4. FDA. HIGHLIGHTS OF PRESCRIBING INFORMATION: OXYCODONE. In: US_Food_and_Drug_Administration, ed. Silver Spring, MD2018.
5. FDA. HIGHLIGHTS OF PRESCRIBING INFORMATION: PERCOCET. In: US_Food_and_Drug_Administration, ed. Silver Spring, MD2018.
6. FDA. HIGHLIGHTS OF PRESCRIBING INFORMATION: OXYCONTIN. In: US_Food_and_Drug_Administration, ed. Silver Spring, MD2018.
7. CDC. Drug overdose deaths in the United States hit record numbers in 2014. http://www.cdc.gov/drugoverdose/epidemic/index.html. Published 2016. Accessed September 7, 2016.
8. Cochran G, Gordon AJ, Lo-Ciganic WH, et al. An Examination of Claims-based Predictors of Overdose from a Large Medicaid Program. *Med Care.* 2016.
9. Witkiewitz K, Vowles KE. Alcohol and Opioid Use, Co-Use, and Chronic Pain in the Context of the Opioid Epidemic: A Critical Review. *Alcoholism, clinical and experimental research.* 2018;42(3):478-488.
10. Hartzler B, Donovan DM, Huang Z. Comparison of opiate-primary treatment seekers with and without alcohol use disorder. *J Subst Abuse Treat.* 2010;39(2):114-123.
11. Hser Y-I, Mooney LJ, Saxon AJ, Miotto K, Bell DS, Huang D. Chronic pain among patients with opioid use disorder: Results from electronic health records data. *Journal of substance abuse treatment.* 2017;77:26-30.
12. Price AM, Ilgen MA, Bohnert AS. Prevalence and correlates of nonmedical use of prescription opioids in patients seen in a residential drug and alcohol treatment program. *J Subst Abuse Treat.* 2011;41(2):208-214.
13. Esser MB, Guy GP, Jr., Zhang K, Brewer RD. Binge Drinking and Prescription Opioid Misuse in the U.S., 2012-2014. *American journal of preventive medicine.* 2019;57(2):197-208.
14. Compton WM, Jones CM, Stein JB, Wargo EM. Promising roles for pharmacists in addressing the U.S. opioid crisis. *Research in social & administrative pharmacy : RSAP.* 2019;15(8):910-916.
15. AccreditationCouncilForPharmacyEducation. *Guidance For The Accreditation Standards And Key Elements For The Professional Program In Pharmacy Leading To The Doctor Of Pharmacy Degree.* Chicago, IL: Accreditation Council for Pharmacy Education;2015.
16. Shane A, Argáez C. Pharmacist-Led Medication Reviews: A Review of Clinical Utility and Cost-Effectiveness*Canadian Agency for Drugs and Technologies in Health.* 2019.
17. Choi YJ, Kim H. Effect of pharmacy-led medication reconciliation in emergency departments: A systematic review and meta-analysis. *Journal of clinical pharmacy and therapeutics.* 2019;44(6):932-945.
18. Brown JVE, Walton N, Meader N, et al. Pharmacy-based management for depression in adults. *The Cochrane database of systematic reviews.* 2019;12(12):Cd013299.
19. Khorassani F, Tellier S, Tsapepas D. Pharmacist's Role in Improving Medication Adherence in Transplant Recipients With Comorbid Psychiatric Disorders. *J Pharm Pract.* 2019;32(5):568-578.
20. Lee H, Ryu K, Sohn Y, Kim J, Suh GY, Kim E. Impact on Patient Outcomes of Pharmacist Participation in Multidisciplinary Critical Care Teams: A Systematic Review and Meta-Analysis. *Crit Care Med.* 2019;47(9):1243-1250.
21. Parajuli DR, Kourbelis C, Franzon J, et al. Effectiveness of the Pharmacist-Involved Multidisciplinary Management of Heart Failure to Improve Hospitalizations and Mortality Rates in 4630 Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Card Fail.* 2019;25(9):744-756.

22. Segal EM, Bates J, Fleszar SL, et al. Demonstrating the value of the oncology pharmacist within the healthcare team. *J Oncol Pharm Pract.* 2019;25(8):1945-1967.
23. Cochran G, Bacci JL, Ylioja T, et al. Prescription opioid use: Patient characteristics and misuse in community pharmacy. *Journal of the American Pharmacists Association : JAPhA.* 2016.
24. Cochran G, Chen Q, Field C, et al. A community pharmacy-led intervention for opioid medication misuse: A small-scale randomized clinical trial. *Drug Alcohol Depend.* 2019;205:107570.
