Study Protocol

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NIDA CTN-0075: Buprenorphine Physician-Pharmacist Collaboration in the Management of Patients with Opioid Use Disorder (Pharm-OUD-Care)

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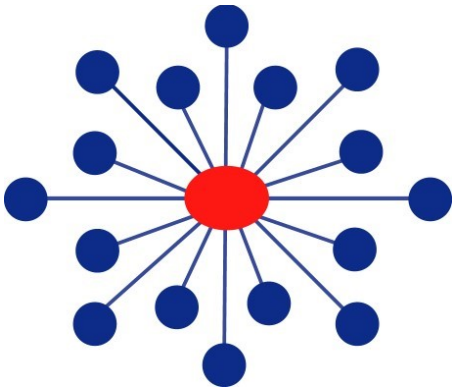

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Buprenorphine Physician-Pharmacist Collaboration in the Management of Patients with Opioid Use Disorder (Pharm-OUD-Care)

Lead Investigator (LI): Li-Tzy Wu, ScD, RN, MA

Co-LI: Paolo Mannelli, MD

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PROTOCOL DEVELOPMENT TEAM

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

Co-LI: **Paolo Mannelli, MD**
Mid Southern Node
Duke University

CCTN Scientific Officer: **Udi Ghitza, PhD**
National Institute on Drug Abuse

Data and Statistics Center (DSC): **Paul Van Veldhuisen, PhD**
DSC Principal Investigator
The Emmes Corporation

Clinical Coordinating Center (CCC): **Robert Lindblad, MD**
CCC Principal Investigator
The Emmes Corporation

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1.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AACP	American Association of Colleges of Pharmacy
AE	Adverse Event
APhA	American Pharmacists Association
AST	Aspartate Aminotransferase
ALT	Alanine Aminotransferase
CARA	Comprehensive Addiction and Recovery Act of 2016
CCC	Clinical Coordinating Center
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendment
CoC	Certificate of Confidentiality
CCTN	Center for the Clinical Trials Network
CDTM	Collaborative Drug Therapy Management
CMS	Center for Medicare and Medicaid Services
CPA	Collaborative Practice Agreement
CRF	Case Report Form
CTN	Clinical Trials Network
DEA	Drug Enforcement Agency
HHS	Department of Health and Human Services
DSC	Data and Statistics Center
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ED	Emergency Department
EDC	Electronic Data Capture
EHR	Electronic Health Record
ERC	Ethics Review Committee
FPFV	First Participant First Visit
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
GEE	Generalized Estimating Equation
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
LFTs	Liver Function Tests
LI	Lead Investigator
LN	Lead Node
LPLV	Last Participant Last Visit
MAT	Medication-Assisted Treatment
MOP	Manual of Operating Procedures

Abbreviation	Definition
MTM	Medication Therapy Management
NIDA	National Institute on Drug Abuse
OCA	Operational Care Agreement
OBBT	Office-Based Buprenorphine Treatment
OHRP	Office for Human Research Protections
OUD	Opioid Use Disorder
PDMP	Prescription Drug Monitoring Program
PI	Principal Investigator
RCT	Randomized Controlled Trial
Rx	Prescription
SAE	Serious Adverse Event
SAMHSA	Substance Abuse and Mental Health Services Administration
SOP	Standard Operating Procedure
SUD	Substance Use Disorder
SUSAR	Serious Unanticipated Serious Adverse Reaction
TLFB	Timeline Followback
UDS	Urine Drug Screen
US	United States
QA	Quality Assurance

2.0 STUDY SYNOPSIS AND SCHEMA

2.1 Study Objectives

The overall objective of this study is to explore the feasibility and acceptability of transitioning office-based buprenorphine treatment (OBBT) of adult patients with opioid use disorder (OUD) from physicians to pharmacists. Information generated from this pilot study will be used to inform the design of a future randomized controlled trial (RCT), which will test the effect of a physicianpharmacist collaborative care model in the management of patients with OUD. This pilot study will assess the feasibility and acceptability of the collaborative care model by measuring recruitment rate, treatment retention rate, treatment compliance rate, and participants' substance use. Treatment fidelity; participant, physician, and pharmacist satisfaction with OUD care; participant safety; and the pharmacists' use of electronic health records (EHR) and the Prescription Drug Monitoring Program (PDMP) will also be explored.

The clinical significance of this pilot study is to explore a coordinated care model based on an operational agreement protocol among members of the same health care team that can shift the work burden from OBBT physicians to pharmacists during buprenorphine maintenance. Through this distribution of work, physicians are better enabled to treat a higher number of patients with OUD while helping pharmacists develop OUD and substance use disorder (SUD) care skills management, thus more effectively assisting in the reduction of medication diversion and doctor shopping among this patient population. This Operational Care Agreement (OCA; see **SOP for OCA** in the Manual of Operating Procedures (MOP)) defines the tasks and responsibilities of OBBT physicians and community pharmacists in the management of OUD. Under the OCA, a licensed OBBT physician diagnoses patients, supervises patient care, and refers patients to a pharmacist under a protocol that allows the pharmacist to perform specific patient care functions (Giberson *et al*., 2011). Under this agreement, pharmacists working within the context of a defined protocol are permitted to assume professional responsibility for performing patient assessments, administering medications, and monitoring medication regimens. The overall results of this study will open new research venues to accelerate collaborative opportunities among primary care providers, addiction providers and researchers, and pharmacists (e.g., NIDA, American Pharmacists Association).

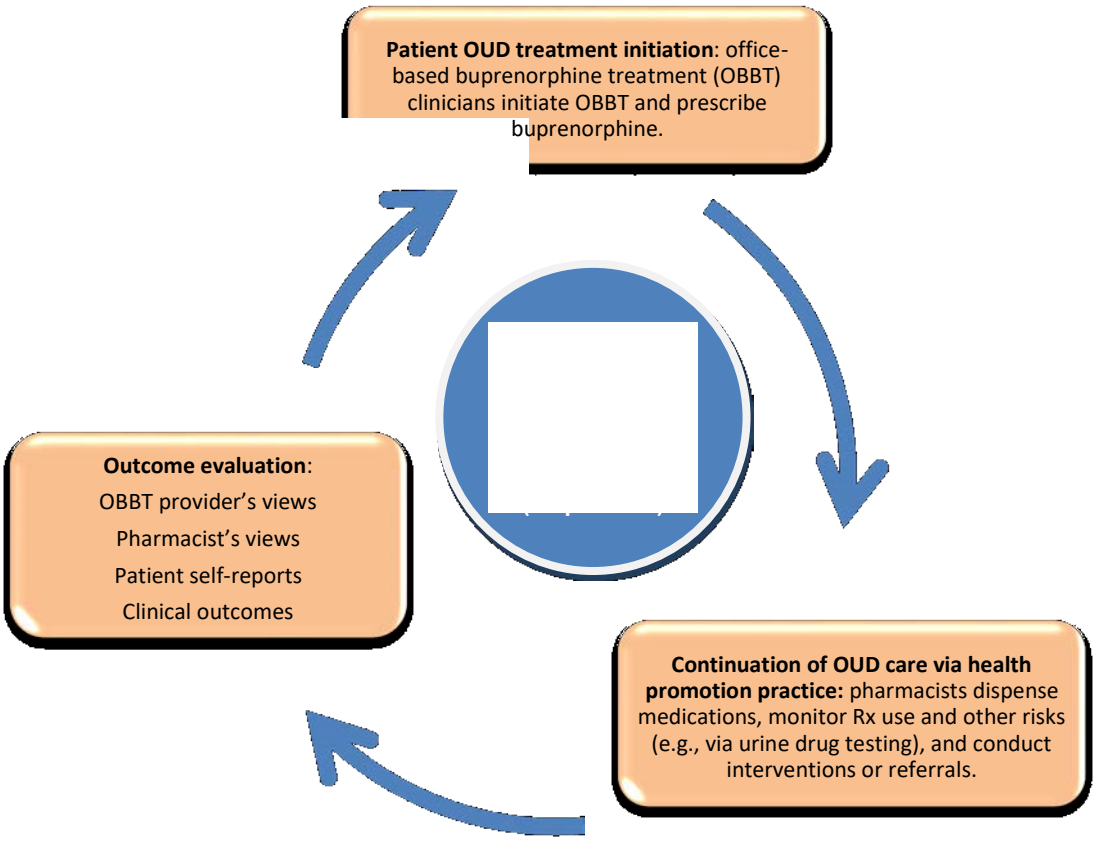
2.2 Study Design

This pilot study will use a non-randomized prospective design to collect feasibility data and operational information regarding the development of a physician-pharmacist collaborative care model defined by an operational care agreement for the management of patients with OUD. Pharmacists are health professionals. To explore the feasibility, this pilot study focuses broadly on licensed pharmacists in a variety of pharmacy settings, regardless of their prescriber status.

The conceptual model of physician-pharmacist collaboration in the management of patients with opioid use disorder (Figure 1): This pilot study builds on existing evidence demonstrating the key role of the pharmacist within the health care team to help improve delivery and accessibility of medical treatment, as well as initial indications of a positive collaboration between physician and pharmacist in the management of OUD (APhA, 2014; DiPaula & Menachery, 2015). Specifically, pharmacists are ideally positioned to engage in efforts aimed at improving OUD care management and drug overdose prevention (APhA, 2014). Pharmacists not only dispense prescription medications ("gatekeepers"), but also may be involved in educating patients about safe medication practices (including medication storage and disposal), identifying red flags that warrant further investigation (e.g., diversion, improper prescribing, drug-drug

interaction), and engaging in care coordination (Green *et al*., 2015). Regulations are in place that would allow a more direct intervention of pharmacists in the management of OUD medications as part of a treatment team (Bluml, 2005; CMS, 2016a; Giberson *et al*., 2011). A physicianpharmacist collaborative buprenorphine maintenance practice piloted at the same clinical setting with the help of a medical assistant has suggested that patient care can be improved by providing a treatment continuum (DiPaula & Menachery, 2015). Benefits included enhanced communication, reduced physician burden, enhanced monitoring for diversion, and reduced cost (DiPaula & Menachery, 2015). When patients initiate OBBT for OUD, they are expected to refill their buprenorphine medications approximately monthly and may receive medication use counseling at the pharmacy. The regular frequency with which patients visit the pharmacy to obtain buprenorphine refills offers an opportunity to evaluate pharmacy-based OUD care, including pharmacist-operated medication management under the supervision of a physician.

Figure 1. The conceptual model of physician-pharmacist collaboration in the management of patients with opioid use disorder



2.2.1 Overview of Study Design

Study design:

For the purpose of evaluating the feasibility of and obtaining operational information to guide a future multi-site RCT of pharmacy-based OUD care, we will implement a non-randomized prospective study design that will take place over a period of approximately 16-19 months. The overarching goal of the study is to explore the feasibility of the pilot physician-pharmacist

collaborative OUD care model, as well as OUD treatment outcomes and safety measures. In this study, pharmacists are defined broadly as *community pharmacists*. The intent to include a range of treatment settings and choosing community pharmacists versus a smaller subset of clinical pharmacists is related to generalizability. In particular, the model of collaboration is designed to follow general guidelines and be applicable to the participation of pharmacists in other states across the U.S.

The community pharmacist and the local pharmacy store are ubiquitous, similar to the mailman and post office. The identification of community retail pharmacists and pharmacies to be involved with buprenorphine treatment management guarantees a basic level of generalizability to the design and potential significance to feasibility data gathered in this pilot study.

Study sites:

Approximately 3-4 outpatient or ambulatory clinical sites will be included in this pilot study in order to explore the feasibility of implementing the interventional model in different clinical environments (e.g., academic, community-based, primary care). Each clinical site may include up to 4 buprenorphine physicians. A pharmacy typically includes 2 or 3 pharmacists, and buprenorphine physicians often have established working relationships with certain pharmacies. To reflect the real-world situation, up to 4 buprenorphine physicians at one site will collaborate with up to 3 pharmacists at a pharmacy in the management of patients with OUD.