25. NIDA. Validation of a Community Pharmacy-based Prescription Drug Monitoring Program Risk Screening Tool (PHARMSCREEN) (NIH HEAL Initiative). https://www.drugabuse.gov/about-nida/organization/cctn/ctn/research-studies/validation-community-pharmacy-based-prescription-drug-monitoring-program-risk-screening-tool. Published 2020. Accessed May 12, 2020.
26. McNeely J, Wu LT, Subramaniam G, et al. Performance of the Tobacco, Alcohol, Prescription Medication, and Other Substance Use (TAPS) Tool for Substance Use Screening in Primary Care Patients. *Annals of internal medicine.* 2016;165(10):690-699.
27. Viswanathan M, Kahwati LC, Golin CE, et al. Medication therapy management interventions in outpatient settings: A systematic review and meta-analysis. *JAMA Internal Medicine.* 2015;175(1):76-87.
28. Cochran G, Field C. Brief Intervention and Social Work: A Primer for Practice and Policy. *Social Work in Public Health.* 2013;28(3-4):248-263.
29. Strobbe S. Prevention and screening, brief intervention, and referral to treatment for substance use in primary care. *Prim Care.* 2014;41(2):185-213.
30. Beich A, Thorsen T, Rollnick S. Screening in brief intervention trials targeting excessive drinkers in general practice: systematic review and meta-analysis. . *BMJ: British Medical Journal.* 2003;327(7414):536-540.
31. Bertholet N, Daeppen J-B, Wietlisbach V, Fleming M, Burnand B. Reduction of Alcohol Consumption by Brief Alcohol Intervention in Primary Care: Systematic Review and Meta-analysis. *Archives of Internal Medicine.* 2005;165(9):986-995.
32. Wingood GM, DiClemente RJ. The ADAPT-ITT Model: A Novel Method of Adapting Evidence-Based HIV Interventions. *JAIDS Journal of Acquired Immune Deficiency Syndromes.* 2008;47 Suppl 1, The First National Scientific Meeting of the Social and Behavioral Science Research Network(Supplement 1):S40-S46.
33. Moon J, Kolar C, Brummel A, Ekstrand M, Holtan H, Rehrauer D. Development and Validation of a Patient Satisfaction Survey for Comprehensive Medication Management. *Journal of managed care & specialty pharmacy.* 2016;22(1):81-86.
34. Thayaparan AJ, Mahdi E. The Patient Satisfaction Questionnaire Short Form (PSQ-18) as an adaptable, reliable, and validated tool for use in various settings. *Medical Education Online.* 2013;18:10.3402/meo.v3418i3400.21747.
35. Sobell M, Sobel lL, Bogardis J, Leo G, Skinner W. Problem drinkers' perceptions of whether treatment goals should be self-selected or therapist-selected. *Behav Ther.* 1992;23:43-52.
36. Sobell L, Sobell M, eds. *Timeline follow-back: a technique for assessing self-reported alcohol consumption, in Measuring Alcohol Consumption: Psychosocial and Biological Methods.* Totowa, NJ: Humana Press; 1992. J. A, R. L, eds.
37. Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test. *Archives Of Internal Medicine.* 1998;158(16):1789-1795.
38. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. *Implementation science : IS.* 2009;4:50.
39. CFIR.org. The Consolidated Framework for Implementation Research. https://cfirguide.org/. Published 2020. Accessed January 9, 2020.
40. Helfrich CD, Li YF, Sharp ND, Sales AE. Organizational readiness to change assessment (ORCA): development of an instrument based on the Promoting Action on Research in Health Services (PARIHS) framework. *Implementation science : IS.* 2009;4:38.

41. Crouch M, McKenzie H. The logic of small samples in interview-based qualitative research. *Social Science Information.* 2006;45(4):483-499.
42. Guest G, Bunce A, Johnson L. How Many Interviews Are Enough?:An Experiment with Data Saturation and Variability. *Field Methods.* 2006;18(1):59-82.
43. IQVIA Institute. *Medicine Use and Spending in the U.S. A Review of 2017 and Outlook to 2022.* Durham, NC: IQVIA Institute 2018.
44. CDC. U.S. Opioid Prescribing Rate Maps. Centers for Disease Control. https://www.cdc.gov/drugoverdose/maps/rxrate-maps.html#:~:text=The%20overall%20national%20opioid%20prescribing%20rate%20declined%20from%202012%20to,168%20million%20total%20opioid%20prescriptions). Published 2020. Accessed July 9, 2020.
45. Wilson N, Kariisa M, Seth P, Smith Ht, Davis NL. Drug and Opioid-Involved Overdose Deaths - United States, 2017-2018. *MMWR Morbidity and mortality weekly report.* 2020;69(11):290-297.