Study Population and Sample Size:

1. Taking into account study attrition or dropout (Marcovitz *et al*., 2016; Soyka *et al*., 2008), approximately up to 140 adults aged 18 or older with DSM-5 OUD (defined by DSM-5 OUD Checklist) who are stabilized on buprenorphine may be consented in this study over a period of approximately 6-7 months at 3-4 buprenorphine clinic sites in order for 70 participants to be enrolled in the maintenance phase.

2. Approximately 6-12 (3-4 sites) OBBT physicians: Each study physician may enroll 10 or more patients over a period of 6-7 months to meet the goal for enrolling up to 70 participants (i.e., defined as meeting the study eligibility and enrolling into the maintenance phase). Each OBBT practice requires at least 2 OBBT physicians to participate in the study to reflect the real-life situation.
3. Approximately 6-12 pharmacists (up to 3 community pharmacists at a pharmacy).

Study Intervention/Pharmacy OUD care:

An Operational Care Agreement (see **SOP for OCA** in the MOP) is used to specify the pharmacist-provided patient care services that will be supervised by buprenorphine physicians.

Table 1: Estimated Study Duration

Phase	Total Duration (Months)	Location	Task	1 M	2 M	3 M	4 M	5 M	6 M	7 M	8 M	9 M	10 M	11 M	12 M	13 M	14 M	15 M	16 M	17 M	18 M	19 M
Pharmacist coaching	3-6 M	Pharmacy	Buprenorphine treatment education and training	X	X	X	X	X	X													

OBBT stabilization	6-7 M	OBBT Clinic	Intake/Baseline: OBBT Stabilization				X	X	X	X	X	X	X									
Pharmacy OUD care	13 M	Pharmacy	Maintenance and monthly follow-up				X	X	X	X	X	X	X	X	X	X	X	X	X			
								Pharmacy OUD Maintenance Care Phase														
EHR data collection & analysis	16 M	N/A (Medical Records)	Compare outcomes with matched patients, if data available				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Note: These study phases will overlap. Participants will be consented and enrolled on a rolling basis. Eligible participants may be consented as early as the beginning of the stabilization phase, upon the suggestion of the treating buprenorphine physician. Consented participants will not start pharmacy OUD management care until the stabilization phase ends, when they will be enrolled into the maintenance phase of the study. Pharmacists must complete the Pharmacist Coaching Training Phase before participating in the Pharmacy OUD Maintenance Care Phase.

Study duration:

Each paired study site will start study recruitment on a rolling basis, contingent on the timing of completing site initiation requirements. The estimated total study duration will be approximately 16-19 months. Given the variation across study sites in completing study training and participant enrollment, the duration of study duration will vary by study site. The study will consist of four overlapping phases:

1. Pharmacist Coaching Phase: It may take 3-6 months for all pharmacists and physicians to complete the coaching phase as specified by the SOP for Pharmacist Coaching in the MOP (3-6 months per pharmacist).

2. Consent and Enrollment Phase: Patients with OUD who are considered clinically stabilized and in OUD treatment for no more than 12 months since the start of the current OUD treatment episode will be recruited and consented. Participants will be consented in the study during their stabilization visits and enrolled in the maintenance phase at the end of their stabilization visits. Enrollment will be completed on a rolling basis. It may take 6-7 months for all participants to be consented and enrolled.

3. Pharmacy OUD Care Phase: This phase includes 6 monthly visits at the pharmacy. It will take about 13 months for all participants to complete this phase (6 months per participant).

4. EHR Data Collection and Analysis Phase: This phase involves the comparison of Buprenorphine Visit Checklist outcomes between study participants and matched nonpharmacy treated patients using medical record data, if available. Data from this phase will be utilized as part of the exploratory analyses.

Each participant will be asked to participate in this study for approximately 28-78 weeks. This range accounts for differences in the timing of study enrollment and individual differences in each participant's buprenorphine treatment schedule (e.g., within 12 months since the start of the current OUD treatment episode).

Rationale for study duration:

1. *Pharmacist Coaching Phase*: The coaching phase will include sufficient time for individual education and training, test taking, and coaching meetings (at least 1-2 per month). Based on the coaching plan, it is estimated that each pharmacist may complete coaching within 3-6 months.

2. *Consent and Enrollment Phase (to be completed during the OBBT care stabilization period)*: Based on the time allotted for consent and enrollment, it is estimated that each study site may recruit about 4-6 participants per month, or approximately 2-3 participants per buprenorphine prescribing physician per month. Potential participants will be prescreened and consented (i.e., sign the informed consent form) before the end of the stabilization period. The buprenorphine stabilization phase may take around 2-4 months per patient. However, the duration can vary depending on individual clinical conditions, with some patients needing more clinical monitoring by the buprenorphine physician and/or a longer time to be considered clinically stabilized. Thus, participant recruitment and consent may start before the stabilization phase is completed, and it will include patients receiving buprenorphine treatment for no more than 12 months for the current OUD treatment episode. The stabilization visit (Intake/Baseline) at the buprenorphine treatment clinic will be included among the study visits to establish treatment continuity with the subsequent pharmacist visits, as the participant is enrolled into the maintenance phase of the study.

3. *Pharmacy OUD Care Phase (Maintenance)*: Following buprenorphine induction and stabilization, maintenance visits will occur for 6 months, as this length of time is considered to be an adequate observation period to detect changes in treatment outcome among patients receiving OBBT for OUD (Mattick *et al*., 2014; Potter *et al*., 2013; Soyka *et al*., 2008; Fiellin *et al*., 2006; Schottenfeld *et al*., 2005). From the buprenorphine physician standpoint, the proposed observation time seems adequate to explore the ability of a pharmacist to manage and comply with a range of clinical scenarios and potential challenges offered by office-based buprenorphine treatment.

2.3 Outcome Assessments

One of the primary goals of the study is to monitor and reduce opioid and other drug use, as well as to explore the possibility of doing so with the help of the pharmacist. Outcome assessments will be conducted at each monthly visit throughout the maintenance phase of the study. Where applicable, assessments will be completed during the screening/baseline phase (following consent) to establish a baseline. Assessments will focus mainly on the feasibility and treatment outcome measures, which include the following:

Primary:

- Rate of recruitment among patients with OUD, defined as the number of participants recruited (i.e., signed the informed consent form) per month and by site. The average monthly rate of participants entering the maintenance phase among potential participants who were consented will also be calculated. We will also evaluate the number of potential participants pre-screened and the reasons for pre-screen failure and screen failure.
- Treatment retention: proportion of scheduled visits completed for Visit 2 through Visit 7.
- Opioid and other substance use: measured via urine drug screen and self-report (Timeline Followback).

- Medication compliance: measured by film count/dose reconciliation at each visit (proportion of expected buprenorphine use in relation to actual use).

Secondary:

- Treatment fidelity: adherence of physician and pharmacist to the Buprenorphine Visit Checklist using the Buprenorphine Visit Monitor form.
- Indicators of satisfaction with treatment delivery measured by participants, pharmacists, and physicians using the Treatment Satisfaction Survey.
- Participant safety measures over time: fatal and non-fatal substance-related overdoses and substance-related emergency department (ED) visits or hospitalizations, measured by self-report.
- Pharmacist's use of the Prescription Drug Monitoring Program (PDMP) and communications with the physician(s) to address PDMP reports at each visit, measured via self-report.

Preliminary/exploratory:

- Pharmacist's use of the EHR and PDMP to capture and monitor treatment outcome measures. Binary outcomes will be identified at each visit for measures from the Buprenorphine Visit Checklist that can be captured by or are missing from EHR, and their overlay with measures explored by the PDMP will be identified in a similar binary fashion. This outcome will only be assessed if EHR data are available.
- Use of the EHR to compare treatment outcome measures. A comparison of Buprenorphine Visit Checklist outcomes may be performed between study participants and matched non-pharmacy treated patients, if EHR data are available.

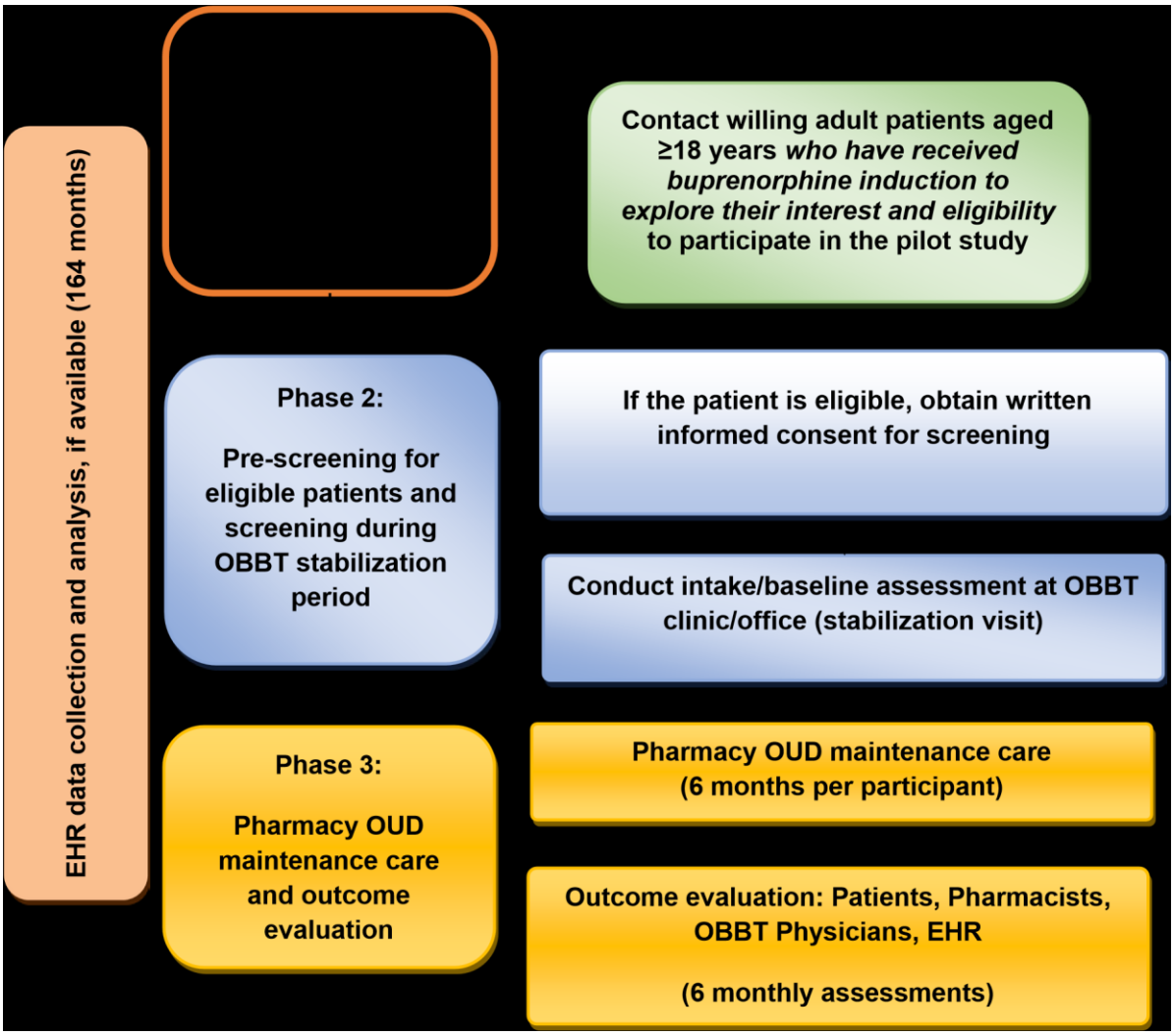
Depending on the access to the EHR, the EHR-related data elements may be collected by medical record abstraction.

Safety Reporting: For the purposes of this protocol, the collection and reporting of safety events will be limited to those collected on the Safety Event Response Checklist (see Section 10.5), including overdoses and death of any participant who provided informed consent. This includes any substance use-related ED visits and hospitalizations. The Safety Event Response Checklist will be available to report any safety events that occur during the course of the study.

2.4 Analyses

Because this is a non-randomized pilot study with a small sample size, descriptive analyses will be conducted to describe distributions of primary, secondary, and exploratory outcome measures. Random effects models will be considered and used to assess outcomes that are measured repeatedly throughout the maintenance phase.