46. NIDA. NIDA in the News. https://www.drugabuse.gov/news-events/nida-in-news. Published n.d. Accessed September 3, 2020.
47. Cochran G, Bacci JL, Ylioja T, et al. Prescription opioid use: Patient characteristics and misuse in community pharmacy. *Journal of the American Pharmacists Association.* 2016;56(3):248-256.e246.
48. Darwish M, Bond M, Yang R, Tracewell W, Robertson P, Jr. Assessment of Alcohol-Induced Dose Dumping with a Hydrocodone Bitartrate Extended-Release Tablet Formulated with CIMA(®) Abuse Deterrence Technology. *Clin Drug Investig.* 2015;35(10):645-652.
49. van der Schrier R, Roozekrans M, Olofsen E, et al. Influence of Ethanol on Oxycodone-induced Respiratory Depression: A Dose-escalating Study in Young and Elderly Individuals. *Anesthesiology.* 2017;126(3):534-542.
50. Zacny JP, Gutierrez S. Subjective, psychomotor, and physiological effects of oxycodone alone and in combination with ethanol in healthy volunteers. *Psychopharmacology (Berl).* 2011;218(3):471-481.
51. FDA. *FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines; requires its strongest warning.* Washington, DC: Food and Drug Adminisitration 2016.
52. CDC. *Alcohol Screening And Brief Intervention for People Who Consume Alcohol and Use Opioids.* Atlanta, GA: Centers for Diease Control and Prevention 2018.
53. NIAAA. *Helping patients who drink too much: A clinicians guide.* Bethesda, MD: National Institute on Alcohol Abuse and Alcoholism;2007.
54. Reith TP. Burnout in United States Healthcare Professionals: A Narrative Review. *Cureus.* 2018;10(12):e3681-e3681.
55. IsHak WW, Wen RY, Naghdechi L, et al. Pain and Depression: A Systematic Review. *Harv Rev Psychiatry.* 2018;26(6):352-363.
56. Salas J, Scherrer JF, Ahmedani BK, et al. Gender and the Association between Long-Term Prescription Opioid Use and New-Onset Depression. *J Pain.* 2018;19(1):88-98.
57. Scherrer JF, Salas J, Schneider FD, et al. Characteristics of new depression diagnoses in patients with and without prior chronic opioid use. *Journal of affective disorders.* 2017;210:125-129.
58. Scherrer JF, Salas J, Sullivan MD, et al. The influence of prescription opioid use duration and dose on development of treatment resistant depression. *Preventive medicine.* 2016;91:110-116.
59. Amari E, Rehm J, Goldner E, Fischer B. Nonmedical prescription opioid use and mental health and pain comorbidities: a narrative review. *Canadian journal of psychiatry Revue canadienne de psychiatrie.* 2011;56(8):495.
60. PDMPAssist. *State Profiles West Virginia* Brandeis University PDMP TTC;2016.
61. Seal KH, Shi Y, Cohen G, et al. Association of mental health disorders with prescription opioids and high-risk opioid use in US veterans of Iraq and Afghanistan. *JAMA : the journal of the American Medical Association.* 2012;307(9):940-947.
62. Sullivan MD, Edlund MJ, Zhang L, Unutzer J, Wells KB. Association Between Mental Health Disorders, Problem Drug Use, and Regular Prescription Opioid Use. *Archives of Internal Medicine.* 2006;166(19):2087-2093.
63. Jones JD, Mogali S, Comer SD. Polydrug abuse: A review of opioid and benzodiazepine combination use. *Drug and alcohol dependence.* 2012;125(1-2):8-18.

64. SAMHSA. *Key substance use and mental health indicators in the United States: Results from the 2019 National Survey on Drug Use and Health (HHS Publication No. SMA 18-5068, NSDUH Series H-53). .* Rockville, MD: Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality 2020.
65. ACPE. *Accreditation Standards and Key Elements for The Professional Program In Pharmacy Leading to the Doctor of Pharmacy Degree.* Chicago, IL: Accreditation Council for Pharmacy Education;2015.
66. Inciardi JA, Surratt HL, Kurtz SP, Cicero TJ. Mechanisms of Prescription Drug Diversion Among Drug-Involved Club- and Street-Based Populations. *Pain Medicine.* 2007;8(2):171-183.
67. Cicero T, Kurtz S, Surratt H, et al. Multiple Determinants of Specific Modes of Prescription Opioid Diversion. *J Drug Issues.* 2011;41(2):283-304.
68. CDC. *Select features of state pharmacist collaborative practice laws. .* Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention;2013.
69. Dhital R, Whittlesea CM, Norman IJ, Milligan P. Community pharmacy service users' views and perceptions of alcohol screening and brief intervention. *Drug And Alcohol Review.* 2010;29(6):596-602.