3.0 STUDY FLOWCHART



4.0 INTRODUCTION AND SIGNIFICANCE

4.1 Prescription (Rx) Opioid and Heroin Overdose Epidemic

Rx drug misuse and addiction is an epidemic, and Rx drug overdose (mainly opioids) is a leading cause of accidental death in the United States (CDC, 2012; Volkow *et al*., 2014). The opioid overdose epidemic has been escalating continuously for over a decade (Straus *et al*., 2013; Rudd *et al*., 2016). Rx opioid misuse is linked with a surge of heroin use and serious heroin use problems (Pollini *et al*., 2011; Compton *et al*., 2016). Between 2010 and 2013, the rate of heroininvolved deaths almost tripled; non-Hispanic whites and adults aged 18-44 had the highest opioidinvolved death rate (Hedegaard *et al*., 2015). Most people who die from Rx opioid/heroin

overdose have been found to be adults 25-64 years old, non-Hispanic whites, or men; moreover, the mortality rate among women in recent years has increased rapidly to approach the rate among men (CDC, 2013a, 2015). Likewise, there has been an increase in opioid-involved treatment admissions to EDs and SUD treatment facilities (Crane, 2015; SAMHSA, 2015).

The rise in rates of opioid overdose deaths is related to a parallel increase in the availability of Rx and illicit opioids (including heroin), as well as the prescribing practices of some physicians (Paulozzi *et al*., 2012; Rudd *et al*., 2016). Physicians are a leading source of Rx opioids for highrisk opioid users (CDC, 2012). Nonmedical opioid users, characterized by frequent use of nonmedical opioids, have been found to be likely to obtain opioids from a physician's prescription or from a drug dealer (Jones *et al*., 2014). About 20% of the patients who were prescribed opioids have been prescribed high doses by either one or more physicians, and these patients were at a much higher risk for opioid-related overdoses (CDC, 2012). Prior data also suggested that about 25–66% of individuals who died of Rx drug overdoses used opioids prescribed to someone else (CDC, 2012). Opioid diversion or sharing is among the contributors to the opioid overdose epidemic (Paulozzi, 2012). Other clinical factors that may increase the likelihood of opioid overdoses include: medical conditions (especially chronic pain), use of high daily doses of opioids, history of mental health or psychiatric problems, substance misuse or SUD, co-use of opioids and benzodiazepines/sedatives, co-use of opioids and alcohol, and obesity (Gudin *et al*., 2013; McHugh *et al*., 2015; Paulozzi, 2012).

Pharmacist-provided interventions:

Pharmacists' unique responsibilities and expertise in dispensing medications, conducting medication management or counseling (especially for chronic conditions), as well as their increased interest in participating in efforts aimed at reducing Rx opioid overdose deaths provide strong foundations to include pharmacists in addiction research and OUD interventions (APhA, 2014). Pharmacists dispense Rx medications (e.g., opioids, naloxone) and have regular contact with patients at risk for opioid overdose. They are especially well-positioned to counsel patients and caregivers about opioid safety and provide naloxone rescue kits to the community.

One key priority for combating the epidemic of opioid overdoses and addiction is to improve the access to medication-assisted treatment (MAT), especially OBBT, for people with OUD (Jones *et al*., 2015; Volkow *et al.*, 2014). In 2015, an estimated 2 million Americans had prescription OUD in the past year, and about 0.6 million Americans had heroin use disorder in the past year (CBHSQ, 2016). Among persons with OUD in the past year, approximately 82% had prescription OUD only, 10% had heroin use disorder only, and 8% had both prescription OUD and heroin use disorder. Of persons with past-year OUD (prescription opioid or heroin use disorder), only about 26% received any type of alcohol or substance use treatment services in the past year, and only 19% received opioid-specific treatment (Wu *et al*., 2016). The low rate of service use for OUD is pervasive across all racial/ethnical groups; furthermore, this underutilization is the most marked amongst the uninsured, members of minority groups, and persons with prescription OUD only (i.e., without concurrent heroin use disorder) (Wu *et al*., 2016).

One major barrier to expanding Medication-Assisted Treatment (MAT) for OUD is related to the limited number of buprenorphine providers who are available and willing to treat OUD with MAT (Jones *et al*., 2015). Non-metropolitan or rural areas have relatively high rates of opioid overdose deaths, but residents in these areas face additional barriers to receiving OUD treatment due to a greater shortage of mental health and/or SUD providers (CDC, 2012; Quest *et al*., 2012; Rosenblatt *et al*., 2015). There is a pressing need to identify collaborative care models that can enhance the buprenorphine-waivered physicians' capability to effectively treat people with OUD

and to ensure that these models are applicable to remote areas where the access to buprenorphine-waivered physicians is limited. The main objective of the proposed physicianpharmacist collaborative care model is to address the significant barrier in the shortage of OBBT providers in the rural or remote areas by increasing pharmacists' skills in managing patients with OUD. Because this is a new area of addiction research, a pilot study that is focused on exploring the feasibility of study recruitment and other study operations is considered appropriate.

OUD is a chronic disorder that is often complicated by comorbidities (Wu *et al*., 2011a, 2011b). Adults with either prescription opioid or heroin use disorder tend to have an onset of OUD in their early 20s and experience more than one disorder episode, from which it may take up to 6-10 years to recover (Wu *et al*., 2011a, 2011b). The monitoring requirements for buprenorphine treatment (which encompass an extended period of OUD treatment), unique medication properties, and risk for diversion justify a significant role for pharmacist intervention. Pharmacists are well-versed in preventative care, patient counseling, and medication education to improve medication adherence and patient safety. Clinical trials have found that pharmacist interventions or pharmacist-provided patient care can improve chronic disease management and patient outcomes (e.g., medication adherence, patient knowledge, quality of life or general health status), and such pharmacist interventions appear to work best when pharmacists work collaboratively with primary care providers (Chisholm-Burns *et al*., 2010; O'Malley, 2011; Tsuyuki *et al*., 2002).

In light of increased concerns for primary care physician shortage, physician-pharmacist collaborative care models are considered an important solution for meeting patients' primary care service needs and mitigating potential adverse effects due to physician shortage (Smith *et al*., 2013). In the U.S., the supply of pharmacists is growing progressively (HHS, 2008). The total active pharmacist supply is projected to grow from 226,000 in 2004 to 305,000 by 2020 and 368,000 by 2030. The number of full-time-equivalent pharmacists is projected to grow from 191,200 in 2004 to 260,000 by 2020 and 319,000 by 2030 (HHS, 2008). Conversely, the U.S. is facing an increased level of primary care physician shortage. The demand for physicians has continued to grow faster than supply, leading to a projected shortfall of between 46,100 and 90,400 physicians (12,500 to 31,100 of which are primary care physicians) by 2025 (AAMC, 2015).

When pharmacists are part of a healthcare team, they can reduce the physician burden by supporting a patient-centered care approach, lowering the cost but not the quality of care (CPNP, 2016). Pharmacists' patient care process and strategies may include: applying evidence-based practices, collecting and assessing subjective and objective information about the patient to develop and implement an individualized plan, monitoring and evaluating the effectiveness of the care plan, and modifying the plan in collaboration with other health care professionals and the patient as needed (JCPP 2014; ASHP 2014). Putting a pharmacist on a healthcare team can reduce adverse drug reactions and lower costs (CDC, 2013b). If patients can go to a pharmacist for day-to-day medication-related management of their non-urgent conditions, physicians can spend more time seeing patients that really need their expertise (CDC, 2013b; Smith *et al*., 2013).

One codified approach to meet the goals of improving patient outcomes and reducing primary care physician burden is with a Collaborative Practice Agreement (CPA) between pharmacists and other health care physicians (CDC, 2013b). The CPA is a formal agreement in which a licensed physician makes a diagnosis, supervises patient care, and refers patients to a pharmacist under a protocol that allows the pharmacist to perform specific patient care functions (CDC, 2013b). Under the conditions of this agreement, the pharmacists' patient care services and tasks can be specified by the following terms (CDC, 2013b):

- Medication Therapy Management (MTM): MTM is a distinct service or group of services that optimizes therapeutic outcomes for individual patients (Bluml, 2005). MTM includes five core elements: medication therapy review, personal medication record, medicationrelated action plan, intervention and/or referral, and documentation and follow-up.

- Collaborative Drug Therapy Management (CDTM): CDTM is a collaborative practice agreement between one or more providers and pharmacists in which qualified pharmacists working within the context of a defined protocol are permitted to assume professional responsibility for performing patient assessments, counseling, and referrals; ordering laboratory tests; administering medication; and selecting, initiating, monitoring, continuing, and adjusting medication regimens.

In most states the law explicitly authorizes CPAs; in the majority of cases, it allows the pharmacist to provide MTM and CDTM, including, but not limited to, those providing direct contact with the prescribing physician (CDC, 2013b). The earlier Asheville Projects of pharmacist interventions in a collaborative healthcare team for diabetes, hypertension, and asthma care management in North Carolina demonstrated the feasibility and success of implementing pharmacist-provided care in improving clinical outcomes and lowering costs of care (Bunting *et al*., 2006, 2008; Cranor *et al*., 2003; Fera *et al*., 2009). Asheville Projects' success has inspired the development of similar efforts (e.g., MTM, CDTM) by the American Pharmacists Association (APhA) and others (Smith, 2009). The Asheville Projects' model showed significant savings on overall health spending and improved patient health (e.g., a significant reduction in the number of sick days) (CDC, 2013b).

Guided by the CPA, pharmacy health promotion practices, and OBBT guidelines, this pilot study will *explore* the feasibility of a physician and pharmacist collaborative care model that is defined by an Operational Care Agreement (OCA) between OBBT physicians and community pharmacies (APhA, 2014; Bluml, 2005; CMS, 2016a; Giberson *et al*., 2011; Green *et al*., 2015; Kampman and Jarvis, 2015). State-specific requirements of a CPA can limit the generalizability of the proposed study to other states. In addition, the national epidemic of opioid overdoses suggests the need for developing a feasible collaborative care model that can be applicable and acceptable to the general community pharmacists in order to increase its adoption and subsequent implementation. Thus, this pilot study seeks to explore the feasibility of a collaborative care model defined by an Operational Care Agreement that incorporates evidence-based OUD management care into the regular scope of community pharmacy practices, which fit into what pharmacists are doing or are prepared to do. An Operational Care Agreement between one or more buprenorphine physicians and pharmacists is developed to operationalize tasks and responsibilities in the management of patients with OUD for this pilot study (APhA, 2014; Bluml, 2005; CMS, 2016a; Green *et al*., 2015; Kampman and Jarvis, 2015).

Involvement of pharmacists with OUD treatment:

Recent federal opioid initiatives and the Comprehensive Addiction and Recovery Act of 2016 provide a framework to promote pharmacists' expanded roles in providing patient care activities to prevent opioid overdoses and improving OUD treatment (such as expanding access to naloxone and allowing partial fills for Schedule II controlled substances). The growing importance of pharmacists' roles for OUD management is confirmed in the 2016 guideline document 'Opioid Use Disorders: Interventions for Community Pharmacists' (CPNP, 2016), which indicates a stepby-step process for managing safe and appropriate access to opioids while protecting the public from the hazard of prescription misuse and addiction.

The clinical importance of pharmacist support in OUD treatment management has been explored in the literature. In France, community pharmacies routinely supervise buprenorphine dosing. In addition to being supportive of primary care physicians in prescribing buprenorphine, this supervision has been found as useful as urine monitoring of drug use in preventing diversion/misuse (Fatseas and Auriacombe, 2007). Opportunities for pharmacy involvement have received preliminary evaluation in the United States. A survey of 179 pharmacies found that 77% were willing to participate in dispensing buprenorphine (Lofwall *et al*., 2010). Some reasons for limited interest from pharmacies included not stocking buprenorphine, being too busy, or having insufficient staff, which highlight the importance of a concerted effort held by a healthcare team. One study has suggested that close collaboration between pharmacists and physicians contributes to a reduction in the physician's visit time and buprenorphine treatment cost (DiPaula and Menachery, 2015). A similar physician and pharmacist coordinated care model was utilized in the management of a methadone program in primary care with comparable positive results (Merril *et al*., 2005). These available but limited studies on OUD care support the proposed pilot study of a collaborative OBBT-physician and pharmacist OUD care model.

Taken together and given the high prevalence of untreated OUD and the relatively low number of available OBBT providers, there is a critical need to develop coordinated care models that can mitigate the shortage of OBBT providers by improving buprenorphine-waivered physicians' efficiency in managing OUD treatment and follow-up care (e.g., increasing the number of the patients with OUD treated by an OBBT provider). Community pharmacists' expertise in pharmacotherapy management and monitoring, medication education, and care coordination can assist with OUD care management, which may contribute to the efficient delivery of OUD care (APhA, 2014; DiPaula and Menachery, 2015).

4.2 Significance to the Field and Sustainability

To help combat the opioid epidemic, the U.S. Department of Health and Human Services (HHS) released a new rule in 2016 to allow qualified physicians to increase the total number of patients with OUD that they can treat with buprenorphine from 100 to 275 (Federal Register, 2016). The U.S. House of Representatives (2016) approved the Comprehensive Addiction and Recovery Act to promote a multi-faceted federal response to addressing the opioid epidemic, and which considers pharmacists key players of a healthcare team in curbing the opioid overdose epidemic (APhA, 2016a). Although the federal initiatives in supporting the expansion of OBBT are critical to improving OUD care (Stein *et al*., 2012), useful care models that can increase the efficiency of delivering the OBBT care to reach patients with OUD are needed to realize the stated goal.

Pharmacists are the most accessible and convenient resources of healthcare professionals. Over 60% of pharmacists reported that they could provide care for a minimum of 11 patients and up to 100 patients per week (APhA, 2016b). Thus, the clinical significance of this pilot study is to explore a coordinated physician-pharmacist OBBT care model that can shift the work burden from OBBT physicians by enabling them to treat a higher number of patients with OUD while helping pharmacists develop OUD and SUD care skills and management. Because of the ubiquity of community pharmacies, such a coordinated physician-pharmacist care model could be further expanded and tested in future RCTs to determine the involvement of pharmacists with patient evaluation, buprenorphine induction, and delivery of OUD treatment in rural areas with reduced access to direct physician care to improve OUD treatment.

As shown from the "landmark" Asheville Projects, the sustainability of the proposed pharmacy OUD care model will need to be evaluated from a value-based care program perspective (Bunting *et al*., 2008; Cranor *et al*., 2003; CDC, 2013b). The outcome will measure indicators of better

health, better care, and lower costs (CMS, 2016b). This pilot test will focus on the feasibility and indicators of health and healthcare status. The results will be used to design a full RCT to evaluate full indicators of a value-based care model for informing sustainability and health policy. Although a cost analysis will not be implemented in the pilot study, it is appropriate for the future full RCT. The Centers for Medicare and Medicaid Services (CMS) and private insurance programs have supported the pharmacists' MTM for qualified patients in an attempt to improve therapeutic outcomes, reduce the risk of adverse events, and lower cost (CMS, 2016a). Pharmacist collaborative care agreements have been implemented nationally and promoted by the Centers for Disease Control and Prevention (CDC, 2013b). Given that opioid overdose and addiction are among the most pressing public health crises in the nation, these multiple factors indicate the promise of sustainability.

4.3 Policy Support for Transforming Pharmacy Practices to Address OUD

Pharmacists not only dispense opioids and other medications, but also can be involved in educating patients about safe medication practices and medication storage and disposal, identifying red flags of diversion or improper prescribing for further evaluation, and engaging in care coordination (Green *et al*., 2015). The American Pharmacists Association (APhA) has promoted efforts to expand the role of the pharmacist from a primary medication dispenser to a patient-centered care provider, which encourages pharmacists to use a team-based approach to engage patients in their pharmacy practice and optimize medication outcomes (APhA, 2014, 2016b). One key focus of this expanded role is to increase training and education in prescription drug abuse and addiction for pharmacists, in order to facilitate the use of strategies or tools to address opioid addiction (APhA, 2014). Likewise, the American Association of Colleges of Pharmacy (AACP) announced that 54 colleges and schools of pharmacy have committed to joining the fight against prescription drug abuse by educating and training student pharmacists about lifesaving overdose interventions, including how to counsel patients and their family members on appropriate use of lifesaving medications (AACP, 2016).

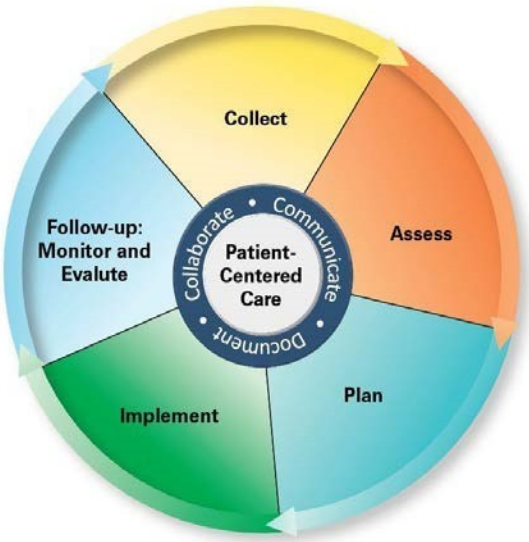
Furthermore, recent healthcare reforms (e.g., the Affordable Care Act) have shifted the landscape of healthcare delivery towards an integrated or coordinated model (e.g., medical homes, community-based care delivery models) by promoting the provision of the full spectrum care in order to improve the overall population health management. As a result, pharmacists have been progressively recognized as integrated members of team-based care delivery models, as they can provide some primary care services to meet the increased demands for primary care services. They can accomplish this by engaging in coordinated care across multiple settings to increase the efficiency in patient care and to mitigate the shortage of primary care providers (Smith *et al*., 2013). Existing medical and OUD evidence suggests that the pharmacist can meet the challenges of managing buprenorphine treatment of OUD within the framework and specifications of a collaborative care agreement (APhA, 2014; CDC, 2013b; DiPaula and Menachery, 2015).

Goal of this pilot study:

Community pharmacists are an under-utilized resource for healthcare professionals in the OUD management efforts. A survey about pharmacists' perceptions and attitudes toward dispensing buprenorphine to patients with OUD suggested that pharmacists expressed positive attitudes towards patients treated for OUD with buprenorphine (Raisch *et al*., 2005). The available research data provides the support to conduct a pilot study of the pharmacy-based coordinated OUD care model. The study goal is guided by the Pharmacists' Patient Care Process Model (**Figure 2**) (JCPP, 2014). The overall findings from this pilot study will be used to guide NIDA CTN's further

research designs, intervention components, and/or treatment approaches within pharmacy settings that are acceptable to pharmacists and feasible within pharmacy practices (JCPP, 2014).

Figure 2. Pharmacists' Patient Care Process Model



•Collect

The pharmacist collects subjective and objective information about the patient.

•Assess

The pharmacist assesses and analyzes the information in the context of the patient's health goals.

•Plan

The pharmacist develops an individual patient-centered care plan.

•Implement

The pharmacist implements the plan with other healthcare professionals and the patient.

- **Follow-up: Monitor and Evaluate**

  The pharmacist monitors and evaluates the plan's effectiveness and helps make modifications as needed.

5.0 OBJECTIVES

5.1 Primary Objectives

The overarching goal of this pharmacy OUD care pilot study is to explore the feasibility and acceptability of shifting the OBBT of OUD from physician to pharmacist care in order to inform the development of a future multi-site RCT. We will achieve this goal by pursuing four primary pilot study objectives. Specific measures of study objectives outcomes are defined in Section 8.0.

1. Calculate the rate of recruitment among patients with OUD, defined as the number of participants recruited (i.e., signed the informed consent form) per month and by site. The average monthly rate of participants entering the maintenance phase among potential participants who were consented will also be calculated. The number of potential participants pre-screened and the reasons for pre-screen failure and screen failure will also be evaluated.

2. Examine retention in treatment, as determined by the proportion of scheduled visits completed for Visit 2 through Visit 7.

3. Examine prevalence of use of opioids/heroin and other substances, measured by the proportion of positive urine drug screens (UDS) at each visit and days of use of

opioids/heroin, and other substances as collected on Timeline Followback (TLFB) over the study duration.

4. Determine medication compliance, measured by film count/dose reconciliation at each visit (proportion of expected buprenorphine use in relation to actual use).

5.2 Secondary Objectives

The secondary objectives are to generate point estimates for:

1. Treatment fidelity: adherence of physician and pharmacist to the Buprenorphine Visit Checklist (Section 10.4) as recorded on the Buprenorphine Visit Monitor form (Section 10.6): proportion of visits showing 80% adherence or higher (Borrelli, 2011).

2. Indicators of satisfaction with treatment delivery by participants measured using the Treatment Satisfaction Survey (adapted from Harland *et al*., 2005) at each visit: proportion of visits in which raters are satisfied (score of 4 on a Likert Scale of 1-5) or very satisfied (score of 5 on a Likert Scale of 1-5). Pharmacist and physician satisfaction with treatment delivery measured using the Treatment Satisfaction Survey on a monthly basis, and a proportion of physician and pharmacist monthly ratings of satisfied or very satisfied will be calculated.

3. Participant safety, as measured by:

   a) Any fatal or non-fatal substance-related overdose measured by self-report.

   b) Any substance-related ED visit or hospitalization, measured by self-report.

4. Pharmacist's use of the PDMP and communications with physician to address PDMP reports including measures of multiple buprenorphine prescriptions, other class II and III medication prescriptions (e.g., communicate with physician to address PDMP reports and record it on the Buprenorphine Visit Checklist at each visit).

5.3 Preliminary/Exploratory Objectives

1. Pharmacist's use of the EHR to capture and monitor treatment outcome measures (monthly measures during the pharmacist OUD management phase). Binary outcomes will be identified at each visit for measures from the visit checklist, and their overlay with measures explored by the PDMP will be identified in a similar fashion. This outcome will only be assessed if EHR data are available.

2. Use of the EHR to compare treatment outcome measures. A comparison of visit checklist outcomes may be performed between study participants and matched non-pharmacy treated patients, if EHR data are available. Depending on the access to the EHR, these EHR data will be collected by medical record abstraction.

6.0 STUDY DESIGN

6.1 Overview of Study Design

This pilot study is not designed to evaluate hypotheses. Given that the proposed study is a new area for the NIDA CTN and that it requires collaborative efforts among health professionals at multiple settings, the focus of this pilot study is to explore the feasibility and understand operational processes and potential challenges. Specifically, this pilot study is designed to explore the acceptability and feasibility of transferring OBBT of OUD from physician to pharmacist care and to inform the development of a future multi-site RCT that will compare physician-based and physician-pharmacist-collaborative OUD buprenorphine treatment. To maximize efficiency of research funding, we have selected design and measures to most effectively assess different aspects of the study. We have also considered the structure and organization of an OBBT physician office and of a community pharmacy in the real-world setting. We will track recruitment, reasons for pre-screen and screen failure, and request the feedback of study participants, buprenorphine physicians and pharmacists regarding satisfaction with treatment. Further, buprenorphine physicians and pharmacists will be asked to provide feedback on their satisfaction of the training/coaching process that will be utilized in the study. Because the study seeks to improve both the quality of OUD care and the involvement of pharmacists in OUD care, the OUD clinic care team and research staff will interact with community pharmacies based on an Operational Care Agreement.

Although generalizability is not the main focus of the pilot study, we have incorporated key components to enhance the applicability and clinical utility of study results. First, we plan to include pharmacies that will collaborate with academic and non-academic sites. The diversity in setting is related to generalizability. Second, we will recruit “the general community pharmacists” to participate in this pilot study (i.e., any licensed pharmacist at an eligible site), and it will not be limited by a smaller subset of clinical pharmacists. In addition, our proposed ‘physician-pharmacist care agreement’ is designed to follow general clinical guidelines for community pharmacists that will allow community pharmacists to incorporate health care for patients receiving buprenorphine for opioid use disorder into their practice. This physician-pharmacist care agreement model will be applicable to pharmacists in other states across the country.