70. Riffkin R. Americans Rate Nurses Highest on Honesty, Ethical Standards. Gallup. http://www.webcitation.org/6hZbvKPDQ. Published 2014. Accessed May 17, 2016.
71. Peacock G, Kidd R, Rahman A. Patient care services in independent community pharmacies: A descriptive report. *Journal of the American Pharmacists Association.*47(6):768a-771a.
72. Cochran G, Field C, Lawson K, Erickson C. Pharmacists' knowledge, attitudes and beliefs regarding screening and brief intervention for prescription opioid abuse: a survey of Utah and Texas pharmacists. *Journal of Pharmaceutical Health Services Research.* 2013;4(2):71-79.
73. Cochran G, Field C, Lawson K. Pharmacists Who Screen and Discuss Opioid Misuse With Patients: Future Directions for Research and Practice. *J Pharm Pract.* 2015;28(4):404-412.
74. Cochran G, Rubinstein J, Bacci JL, Ylioja T, Tarter R. Screening community pharmacy patients for risk of prescription opioid misuse *Journal of addiction medicine.* 2015;9(5):411-416.
75. Cochran G, Hruschak V, Bacci JL, Hohmeier KC, Tarter R. Behavioral, mental, and physical health characteristics and opioid medication misuse among community pharmacy patients: A latent class analysis. *Research in social & administrative pharmacy : RSAP.* 2017;13(6):1055-1061.
76. Cochran G, McCarthy R, Gordon AJ, Tarter RE. Opioid medication misuse among unhealthy drinkers. *Drug Alcohol Depend.* 2017;179:13-17.
77. Cochran G, Rosen D, McCarthy RM, Engel RJ. Risk Factors for Symptoms of Prescription Opioid Misuse: Do Older Adults Differ from Younger Adult Patients? *J Gerontol Soc Work.* 2017;60(6-7):443-457.
78. Cochran GT, Engel RJ, Hruschak VJ, Tarter RE. Prescription Opioid Misuse Among Rural Community Pharmacy Patients: Pilot Study for Screening and Implications for Future Practice and Research. *J Pharm Pract.* 2017;30(5):498-505.
79. Hruschak V, Hildenbrand AK, Cochran G. Psychiatric comorbidity and co-occurring opioid misuse: Depression mediates the relationship between post-traumatic stress disorder and opioid misuse in community pharmacy settings. *Substance abuse : official publication of the Association for Medical Education and Research in Substance Abuse.* 2020;41(1):77-84.
80. Cochran G, Gordon AJ, Field C, et al. Developing a framework of care for opioid medication misuse in community pharmacy. *Research in Social and Administrative Pharmacy.* 2016;12(2):293-301.
81. Webb K, Cernasev A, Li MS, Gatwood J, Cochran G, Hohmeier KC. An Exploratory Study of Pharmacist Perceptions of Opioid Interventions for Acute Pain. *Journal of Pharmacy Technology.* 2021;37(1):36-44.
82. Hohmeier KC, Cernasev A, Sensmeier M, Barenie R, Cochran G. Student Pharmacist Perceptions of the Pharmacists Role in Methadone for Opioid Use Disorder. *Sage Open Medicine.* In press.
83. Cochran G, Smid MC, Krans EE, et al. A pilot multisite study of patient navigation for pregnant women with opioid use disorder. *Contemporary clinical trials.* 2019;87:105888.
84. Richter KP, Faseru B, Shireman TI, et al. Warm Handoff Versus Fax Referral for Linking Hospitalized Smokers to Quitlines. *American journal of preventive medicine.* 2016;51(4):587-596.
85. Mussulman LM, Faseru B, Fitzgerald S, Nazir N, Patel V, Richter KP. A randomized, controlled pilot study of warm handoff versus fax referral for hospital-initiated smoking cessation among people living with HIV/AIDS. *Addict Behav.* 2018;78:205-208.

86. Ober AJ, Watkins KE, McCullough CM, Setodji CM, Osilla K, Hunter SB. Patient predictors of substance use disorder treatment initiation in primary care. *J Subst Abuse Treat.* 2018;90:64-72.
87. Kelly T, Hoppe JA, Zuckerman M, Khoshnoud A, Sholl B, Heard K. A novel social work approach to emergency department buprenorphine induction and warm hand-off to community providers. *Am J Emerg Med.* 2020;38(6):1286-1290.
88. Taylor RM, Minkovitz CS. Warm Handoffs for Improving Client Receipt of Services: A Systematic Review. *Matern Child Health J.* 2021.