We will track the problems encountered during the implementation of the study, including organizational readiness to deliver Medication-Assisted Treatment (MAT) services with feedback from physicians, pharmacists and participants, as well as operational feedback or comments from research staff members (e.g., issues discussed during regular project calls). A brief survey questionnaire will be developed to collect such information from physicians and pharmacists. We will discuss possible solutions and recommendations at the regular project meetings and summarize them in the final study report.

Study setting:

Approximately up to 4 clinical sites - including approximately up to 4 pharmacy sites - will be included in this pilot study in order to explore the feasibility and acceptability of the interventional model in different clinical environments (e.g., academic, community-based, primary care). Based on the practice considerations that 2 or more buprenorphine physicians often work together at a clinical site and that patients tend to have a regular pharmacy for refilling buprenorphine prescriptions, this pilot study will explore a collaborative care model between 2 or more buprenorphine physicians and pharmacists at a community pharmacy setting. In order to test the reproducibility and generalizability of the pilot study intervention in a future study, an Operational

Care Agreement (see **SOP for OCA** in the MOP) will be adopted to define and specify the pharmacist-provided patient care services that will be recognized by physicians, consistent with evidence-based OBBT of OUD.

This pilot also will explore the use of the PDMP for OBBT care by physicians and pharmacists, and whether pharmacists have access to the EHR. Pilot data have shown the workflow, ease of use, and added technical value of presenting PDMP data in the EHR system by integrating the EHR and PDMP systems (Indiana, PDMP-INSPECT 2102). However, simultaneous use of the PDMP and EHR is typically limited to ED settings and has only been achieved through separate access to each system (i.e., the systems have not yet been successfully combined) (GreenwoodEricksen *et al*., 2016; SAMHSA, 2013).

Design:

This pilot study consists of a single-arm, 24-week (pharmacist OUD maintenance intervention), open-label, pilot study of pharmacist-provided buprenorphine maintenance treatment of OUD.

Study participants and enrollment:

Study participants will be adults aged ≥18 years with OUD who have completed buprenorphine induction at the study clinical sites. We will track the rate of participant recruitment (approximately up to 140 adults may be consented in order to enroll 70 participants into the study maintenance phase) and retention in treatment to estimate the duration of study recruitment and treatment required for a future multi-site RCT. Participants will be considered "recruited" once they have signed the informed consent form. *The proposed sample size takes into account possible attrition during the early stage of the study, as prior studies suggest that approximately up to 50% of participants may drop out at some point during 6 months of treatment. Of note, approximately 30% to 40% of the participants that drop out are usually lost to follow up in the induction-early stabilization phases of buprenorphine treatment (Marcovitz et al., 2016; Soyka et al., 2008).* If the study timeline allows, additional participants will be recruited with the main intent to replace participants who discontinue from the study early (i.e., prior to Visit 2 or 3). Although all pharmacists are expected to complete the pharmacist training and coaching on buprenorphine treatment within 3-6 months, it is anticipated that pharmacists may complete this training after 34 months. Thus, study recruitment may begin as early as the 3rd or 4th month. Pharmacists must successfully complete the buprenorphine treatment coaching phase before they can begin the pharmacist intervention.

The study will recruit and consent patients with OUD that have been considered clinically stabilized and in the OUD treatment for **no more than 12 months** since the start of the current OUD treatment episode. During the stabilization phase, participants may be recruited into the study (i.e., complete the informed consent process and begin preliminary study assessments) before the last stabilization visit. The screening/intake and baseline assessments, together referred to as Visit 1 or the Intake/Baseline Visit, may be completed on more than one occasion within a short period of time, depending on the participant's schedule. The Intake/Baseline Visit will include the stabilization visit at the OBBT physician's office. Following completion of buprenorphine stabilization, participants will be transitioned to maintenance visits with the pharmacist. During this maintenance period, each participant will complete 6 monthly visits (i.e., every 4 weeks) at the pharmacy for buprenorphine management. Each of these 6 visits with the pharmacist will include the following procedures and assessments: collection of urine samples to confirm self-reported substance use/abstinence, medication compliance through recount and reconciliation, safety event assessment, psychosocial treatment engagement, and treatment satisfaction assessment.

Primary outcomes:

Primary outcomes of treatment participation retention at 24 weeks, opioid and other substance use, and medication compliance will be assessed at each visit.

6.2 Duration of Study and Visit Schedule

Taking into account study attrition or dropout, approximately up to 70 adults stablized on buprenorphine may be consented and enrolled in the maintenance phase of the study over a period of approximately 6-7 months at 3-4 buprenorphine clinic sites. Each participant may be engaged in the overall study for approximately 28-40 weeks as follows:

- Approximately 4-8 weeks: pre-screening, consent, and screening (beginning as early as the first stabilization visit), including the time for buprenorphine stabilization. It is possible that this period may last up to 16 weeks. Once all study eligbility criteria are confirmed, the participant may proceed to enrollment into the maintenance phase of the study.
- 24 weeks (6 visits total): maintenance treatment with monthly study visits.

Buprenorphine physicians and community pharmacists will be involved with the study for an additional 3-6 months of education, training, and coaching (see **Table 1**). This coaching/training phase will be completed prior to enrolling the first study participant.

6.3 The Rationale for Study Duration

(24-week pharmacy OUD intervention and timing of pharmacist treatment initiation)

Study time periods have been developed to facilitate the participation of otherwise busy professionals and reproduce 'real world' clinical conditions. The coaching phase is designed to include sufficient time for individual education and training, test taking, and coaching meetings (at least 1-2 per month). Based on the time allotted for consent and enrollment, it is estimated that each study site may recruit about 4-6 participants per month, or approximately 2-3 participants per buprenorphine prescribing physician per month. The buprenorphine stabilization phase may take 2-4 months. However, the duration can vary depending on the individual clinical conditions, with some patients needing more clinical monitoring by the buprenorphine physician, and/or more time to be considered clinically stabilized. Thus, participant recruitment and consent may start before the stabilization phase is completed, and it will include patients receiving buprenorphine treatment for no more than 12 months for the current OUD treatment episode. Depending on the participant's schedule, baseline assessments may be completed over multiple visits to the OBBT clinic. The stabilization visit at the buprenorphine treatment clinic (Intake/Baseline) will be included among the study visits to establish treatment continuity with the subsequent pharmacist visits. The main purpose of this pilot study is to assess the feasibility and acceptability of shifting the OBBT of OUD from physician to pharmacist in order to inform the development of a future multisite trial. We have, therefore, opted to study the phase of buprenorphine maintenance and test the aptitude of the pharmacist in managing treatment once the patient is considered clinically stabilized. A length of 24 weeks for the pharmacy OUD intervention allows sufficient time for detecting significant changes in outcomes as suggested in the literature (Mattick *et al*., 2014; Potter *et al*., 2013; Soyka *et al*., 2008; Fiellin *et al*., 2006; Schottenfeld *et al*., 2005) and confirmed by clinical experience.

7.0 STUDY POPULATION

Taking into account study attrition or dropout (Marcovitz *et al*., 2016; Soyka *et al*., 2008), approximately up to 70 adults stabilized on buprenorphine may be consented and enrolled in this study (i.e., defined as meeting the study eligibility and enrolling into the study maintenance phase) over a period of approximately 6-7 months at 3-4 buprenorphine clinic sites.

7.1 Inclusion Criteria

Individuals participating in the pilot study must:

1. Be adults aged 18 years or older.

2. If female, use adequate birth control methods.

3. Meet DSM-5 criteria for past-year OUD.

4. Have completed buprenorphine induction for OUD.

5. Have expressed the intention to receive maintenance (≥6 months) buprenorphine treatment.

6. Be willing to receive pharmacist administered buprenorphine maintenance treatment.

7. Be willing and able to provide written informed consent and HIPAA authorization.

8. Be able to read and communicate in English.

9. Be able to comply with buprenorphine treatment policies.

7.2 Exclusion Criteria

Individuals will be excluded from the pilot study participation if they:

1. Have a serious medical, psychiatric or substance use disorder that, in the opinion of the study physician, would make study participation hazardous to the participant, compromise study findings, or prevent the participant from completing the study.

   Examples Include:

   Disabling or terminal medical illness (e.g., heart failure, cirrhosis or end-stage liver disease, acute hepatitis or moderate to severe renal impairment) as assessed by medical history, review of systems, physical exam, and/or laboratory assessments; current severe, untreated or inadequately treated mental health disorder (e.g., active psychosis, uncontrolled manic-depressive illness) as assessed by mental health history and/or clinical interview; current severe benzodiazepine or other substance use requiring medical detoxification; suicidal or homicidal ideation requiring immediate attention.

2. Have known allergy or hypersensitivity to buprenorphine, naloxone, or other components of the buprenorphine/naloxone formulation.
3. Have aspartate aminotransferase (AST) or alanine aminotransferase (ALT) liver enzymes greater than 5 times the upper limit of normal on screening phlebotomy performed within 60 days prior to the date of the Intake/Baseline Visit (Visit 1).
4. Have chronic pain requiring ongoing pain management with opioid analgesics.
5. Currently in jail, prison or any overnight facility as required by court of law or pending legal action that couldprevent participation in study activities (i.e., unable to complete 6 months of pharmacy-based OUD management).
6. Pregnant or breastfeeding at the time of screening.

7.3 Participant Recruitment

Study participants will be recruited from participating buprenorphine ambulatory, outpatient or primary care clinics, which will serve as study sites. These outpatient offices/clinics typically offer a broad array of on-site case management, social work, and counseling support services to engage and retain OUD patients in care. Members of the OUD clinic care team will be informed about the pilot study and asked to refer potential participants who are interested in learning more about the study to clinic research staff for pre-screening. Specific recruitment procedures (e.g., local educational activities, community outreach, print and web- based advertisements, etc.) will vary by site accordingly to local needs and established procedures of buprenorphine patient enrollment in research.

Each Site Principal Investigator (PI) or Investigator will be a buprenorphine-waivered physician with a population of patients active in treatment sufficient to reach the recruitment goals. Each Site PI will work with at least one additional buprenorphine provider. We anticipate excellent cooperation between these providers in approaching potential participants and having the ability to function as backups for one another during the study period.

If a potential study participant is interested in learning more about the study, a study staff member will meet with the participant to discuss the study. Potential participants will have initiated buprenorphine treatment (i.e., completed the induction phase) and will be briefly instructed regarding the study. If the potential participant is interested in joining the study, the study staff member will commence the formal informed consent process. Potential participants will have to demonstrate an understanding of the study requirements as part of the consent process prior to providing written informed consent. Strict ethical guidelines regarding professional conduct and confidentiality will be enforced for all study staff.

Recruiting participants in clinical settings poses many challenges to pre-screening and consenting potential participants, including the rapid pace of care, interruptions in clinical workflow, clinic productivity requirements, space limitations, and participants not feeling well enough to meet with research staff (Berkman *et al*., 2001; Falcon *et al*., 2011). To minimize the impact of these challenges, research staff will spend considerable time interacting with clinical staff, familiarizing themselves with clinic patient flow, and learning how to communicate and negotiate with clinic staff regarding the necessary space and time to meet with potential study participants. Site Investigators will help facilitate negotiation of space and time requirements and serve as a resource to research staff regarding clinic procedures. Staff and sites with experience and expertise in buprenorphine treatment of OUD and conducting research studies in outpatient clinic settings will be prioritized for site selection.

The study staff member conducting the Intake/Baseline Visit will negotiate the location of the visit as necessary to protect confidentiality and respect clinic patient flow. Each study site will be compensated for space use based on the number of study visits. If necessary, the potential participant will be given the option to participate in study screening and consent procedures in a nearby exam room or staff/patient lounge if it is unoccupied, or to reschedule the visit for another time. If a participant feels ill during the interview, research staff will stop and reschedule the visit. Although all attempts will be made to conduct the intake/baseline assessments over 1 or 2 visits, it is possible that they may be completed over multiple visits to the OBBT clinic, depending on the participant's schedule.

7.3.1 Special Populations to Consider

This study may consent and enroll persons involved in the criminal justice system who are receiving OBBT for OUD and who will be available to complete 6 months of pharmacy-based OUD management. Parolees who are persons living in the community and sentenced to community-supervised monitoring may be consented and enrolled. Parolees who are detained in a treatment center as a condition of parole will NOT be consented and enrolled. Probationers (individuals wearing monitoring devices) may also be consented and enrolled, depending on their level of involvement with the criminal justice system. The study will not recruit persons incarcerated/detained in a correctional facility, persons who are pending trial, or persons who otherwise meet the definition of a prisoner as delineated in 45 CFR 46.303(c). However, the study will not exclude parolees and probationers if the persons will be available to complete 6 months of pharmacy-based OUD management. Those participants who become incarcerated or otherwise meet CFR-defined prisoner criteria during the course of their involvement with this study will be withdrawn from study participation. Research staff will assess each participant's prisoner status at each visit, prior to conducting any research-related procedures. If a participant becomes incarcerated or otherwise meets the 45 CFR 46 definition of a prisoner, all applicable guidelines will be followed, including any required reporting to the IRB or other institution.

7.4 Number of Sites

Approximately 3-4 primary care, outpatient, or ambulatory clinics will serve as study sites, with two or more buprenorphine-waivered physicians per site. Each primary care, outpatient, or ambulatory clinic will be paired with a community pharmacy site, such that up to 3-4 community pharmacy sites, with up to 3 pharmacists per site, will participate in the study. Each physician will supervise the activities in the study of one or more community pharmacists.

7.5 Site Characteristics

Buprenorphine treatment clinics will be selected on the basis of the following characteristics:

- Provide buprenorphine treatment to OUD patients at a primary care, outpatient, or ambulatory care setting.
- Have a sufficient number of potential participants to achieve study recruitment goals (i.e., the OBBT clinic is expected to have the capability (e.g., structure, personnel) to treat at least 10 new patients per month).
- Have at least two buprenorphine-waived physicians in good standing with their State Medical Board and willing to stipulate an Operational Care Agreement and coach and supervise pharmacists in the use of buprenorphine for the management of OUD.

- Have prior experience in clinical data collection or have previously participated in research/clinical studies.
- Offer addiction counseling services as part of usual care on-site, or be able to refer participants to such services offered at an affiliated or nearby location (not required but encouraged).
- Have adequate and safe tele-communication tools (phone, fax, email) to share protected health information regarding participants with pharmacists.

Pharmacy sites will be selected on the basis of the following characteristics:

- Have at least 2 years of experience with storing and dispensing class II and III controlled substances.
- Have direct experience with dispensing buprenorphine treatment for OUD.
- Have Clinical Laboratory Improvement Amendment (CLIA) certificate of Waiver to perform lab tests (or be willing to obtain the CLIA certificate of Waiver before the study initiation.)
- Have at least one pharmacist in good standing with their State Board and willing to stipulate an Operational Care Agreement and comply with training and study guidelines.
- Have available private areas (e.g., small room or office) to conduct visits with study participants.
- Have adequate and safe tele-communication tools (phone, fax, email) to share protected health information regarding participants with buprenorphine physician(s).

We will develop and use the site inventory/selection form (site survey) to collect this information from clinical and pharmacy sites in the geographical area identified for participation in the study. This form will briefly summarize the characteristics of the study and inquire on the characteristics of the site required for participation as reported above. In the case of the community pharmacies, we will also ask about reasons for participation and non-participation in the trial during discussions with potential study sites (e.g., lack of time, plethora of/insufficient staff, willingness/unwillingness to deal with substance users, concerns with losing business, intent to increase clientele, fear of not being up to the task, desire to show competency in the matter, etc.). We will use organizational readiness questions (to be completed by physicians, pharmacists, and clinic/pharmacy staff or managers) to explore participating sites' barriers and/or facilitators to OUD treatment.

7.6 Rationale for Site Selection

A pilot study is a requisite initial step in exploring a novel intervention or an innovative application of an existing intervention, which is often limited to testing the feasibility of the treatment at a single site (Leon *et al.*, 2011). As the different components of treatment and the environment in which the treatment is delivered are particularly important in this case, we intend to assess the feasibility and generalizability of this model at different sites, including academic and community clinics. Sites that have an adequate number of new buprenorphine treated participants per month will be selected for participation.

Depending on the number of study physicians at a study site, we will need to enroll approximately 10-20 or more participants per site over 6-7 months of recruitment in order to meet the recruitment goal. We will track the reasons for pre-screen failure and the ratio of participants who have signed the informed consent form among those who have undergone the prescreening process (i.e., have been approached for potential participation and have had the study described to them, and

were eligible on the pre-screen) to help project the expected recruitment in a subsequent multi-site full-scale study.

8.0 OUTCOME MEASURES

8.1 Primary Outcome Measures

As this is a feasibility study, there are several outcomes of interest, all of which are important to evaluating the potentiality of a full-scale RCT and informing the power calculations and design of this subsequent RCT. There will be no formal hypothesis testing for these outcome measures, since only estimation is of interest.

The primary outcome measures for this feasibility pilot study are:

1. Rate of recruitment of participants into trial

The recruitment rate will be assessed on a monthly basis until the enrollment target is reached. The recruitment rate is operationalized as the total number of participants consented in one month. The per-month proportion of consented participants reaching the the maintenance phase will also be calculated, as well as the per-month proportion of pre-screened participants that were consented. These rates will be used to estimate the speed at which a future multi-site RCT could consent, enroll, and randomize participants. Site-specific rates will also be computed to inform the design of the full-scale trial.

2. Retention in treatment

Retention in treatment is defined as the proportion of scheduled visits completed (i.e., pharmacy OBBT maintenance phase visits) for Visit 2 through Visit 7. Not counting the Intake/Baseline Visit, the number of expected visits for all participants at the pharmacy is 6, based on 1 visit per month for the 6 months of the pharmacy OBBT maintenance phase.

3. Opioid and other substance use

The prevalence of use of opioids/heroin, measured by the proportion of positive urine drug screens (UDS) at each visit and days of use of opioids/heroin as collected on Timeline Followback (TLFB) over the study duration will be examined.

4. Medication compliance

Buprenorphine will be provided in the form of buprenorphine-naloxone sublingual film (Suboxone®). Medication compliance will be measured by film count/dose reconciliation at each visit (i.e., film count). The proportion of expected buprenorphine use in relation to actual use will be calculated at each visit.

8.2 Secondary Outcome Measures

There are also several secondary outcome measures. These outcomes will also be used to help explore whether and how to proceed with a future full-scale study.

The secondary outcome measures for this pilot study are:

1. Treatment fidelity

Treatment fidelity will be defined by adherence of physician and pharmacist to the Buprenorphine Visit Checklist (Section 10.4) using the Buprenorphine Visit Monitor form: proportion of visits showing 80% adherence or higher (Borrelli, 2011).

2. Satisfaction of participants, physicians and pharmacists with OUD care

Satisfaction with treatment delivery by participants will be measured using the Treatment Satisfaction Survey (adapted from Harland *et al.*, 2005) at each visit. The proportion of visits in which participants are satisfied (score of 4 on a Likert Scale of 1-5) or very satisfied (score of 5 on a Likert Scale of 1-5) will be calculated. Pharmacist and physician satisfaction with treatment delivery will be measured using the Treatment Satisfaction Survey on a monthly basis, and a proportion of physician and pharmacist monthly ratings of satisfied or very satisfied will be calculated.

3. Participant safety, as measured by:

a) Any fatal or non-fatal substance-related overdose measured by self-report.

b) Any substance-related ED visit or hospitalizationmeasured by self-report.

4. Pharmacist's use of the PDMP

Pharmacist's use of the PDMP and communications with physician to address PDMP reports, including measures of multiple buprenorphine prescriptions and other class II and III medication prescriptions, will be evaluated by self-report on the checklist at each visit.

8.3 Preliminary/exploratory Outcome Measures

1. Pharmacist's access to the EHR to capture and monitor treatment outcome measures

Binary outcomes will be identified at each visit for measures from the Buprenorphine Visit Checklist, and their overlay with measures explored by the PDMP will be identified in a similar binary fashion. This outcome will only be assessed if EHR data are available.

2. Use of the EHR to compare treatment outcome measures

A comparison of visit checklist outcomes may be performed between study participants and matched non-pharmacy treated patients, if EHR data are available. Depending on the access to the EHR, such EHR data will be collected by medical record abstraction.

9.0 STUDY PROCEDURES

9.1 Study Phases

The pilot study will include 3 overlapping phases that are projected to take up to 16-19 months and reflect the fact that participants will be consented and enrolled on a rolling basis.

Table 2: Timeline of study phases

Phase	Phase 1	Phase 2	Phase 3
Location	Pharmacy	OBBT Clinic	Pharmacy

Activity	Pharmacist coaching, education	Buprenorphine stabilization (pre-screening, consent, and screening)	Buprenorphine maintenance
Total Duration	Up to 16-24 weeks (3-6 months)	Up to 16-20 weeks (6-7 months)	24 weeks (6 months) per participant; up 13 months for all participants to complete

9.2 Screening and Baseline Procedures

9.2.1 Informed Consent Procedures (OBBT Clinic)

During the pre-screening phase, potential participants may be identified among patients with OUD receiving OBBT at the study sites. Patients will be either self-referred or referred by providers or other sources in the community. Patients who have completed OBBT induction and show interest in the pilot study will be approached by research staff before completion of the stabilization phase, and have explained to them the study procedures and the potential risks and benefits of participating in the trial. Staff will be available to answer questions about the consent form while participants are reviewing it. After signing the consent form, participants will be provided with a copy of the signed form to keep for their records. The process may take approximately 30 minutes. All participants who sign the Informed Consent Form will be added to the Master Enrollment Log. Following consent, participants will enter the screening phase of the study, which is comprised of the completion of screening and baseline assessments at Visit 1.

Information regarding potential participants pre-screened and participants consented, as well as reasons for pre-screen and screen failure, will be collected. This information will be consolidated and developed into a web report.

9.2.2 HIPAA Authorization and Medical Record Release Form

Study sites may be required by their institutions and/or the single IRB of Record to obtain authorization from participants for use of protected health information. Sites and/or a Lead Node representative will be responsible for communicating with the institution(s), IRB(s) or Privacy Board(s) and obtaining the appropriate approvals or waivers to be in regulatory compliance.

Participants will complete *Medical Record Release Forms* throughout the study (as applicable), including at the time of Informed Consent and/or intake/baseline, to grant permission to study staff to review inpatient, outpatient, mental health, and substance use treatment medical records as needed.

9.2.3 Intake and Baseline Assessment (OBBT Clinic)

The data collected from the intake/baseline assessments will be primarily utilized to determine each participant's eligibility for continuation to the maintenance phase of the study. After the prescreening and consent process is complete (i.e., participant has signed the informed consent form), study staff will prepare a new research data record for the participant and administer the intake/baseline assessments. Because participants may be consented (i.e., sign the informed consent form) at any time during the stabilization visits, some participants may complete all intake and baseline assessments on the same day, while others may complete these assessments over the course of multiple visits (conducted within a short period of time). All efforts will be made to

conduct the intake/baseline assessments over 1 or 2 visits; however, in rare cases it is possible that it will take more than 2 visits to complete these assessments, depending on the participant's schedule. The intake/baseline assessments will focus on collecting inclusion and exclusion criteria, demographics and other information related to recruitment (e.g., locator form, pregnancy and birth control assessment for women of childbearing potential). The baseline assessments, detailed in Section 10.0, will capture the participant's clinical presentation and treatment history, as well as measures of efficacy and safety (see **Study Assessment Timetable (Table 3)**). In total, the intake/baseline assessments will take approximately 45-60 minutes to complete.

Information on the reasons for screen failure (i.e., reasons the participant did not reach the maintenance phase) willl be collected and summarized in a web report.

9.2.4 Randomization

This pilot study is not a randomized trial and thus will not utilize a randomization method.