89. NIDA. Opioid Summaries by State. https://www.drugabuse.gov/drug-topics/opioids/opioid-summaries-by-state. Published 2020. Accessed August 29, 2020.
90. CDC. Drunk Driving State Data and Maps. https://www.cdc.gov/motorvehiclesafety/impaired_driving/states-data-tables.html. Published 2016. Accessed August 3, 2020.
91. Spillane S, Shiels MS, Best AF, et al. Trends in Alcohol-Induced Deaths in the United States, 2000-2016. *JAMA Netw Open.* 2020;3(2):e1921451-e1921451.
92. Reinert DF, Allen JP. The alcohol use disorders identification test: an update of research findings. *Alcohol Clin Exp Res.* 2007;31(2):185-199.
93. Krans EE, Dunn SL. Health care use patterns of opioid-dependent pregnant women. *Obstetrics and gynecology.* 2014;123 Suppl 1:61S-61S.
94. Lejeune C, Simmat-Durand L, Gourarier L, Aubisson S. Prospective multicenter observational study of 260 infants born to 259 opiate-dependent mothers on methadone or high-dose buprenophine substitution. *Drug Alcohol Depend.* 2006;82(3):250-257.
95. Patrick SW, Dudley J, Martin PR, et al. Prescription opioid epidemic and infant outcomes. *Pediatrics.* 2015;135(5):842-850.
96. Pritham UA, Paul JA, Hayes MJ. Opioid dependency in pregnancy and length of stay for neonatal abstinence syndrome. *Journal of obstetric, gynecologic, and neonatal nursing : JOGNN / NAACOG.* 2012;41(2):180-190.
97. Stanhope TJ, Gill LA, Rose C. Chronic opioid use during pregnancy: maternal and fetal implications. *Clinics in perinatology.* 2013;40(3):337-350.
98. CDC. Alcohol Use in Pregnancy. https://www.cdc.gov/ncbddd/fasd/alcohol-use.html#:~:text=Alcohol%20in%20the%20mother's%20blood,alcohol%20spectrum%20disorders%20(FASDs). Published 202. Accessed August 27, 2020.
99. Eisen SV, Normand SL, Belanger AJ, Spiro A, 3rd, Esch D. The Revised Behavior and Symptom Identification Scale (BASIS-R): reliability and validity. *Med Care.* 2004;42(12):1230-1241.
100. Altman EG, Hedeker D, Peterson JL, Davis JM. The Altman Self-Rating Mania Scale. *Biological psychiatry.* 1997;42(10):948-955.
101. Leon AC, Davis LL, Kraemer HC. The Role and Interpretation of Pilot Studies in Clinical Research. *Journal of psychiatric research.* 2011;45(5):626-629.
102. Cochran G, Chen Q, Field C, et al. A community pharmacy-led intervention for opioid medication misuse: A small-scale randomized clinical trial. *Drug Alcohol Depend.* 2019;205: 107570.
103. Gold SM, Enck P, Hasselmann H, et al. Control conditions for randomised trials of behavioural interventions in psychiatry: a decision framework. *Lancet Psychiatry.* 2017;4(9):725-732.
104. CMS. *Drug Diversion Toolkit: Patient Counseling--A Pharmacists Repsonsibility to Ensure Compliance.* Washington DC: CMS;2014.
105. TennesseeBoardofPharmacy. *News.* Nashville, TN: Tennessee Board of Pharmacy;2017.
106. UtahAdministrativeCode. Operating Standards - Patient Counseling. In: Rules D, ed. *R156-17b-610*2019.
107. Moyers TB, Rowell LN, Manuel JK, Ernst D, Houck JM. The Motivational Interviewing Treatment Integrity Code (MITI 4): Rationale, Preliminary Reliability and Validity. *Journal of substance abuse treatment.* 2016;65:36-42.
108. Moyers TB, Manuel JK, Ernst D. *Motivational Interviewing Treatment Integrity Coding Manual 4.1.* Albuquerque, NM: University of New Mexico, Center on Alcohol, Substance use, And Addictions (CASAA);2014.
109. Perlroth D, Marrufo G, Montesinos A, et al. *Medication Therapy Management in Chronically Ill Populations: Final Report* Burlingame, CA: Acumen, LLC;2013.

110. APhANACDSF. Medication therapy management in pharmacy practice: Core elements of an MTM service model (version 2.0). *J Am Pharm Assoc.* 2008;48:341-353.
111. Bluml BM. Definition of medication therapy management: development of professionwide consensus. *Journal of the American Pharmacists Association : JAPhA.* 2005;45(5):566-572.
112. APhA/NACDSF. *Medication Therapy Management in Pharmacy Practice: Core Elements of an MTM Service Model, 2.0.* Washington DC: American Pharmacists Association and National Association of Chain Drug Stores Foundation;2008.