9.3 Use of EHR Data

The study team will obtain IRB approval to review and analyze available EHR data of matched non-study participants to collect biological and safety measures and for exploratory outcomes purposes, if the EHR data are available. Potential matching participants will be adults with OUD receiving buprenorphine treatment at the study sites who do not participate in this pilot study. They will be selected based on participant inclusion and exclusion criteria. Participants' key clinical information will be obtained from the EHR data and compared with some key information from the Buprenorphine Visit Checklist. Investigators will request a waiver of both HIPAA authorization and informed consent from the IRB of Record to use this de-identified information for the analysis. Further, the pharmacists' access to the EHR data will be explored by the Buprenorphine Visit Checklist. We expect some challenges regarding pharmacists' access to the EHR data; therefore, pharmacists' access to the EHR data are considered exploratory for the pilot study.

Throughout the study and/or at the end of the study, research staff will obtain proper permission to review each participant's medical record to abstract relevant medical information from all study visits, including the Intake/Baseline Visit. The research staff will conduct the medical record review with the EHR or paper records located at the practice. If a practice is not adopting EHR, paper records will be used to collect biological test results and safety information.

9.4 Study Interventions

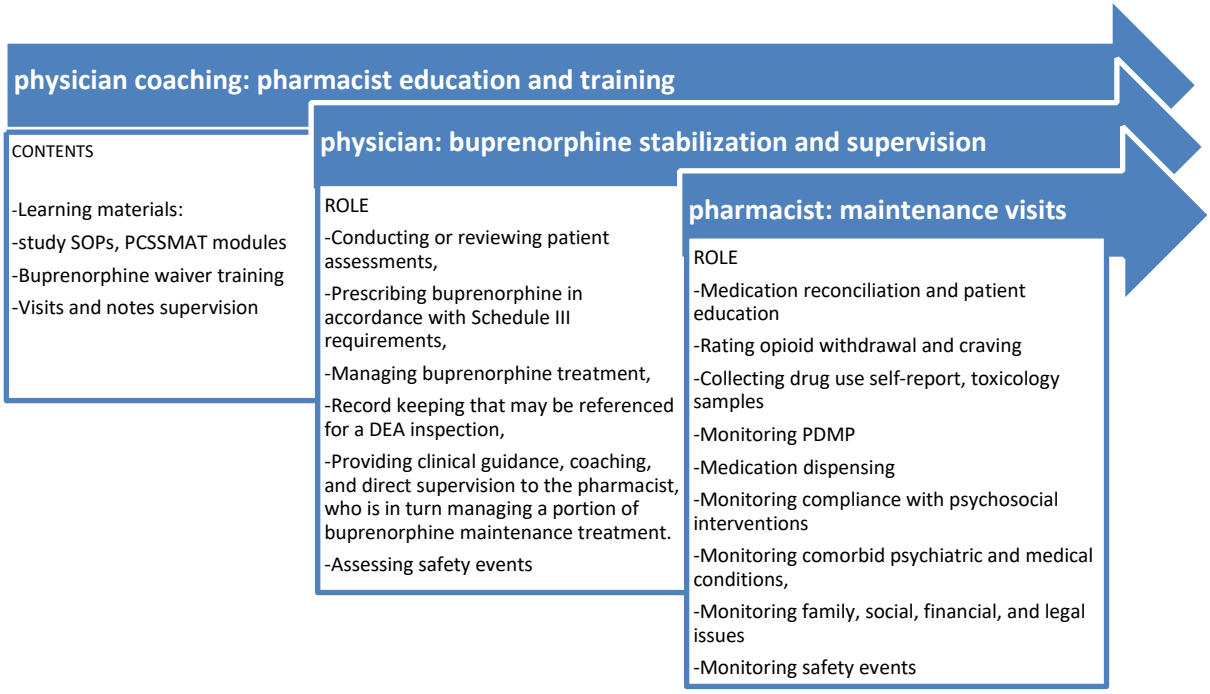
9.4.1 Overview of Study Interventions

Typically, the initiation phase of OBBT begins with a low dose of buprenorphine and is followed by increasing doses over several days to minimize the likelihood of precipitating opioid withdrawal. After initiation, buprenorphine may be taken once or twice daily. Once a stable dose of buprenorphine is established, a therapeutic dose can be maintained over a stable period of time (SAMHSA, 2004; Kampman and Jarvis 2015).

This study will assign a pharmacist to manage the buprenorphine maintenance phase of the treatment (**Figure 3**: **Transitional Treatment Model and Roles**). In this pilot study model, the buprenorphine physician will be responsible for various aspects of patient treatment following induction, including:

- conducting or reviewing patient assessments (including but not limited to drug testing),
- prescribing buprenorphine in accordance with Schedule III requirements,
- managing buprenorphine stabilization,
- record keeping that may be referenced for a DEA inspection, and
- providing clinical guidance, coaching, and supervision to each pharmacist, who is in turn managing a portion of buprenorphine maintenance treatment.

Figure 3: Transitional Treatment Model and Roles



The research staff will assist with the study data collection and facilitate the communication between physician and multiple pharmacists, as well as between providers and LIs.

Co-LI (Mannelli) will serve as a coaching and research/clinical supervisor, as well as a treatment fidelity monitor.

9.4.2 Pharmacist Coaching Timeline and Procedures (see SOP for Pharmacist Coaching in the MOP)

The training phase will be completed within 3-6 months before the pilot clinical trial phase. This training phase will include pharmacist education and coaching regarding OBBT management, as well as study-specific protocol and assessment training. Pharmacist coaching for OBBT management will involve buprenorphine physicians, pharmacists, and Lead Investigators.

Coaching model rationale:

The approach that will be utilized in this study intends to provide standard, up-to-date knowledge that a physician who wants to be certified for buprenorphine would receive, including specific evaluations and passing grades. In addition, physicians and pharmacists are educated on aspects of the study relevant to their intervention and interactions.

Coaching model overview:

Coaching meetings: Each pharmacist will complete between 8-10 coaching meetings (either in-person or web-based) with the supervising physician. Each meeting will be approximately 1-2 hours in duration (at least 1 hour).

Coaching participants: Study physicians will have an active part and engage study pharmacists in this coaching model. In order to complete the coaching phase and proceed with the study, each pharmacist must pass the training tests where provided (i.e., based on the PCSS-MAT or equivalent materials) and participate in at least 80% (8 of 10) of the coaching sessions.

Coaching and Study Materials: The Providers' Clinical Support System (PCSS) for Medication-Assisted Treatment (MAT) educational modules (encompassing 5 mandatory modules and 1 optional module) will be utilized throughout this study, including the following subjects: clinical evaluation of SUD, overdose, withdrawal, comorbid psychiatric disorders, and buprenorphine legislation/guidelines/biological testing (PCSS-MAT, 2016).

The following OBBT-related coaching materials are expected to be completed within 3-6 months for all study pharmacists and physicians:

- SOP for the Operational Care Agreement,
- PCSS educational modules 1-2,
- PCSS educational modules 3-4,
- Educational module 5,
- Buprenorphine waiver training and decisional trees.

In addition, physicians and pharmacists are required to participate in protocol–specific presentations and meetings (e.g., study design, materials, forms reviewing, study MOP).

Each pharmacist will be individually evaluated for satisfactory training completion, and pharmacists who are not considered ready at the end of the training (as operationalized in the MOP) will be required to receive additional individual training before their participation in the study begins.

9.4.3 SOP for the Management of Patients Receiving Pharmacy-Based OUD Management (Operational Care Agreement) (see MOP)

The SOP for the Operational Care Agreement will address:

- Visit components, biological testing: routine and extra testing, treatment monitoring and compliance (diagrams, forms);
- Buprenorphine dose and dose changes criteria (associated decisional tree);
- Treatment plan;
- Special presentations;
- Management of no-show participants, overdose prevention, withdrawal management, psychiatric or medical emergencies;

- Contacts with supervising physician, research staff, LIs; coaching as articulated in the treatment phase of the study.

9.4.4 Replicability of Training and Treatment Structure

Intervention Fidelity (Evaluation of Treatment Integrity) and Quality Control

Integrity Evaluation and Treatment Fidelity evaluation will measure the replicability of training. Elements of fidelity include a common training path for pharmacists and buprenorphine prescribing physicians, which offers standard knowledge, measurable treatment goals and results (e.g., passing scores). As structured, the training will be replicable and generate reproducible results. To address possible weaknesses of the training and treatment structure, the LIs will collect feedback from the physicians and pharmacists who participated in the pilot study at the end of the coaching phase and again after last study visit using the ad hoc Buprenorphine Education Feedback Questionnaire (see Section 10). This feedback will be used to improve the training phase and help to develop a 'curriculum' that will be utilized in a future randomized, multisite study. A progress note checklist (Buprenorphine Visit Checklist, Section 10) will be used by physicians and pharmacists so that treatment structure, fidelity, and replicability can be monitored. The use of the Buprenorphine Visit Checklist will facilitate supervision of treatment quality of the physicians' and pharmacists' care of patients. Quality control will also include LI supervision/resolution of clinical and research queries.

Supervision of Pharmacists

The buprenorphine certified physician will supervise 1 or more pharmacist(s) during the buprenorphine maintenance phase. Supervision will be exerted as follows:

(a) Confirm the daily dose of buprenorphine at the end of each visit via email, telephone, computer teleconference (e.g., Skype), or other type of telecommunications;

(b) Conduct regular clinical review meetings, in person or via remote communication, regarding all open clinical cases. These meetings will occur monthly or more frequently if physician, pharmacist, or LIs deem it necessary; and

(c) Communicate with the pharmacist regarding specific patients. At any time, pharmacist or physician may request a contact regarding a specific patient. A research staff member will facilitate interactions and keep track of reason, characteristics, and frequency of the communications.

Approximately twenty percent (20%) of each pharmacist's progress notes, randomly selected, will be scored by the supervising physician using the Buprenorphine Visit Monitor form (Complete, Incomplete, or N/A for each section of the Buprenorphine Visit Checklist). A score of Incomplete in any section will be discussed between the pharmacist and physician as part of the supervision activity, and all discussions will be documented. If more than two Incomplete sections are identified per visit, this will determine a change of course and closer monitoring of visits/notes. If more than two insufficient visits (i.e., with more than 2 Incomplete sections) are identified per pharmacist, or by decision of LIs, additional training will be assigned.

Supervision of Physicians and Pharmacists

The Co-LI (Mannelli) has more than 25 years of clinical and research experience in the management of buprenorphine for OUD. For evaluation purposes, Co-LI (Mannelli) will randomly monitor pharmacist visits and score treatment fidelity based on scoring sheets, which will weigh

different aspects of treatment and therapeutic interaction. At least 1 visit will be performed per pharmacist, and the Co-LI will perform the supervision by using the Buprenorphine Visit Monitor Form (Section 10). The Co-LI will intervene in any unresolved issue between the physician and pharmacist when prompted by either physician or by a research staff member, particularly in cases of unanswered requests and low-scored or incomplete Buprenorphine Visit Checklists. The Co-LI will also participate in at least one regular clinical review meeting per physician/pharmacist.

Tracking Implementation Problems and Readiness to Deliver Treatment

We will collaborate with CTN DSC/CCC about the approach to track the problems encountered during the implementation of the study with feedback from physicians, pharmacists, participants, and help from a research staff member. We will discuss possible solutions and recommendations at regular project meetings and summarize them in the final study report. The resulting tracking list/document can be reported to the DSMB upon request.

In addition, we will collaborate with CTN DSC/CCC to conduct two brief surveys of physicians and pharmacists, as well as staff/managers of participating sites, regarding organizational readiness in implementing MAT services (a first survey before the study initiation, a second survey after the completion of the study). The content of the survey will be framed to understand barriers and facilitators of implementing MAT at their facilities (e.g., administrative support, staffing, training, and organizational processes in place). Participants of the organizational readiness survey will be compensated via a $25 gift card for completion of each survey ($50 total).

9.5 Buprenorphine Stabilization and Maintenance Visits

9.5.1 Buprenorphine Stabilization Visits

(OBBT clinic visits with buprenorphine physician; up to 16-20 weeks per participant)

The stabilization phase has begun when a patient is experiencing no withdrawal symptoms, minimal or no side effects, and no longer has uncontrollable cravings for opioid agonists (SAMHSA, 2004; Kampman and Jarvis 2015). At this point, the physician should identify the lowest dose of buprenorphine at which the patient discontinues or markedly reduces the use of other opioids without experiencing withdrawal symptoms, significant side effects, or cravings. Reduction and elimination of opioid/heroin use (via self-report and negative urine toxicology) represent the key target goals of this phase. Participants will enter into a maintenance phase of treatment when a stable dose of buprenorphine is achieved and maintained for at least 3 weeks.