113. Zingone MM, Malcolm KE, McCormick SW, Bledsoe KR. Analysis of pharmacist charges for medication therapy management services in an outpatient setting. *American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists.* 2007;64(17):1827-1831.
114. Cook PF, Emiliozzi S, Waters C, El Hajj D. Effects of telephone counseling on antipsychotic adherence and emergency department utilization. *Am J Manag Care.* 2008;14(12):841-846.
115. Hill S, Kavookjian J. Motivational interviewing as a behavioral intervention to increase HAART adherence in patients who are HIV-positive: a systematic review of the literature. *AIDS care.* 2012;24(5):583-592.
116. Taitel M, Jiang J, Rudkin K, Ewing S, Duncan I. The impact of pharmacist face-to-face counseling to improve medication adherence among patients initiating statin therapy. *Patient preference and adherence.* 2012;6:323-329.
117. Kaplan JE, Keeley RD, Engel M, Emsermann C, Brody D. Aspects of patient and clinician language predict adherence to antidepressant medication. *Journal of the American Board of Family Medicine : JABFM.* 2013;26(4):409-420.
118. Barkhof E, Meijer CJ, de Sonneville LM, Linszen DH, de Haan L. The effect of motivational interviewing on medication adherence and hospitalization rates in nonadherent patients with multi-episode schizophrenia. *Schizophrenia bulletin.* 2013;39(6):1242-1251.
119. McCauley JL, Back SE, Brady KT. Pilot of a brief, web-based educational intervention targeting safe storage and disposal of prescription opioids. *Addictive behaviors.* 2013;38(6):2230-2235.
120. Zahradnik A, Otto C, Crackau B, et al. Randomized controlled trial of a brief intervention for problematic prescription drug use in non-treatment-seeking patients. *Addiction.* 2009;104(1):109-117.
121. Bohnert AS, Bonar EE, Cunningham R, et al. A pilot randomized clinical trial of an intervention to reduce overdose risk behaviors among emergency department patients at risk for prescription opioid overdose. *Drug Alcohol Depend.* 2016;163:40-47.
122. Cochran G, Gordon AJ, Lo-Ciganic WH, et al. An Examination of Claims-based Predictors of Overdose from a Large Medicaid Program. *Med Care.* 2017;55(3):291-298.
123. Sullivan MD, Edlund MJ, Fan M-Y, Devries A, Brennan Braden J, Martin BC. Risks for possible and probable opioid misuse among recipients of chronic opioid therapy in commercial and medicaid insurance plans: The TROUP Study. *Pain.* 2010;150(2):332-339.
124. Knisely JS, Wunsch MJ, Cropsey KL, Campbell ED. Prescription Opioid Misuse Index: a brief questionnaire to assess misuse. *J Subst Abuse Treat.* 2008;35(4):380-386.
125. Jamison RN, Martel MO, Huang CC, Jurcik D, Edwards RR. Efficacy of the Opioid Compliance Checklist to Monitor Chronic Pain Patients Receiving Opioid Therapy in Primary Care. *J Pain.* 2016;17(4):414-423.
126. Jamison RN, Martel MO, Edwards RR, Qian J, Sheehan KA, Ross EL. Validation of a Brief Opioid Compliance Checklist for Patients with Chronic Pain. *The journal of pain : official journal of the American Pain Society.* 2014;15(11):1092-1101.
127. Jamison RN, Ross EL, Michna E, Chen LQ, Holcomb C, Wasan AD. Substance Misuse Treatment for High Risk Chronic Pain Patients on Opioid Therapy: A Randomized Trial. *Pain.* 2010;150(3):390-400.
128. Denis CM, Gelernter J, Hart AB, Kranzler HR. Inter-observer reliability of DSM-5 substance use disorders. *Drug and alcohol dependence.* 2015;153:229-235.
129. Grant BF, Saha TD, Ruan WJ, et al. Epidemiology of DSM-5 Drug Use Disorder: Results From the National Epidemiologic Survey on Alcohol and Related Conditions–IIIEpidemiology of DSM-5 Drug Use DisorderEpidemiology of DSM-5 Drug Use Disorder. *JAMA Psychiatry.* 2016;73(1):39-47.
130. Rose C, Shahanaghi A, Romero-Gonzalez M, et al. Mortality Associated With Opioid Overdose: A Review of Clinical Characteristics and Health Services Received in the Year Prior to Death. *Psychiatr Serv.* 2019;70(2):90-96.

131. Webster LR. Risk Factors for Opioid-Use Disorder and Overdose. *Anesthesia and analgesia.* 2017;125(5):1741-1748.
132. Becker WC, Sullivan LE, Tetrault JM, Desai RA, Fiellin DA. Non-medical use, abuse and dependence on prescription opioids among U.S. adults: Psychiatric, medical and substance use correlates. *Drug and Alcohol Dependence.* 2008;94(1):38-47.
133. Hudson TJ, Edlund MJ, Steffick DE, Tripathi SP, Sullivan MD. Epidemiology of regular prescribed opioid use: results from a national, population-based survey. *J Pain Symptom Manage.* 2008;36(3):280-288.
134. Keller S, Bann CM, Dodd SL, Schein J, Mendoza TR, Cleeland CS. Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. *Clin J Pain.* 2014;20(5):309-319.
135. Osman A, Barrios FX, Kopper BA, Hauptmann W, Jones J, O'Neill E. Factor structure, reliability, and validity of the Pain Catastrophizing Scale. *Journal of behavioral medicine.* 1997;20(6):589-605.
136. Ware JE. SF-36® Health Survey Update. http://www.sf-36.org/tools/sf36.shtml#MODEL. Published n.d. Accessed July 17, 2015.
137. Spitzer RL, Williams JB, Kroenke K, Hornyak R, McMurray J. Validity and utility of the PRIME-MD patient health questionnaire in assessment of 3000 obstetric-gynecologic patients: the PRIME-MD Patient Health Questionnaire Obstetrics-Gynecology Study. *American journal of obstetrics and gynecology.* 2000;183(3):759-769.
138. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. *JAMA.* 1999;282(18):1737-1744.
139. Smith TC, Smith B, Jacobson IG, Corbeil TE, Ryan MAK. Reliability of Standard Health Assessment Instruments in a Large, Population-Based Cohort Study. *Annals of Epidemiology.* 2007;17(7):525-532.
140. Hides L, Lubman DI, Devlin H, et al. Reliability and validity of the Kessler 10 and Patient Health Questionnaire among injecting drug users. *Australian & New Zealand Journal of Psychiatry.* 2007;41(2):166-168.
141. van Dam D, Ehring T, Vedel E, Emmelkamp PMG. Validation of the Primary Care Posttraumatic Stress Disorder screening questionnaire (PC-PTSD) in civilian substance use disorder patients. *Journal of Substance Abuse Treatment.* 2010;39(2):105-113.
142. Ouimette P, Wade M, Prins A, Schohn M. Identifying PTSD in primary care: Comparison of the Primary Care-PTSD Screen (PC-PTSD) and the General Health Questionnaire-12 (GHQ). *Journal of Anxiety Disorders.* 2008;22(2):337-343.
143. Prins A, Ouimette P, Kimerling R, et al. The primary care PTSD screen (PC-PTSD): Development and operating characteristics. *Primary Care Psychiatry.* 2003;9:9-14.
144. Prins A, Bovin MJ, Smolenski DJ, et al. The Primary Care PTSD Screen for DSM-5 (PC-PTSD-5): Development and Evaluation Within a Veteran Primary Care Sample. *Journal of General Internal Medicine.* 2016;31(10):1206-1211.
145. Humeniuk R, Ali R. *Validation of the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) and Pilot Brief Intervention: A Technical Report of Phase II Findings of the WHO ASSIST Project.* Geneva: WHO;2006.
146. McLellan AT, Alterman AI, Cacciola J, Metzger D, O'Brien CP. A new measure of substance abuse treatment. Initial studies of the treatment services review. *The Journal of nervous and mental disease.* 1992;180(2):101-110.
147. McLellan AT, Hagan TA, Levine M, et al. Does clinical case management improve outpatient addiction treatment. *Drug Alcohol Depend.* 1999;55(1-2):91-103.
148. McLellan AT, Hagan TA, Levine M, et al. Supplemental social services improve outcomes in public addiction treatment. *Addiction.* 1998;93(10):1489-1499.
149. Allen JP, Wilson VB. *Assessing Alcohol Problems: A Guide for Clinicians and Researchers.* Bethesda, MD: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute on Alcohol Abuse and Alcoholism;2003.
150. Ries R, Krupski A, West II, et al. Correlates of Opioid Use in Adults With Self-Reported Drug Use Recruited From Public Safety-Net Primary Care Clinics. *Journal of addiction medicine.* 2015;9(5):417-426.

151. Bertholet N, Cheng DM, Palfai TP, Samet JH, Saitz R. Does readiness to change predict subsequent alcohol consumption in medical inpatients with unhealthy alcohol use? *Addictive behaviors.* 2009;34(8):636-640.
152. Napper LE, Wood MM, Jaffe A, Fisher DG, Reynolds GL, Klahn JA. Convergent and discriminant validity of three measures of stage of change. *Psychol Addict Behav.* 2008;22(3):362-371.
153. Hannöver W, Thyrian JR, Hapke U, Rumpf HJ, Meyer C, John U. The readiness to change questionnaire in subjects with hazardous alcohol consumption, alcohol misuse and dependence in a general population survey. *Alcohol and alcoholism (Oxford, Oxfordshire).* 2002;37(4):362-369.
154. Forsberg L, Halldin J, Wennberg P. Psychometric properties and factor structure of the readiness to change questionnaire. *Alcohol and alcoholism (Oxford, Oxfordshire).* 2003;38(3):276-280.
155. Forsberg L, Ekman S, Halldin J, Rönnberg S. The readiness to change questionnaire: reliability and validity of a Swedish version and a comparison of scoring methods. *British journal of health psychology.* 2004;9(Pt 3):335-346.
156. Robinette RL. The relationship between the Marlowe-Crowne Form C and the validity scales of the MMPI. *Journal of clinical psychology.* 1991;47(3):396-399.
157. Andrews P, Meyer RG. Marlowe-Crowne Social Desirability Scale and short Form C: forensic norms. *Journal of clinical psychology.* 2003;59(4):483-492.
158. Braun V, Clarke V. Using thematic analysis in psychology. *Qualitative Research in Psychology.* 2006;3(2):77-101.
159. Hernandez AV, Steyerberg EW, Habbema JD. Covariate adjustment in randomized controlled trials with dichotomous outcomes increases statistical power and reduces sample size requirements. *J Clin Epidemiol.* 2004;57(5):454-460.
160. Fitzmaurice GM, Laird NM, Ware JH. *Applied Longitudinal Analyses.* Hoboken, NJ: John Wiley & Sons; 2012.
161. Rubin DB. Inference and missing data. *Biometrika.* 1976;63(3):581-592.
162. Serdarevic M, Striley CW, Cottler LB. Sex differences in prescription opioid use. *Curr Opin Psychiatry.* 2017;30(4):238-246.
163. Pisanu C, Franconi F, Gessa GL, et al. Sex differences in the response to opioids for pain relief: A systematic review and meta-analysis. *Pharmacol Res.* 2019;148:104447.
164. Cochran G, Bacci JL, Ylioja T, et al. Prescription opioid use: Patient characteristics and misuse in community pharmacy. *Journal of the American Pharmaceutical Association.* 2016;56(3):248-256.e246.
165. Bauer MS, Damschroder L, Hagedorn H, Smith J, Kilbourne AM. An introduction to implementation science for the non-specialist. *BMC Psychology.* 2015;3(1):32.
166. Ostergren JE, Hammer RR, Dingel MJ, Koenig BA, McCormick JB. Challenges in Translational Research: The Views of Addiction Scientists. *PLoS ONE.* 2014;9(4):e93482.
167. Lobb R, Colditz GA. Implementation Science and its Application to Population Health. *Annual review of public health.* 2013;34:235-251.
168. Kirk MA, Kelley C, Yankey N, Birken SA, Abadie B, Damschroder L. A systematic review of the use of the Consolidated Framework for Implementation Research. *Implementation Science.* 2016;11(1):72.
169. VanDevanter N, Kumar P, Nguyen N, et al. Application of the Consolidated Framework for Implementation Research to assess factors that may influence implementation of tobacco use treatment guidelines in the Viet Nam public health care delivery system. *Implementation Science.* 2017;12(1):27.
170. Serhal E, Arena A, Sockalingam S, Mohri L, Crawford A. Adapting the Consolidated Framework for Implementation Research to Create Organizational Readiness and Implementation Tools for Project ECHO. *J Contin Educ Health Prof.* 2018;38(2):145-151.
171. Warner G, Lawson B, Sampalli T, Burge F, Gibson R, Wood S. Applying the consolidated framework for implementation research to identify barriers affecting implementation of an online frailty tool into primary health care: a qualitative study. *BMC health services research.* 2018;18(1):395-395.
172. Archer S, Smid MC, Kelley AT, Baylis J, Foringer J, Cochran G (2020). Opioid Use in Pregnancy in Rural Communities: An Assessment of Treatment Implementation Needs, Barriers, and Facilitators. Oral presentation, Assocation for Medical Education and Research in Substance Abuse, Virtual Conferce. .

173. Bryan MA, Smid MC, Cheng M, et al. Addressing opioid use disorder among rural pregnant and postpartum women: a study protocol. *Addiction science & clinical practice.* 2020;15(1):33.
174. Lincoln YS, Guba EG. *Naturalistic inquiry.* Vol 75. Thousand Oaks, CA: Sage; 1985.