During the stabilization phase, patients complete visits with the buprenorphine physician regularly (e.g., weekly, bi-weekly, or monthly), depending on their clinical status. A research staff member will be present at the OBBT clinic to help with research procedures and physicians' tasks as needed. Physicians will complete the Buprenorphine Visit Checklist, and the research staff member will help with other research-specific assessments and forms, including UDS and TLFB collection. Following the last stabilization visit or after the patient is considered clinically stablized, the participant will be referred to pharmacist care for maintenance visits.

A stabilization visit will take approximately up to 1 hour to complete and will consist of the following elements:

Stabilization Visit Elements:

1. Medication use and patient education.

2. Opioid withdrawal using the Clinical Opioid Withdrawal Scale (COWS) worksheet (Wesson and Ling, 2003) and opioid craving on a self-rated visual analogue scale of 0100 (McMillan and Gilmore-Thomas, 1996).
3. Collection of substance use via urine toxicology samples and self-report using the TLFB.
4. Monitoring the PDMP.
5. Medication management.
6. Compliance with psychosocial interventions via the Psychosocial Counseling Attendance form.
7. Concomitant medications assessment.
8. Psychiatric and medical problems, family, social, financial, and legal issues, using a modified version of the Problem List Form (NIDA, 1998).
9. Safety events.
10. Suicidality risk evaluation.
11. Treatment plan evaluation (including medication dose adjustments, as needed).

Data for the following components may be abstracted from the medical record, if available, if they occured during the current treatment episode's stabilization phase:

1. Physical exam, up to 6 months prior to consent.
2. Vital sign assessment, up to 1 month prior to consent.
3. Monitoring of the PDMP, up to 1 week prior to consent.
4. Treatment plan, up to 1 month prior to consent.

9.5.2 Buprenorphine Maintenance Visits

(Participant visits with pharmacist; 24 weeks per participant)

When a stable buprenorphine dose is achieved (i.e., the same dose of buprenorphine is maintained for at least 3 weeks), patients enter into the maintenance phase of treatment. In accordance with clinical practice, maintenance visits will occur with the pharmacist at the pharmacy location at least monthly, and study-specific data will be collected at weeks 4, 8, 12, 16, 20, and 24. Visits may also be conducted at shorter intervals, depending on participants' clinical stability. If a participant relapses or destabilizes, he or she should be monitored more frequently. During the maintenance phase, less direct medication dose management and increased monitoring of problematic behavioral areas are usually needed (HRSA, 2016).

In the management of buprenorphine maintenance, the pharmacist will be required to implement and expand a patient centered care approach already implemented in collaboration with other members of the health care team to optimize medication outcomes in the treatment of other medical conditions (CPNP, 2016). This process includes the following evidence-based practices: collect and assess subjective and objective information about the patient to develop and implement an individualized plan, monitor and evaluate the effectiveness of the care plan, and

modify the plan under supervision of physician and in collaboration with patient as needed (JCPP, 2014; ASHP, 2014).

Each maintenance visit will take approximately 30-45 minutes to complete and will consist of the following elements:

Maintenance Visit Elements:

1. Film count/dose reconciliation and patient education.
2. Opioid withdrawal using the Clinical Opioid Withdrawal Scale (COWS) worksheet and opioid craving on a self-rated visual analogue scale of 0-100.
3. Collection of substance use via urine toxicology samples and self-report using the TLFB.
4. Monitoring the PDMP.
5. Compliance with psychosocial interventions via the Psychosocial Counseling Attendance form.
6. Concomitant medications assessment.
7. Psychiatric and medical problems, family, social, financial, and legal issues, using a modified version of the Problem List Form.
8. Safety events.
9. Suicidality risk evaluation.
10. Monitoring the EHR (optional: depending on the access to the EHR).
11. Treatment plan evaluation by physician (including medication dose adjustments, as needed).
12. Dispensing medication following the prescription of supervising physician.

A research staff member will be present at the pharmacy to help with research procedures and pharmacists' tasks as needed. Pharmacists will complete the Buprenorphine Visit Checklist, and the research staff member will help with other research-specific assessments and forms, including UDS and TLFB collection (**Table 3**).

The pharmacist and supervising physician will sign the Operational Care Agreement. As specified in the MOP, scheduling of an earlier follow up visit (2-3 weeks) may be prompted by: poor compliance with medication, study visits, or counseling attendance, or worsening of opioid use (higher number of days of use than the previous month or positive toxicology following a negative sample).

The results of evaluations will be discussed after the visit with the supervising physician who will release buprenorphine prescription contingent on the evaluation results, and the date of the next appointment will be confirmed with the patient. At the end of the 24-week pharmacist management period, the patient will return to the buprenorphine physician's care.

9.5.3 Early Termination Visit (at pharmacy)

This visit will be completed at the pharmacy site for participants who discontinue study participation early (including those who stop buprenorphine treatment prematurely). Baseline clinical and safety measures will be repeated as detailed in Section 10.

9.5.4 Counseling-Psychosocial Intervention

As mandated by guidelines, all providers must have the ability to refer buprenorphine-treated patients to behavioral treatment (SAMHSA, 2004). Despite these regulations, the optimal content of this behavioral treatment remains unknown for this patient population. To date, studies have not provided enough evidence to demonstrate a significant benefit of any one form of psychosocial intervention (such as the addition of a specific type of counseling or self-help group attendance to buprenorphine treatment), and different forms of behavioral treatment can coexist (Copenhaver *et al*., 2007; Dugosh *et al*., 2016). Thus, no specific counseling model will be suggested to participants. Counseling is not delivered as part of the study interventions and is conducted separately from the physician or pharmacist-managed buprenorphine visits, but the occurrence of the event at the study site or other site will be recorded at each visit. At the beginning of treatment, it is recommended that participants attend psychosocial counseling at least once per week. As treatment progresses, counseling frequency will be individualized based on each participant's characteristics and needs, and may lessen in frequency over time.

Each participant's compliance with the psychosocial intervention will be assessed by the Psychosocial Counseling Attendance Form at each visit. The case report form will assess whether the participant's counseling attendance matches what is recommended in the treatment plan. This will be accomplished by participants' self-reports and may be confirmed by contacting or calling the participant's designated family member/significant other (Psychosocial Counseling Attendance Form, Section 10).

9.5.5 Other Medications and Concurrent Treatments

This study will not restrict the use of concomitant prescribed medications, with the exception of opioids. Concurrent medical and psychiatric treatments will be under direct control of the prescribing physician and will be assessed at each scheduled visit for their potential to interact with buprenorphine. Concurrent treatments will be recorded using the Concomitant Medications form and Non-Drug Therapy Log.

9.5.6 Handling of Missed Visits and Substance Use

Given that opioid agonist substitution therapy primarily targets illicit opioid use, and that complete and continuous abstinence from substances requires some time to be achieved, it is possible that opioid or other substance use may present a significant safety concern in the management of participants receiving the buprenorphine therapy.

- If the participant misses a scheduled visit, no additional buprenorphine prescription will be given, and one alternative visit will be scheduled as a make-up visit.

- If opioid use is reported or suspected at any time during treatment, the participant will be contacted to perform at least one random urine drug use test prior to the next scheduled visit if the treating physician deems it appropriate.

- If the participant misses three consecutive visits (e.g., the first monthly visit, the following early substitution visit, and the second monthly visit), he/she will be discontinued from study and contacted by pharmacist/research staff to complete the **Early Termination Visit** and be referred back to the buprenorphine physician.

- The same provision will be adopted when as many as six visits in total need to be rescheduled, or in the case of three consecutive or five non-consecutive positive opioid/heroin urine drug tests.

- Any non-prescribed use of benzodiazepines that is detected will prompt analogue measures to those adopted for opioid use. The abuse of other substances or alcohol is strongly discouraged as part of the treatment plan and will be discussed with the participant, reviewed with the supervising physician and Co-LI (Mannelli) if needed, and reported in the visit progress note.

- Missed visits will be documented using the **Missed Visit CRF**. Under the consideration of Lead Investigator(s), **phone interviews** may be used to collect study assessments for missed visits.

9.6 Participant Discontinuation

All participants will be followed for the duration of the study (24 weeks for pharmacy OUD maintenance) unless they withdraw consent, stop the study medication, die, or the investigator or sponsor decides to discontinue their enrollment for any reason. In addition to what is described in Section 9.5.6 (discontinuation based on missed visits and/or illicit substance use), reasons for the investigator or sponsor to terminate a participant from the study may include, but are not limited to: study participation becoming unsafe, the participant becoming a threat to self or others, lack of funding, or DSMB early termination of the study for safety reasons. Of note, participants who discontinue study medication for any reason will be discontinued from the study. If a participant is discontinued from the study, an Early Termination Visit and End of Medication form should be completed as soon as possible following participant discontinuation to assess the participant's safety.

9.7 Blinding

This study will not utilize a blinding method.

9.8 Participant Reimbursement

Participants will be compensated for their time and transportation to study visits. Participants will be paid $50 for the Intake/Baseline Visit (i.e., for completing assessments for this visit) and $50 for the last study visit (either Visit 7 or the Early Termination Visit). Participants will be paid $40 for attending each of the other visits (Visits 2, 3, 4, 5 and 6). If the participant completes all study visits, total reimbursement will be $300. No reimbursement will be provided for extra visits.

10.0 STUDY ASSESSMENTS

The primary focus of the pilot clinical trial is to explore and assess needs and capability to support CTN's new efforts in engaging pharmacists and connecting pharmacists with primary care and ambulatory providers (e.g., team-based coordinated care model) in OUD-related intervention trials. Study assessments will focus on the feasibility (e.g., recruitment, implementation of the intervention), OUD treatment outcomes, and safety measures.

10.1 Table 3: Study Assessment Timetable

Assessment/Activity	Study visit number	Location
Research Tasks: Clinical Assessments		
Suicidal Risk (SUR)		
P4 Screener (P4S)		
Medical History		
Tobacco Use History		
Timeline Follow Back (TLFB)		
Urine Drug Screen (UDS)		
DSM-5 Checklist		
PhenX Core Tier 1 measures		
Patient Health Questionnaire (PHQ-9)		
Substance Abuse and Addiction Quality of Life and		
Research Tasks: General Assessments		
Missed Visit		
Study Completion		
Protocol Deviations		
Buprenorphine Medication		
End of Treatment Satisfaction Survey		
Demographics		
Buprenorphine Log		
Locator Form		
Master Enrollment Log[1]		
Medical Release Form		
Informed Consent/HIPAA		
Inclusion/Exclusion Checklist		
Prisoner Status Assessment		
Screening/Baseline	Visit 1	OBBT clinic
Stabilization Visit		
Screening/Baseline	Visit 1B	Pharmacy
Stabilization Visit		
Week 1 (1 Week)	Visit 2	Pharmacy
Week 5 (4 Weeks)	Visit 3	Pharmacy
Week 9 (4 Weeks)	Visit 4	Pharmacy
Week 13 (4 Weeks)	Visit 5	Pharmacy
Week 17 (4 Weeks)	Visit 6	Pharmacy
Training/coaching		OBBT clinic

				x		x	x				x	x	x	x		x					x	21 24 Week)	(6 M	Pharmacy Visit 7
	x	x		x		x	x				x	x	x	x		x					x		Pharmacy	Early Termination
x	x*						x		x	x			x			x			x	x	x	As needed		

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Assessment/Activity	Study visit number	Location
Visit 1	1	OBBT clinic
Visit 1B	1B	Pharmacy
Visit 2	2 (1 Month)	Pharmacy
Visit 3	3 (2 Month)	Pharmacy
Visit 4	4 (3 Month)	Pharmacy
Visit 5	5 (4 Month)	Pharmacy
Visit 6	6 (5 Month)	Pharmacy
Early Termination Visit	7	OBBT clinic
Questionnaires		
Recruitment Log		
Buprenorphine Visit Checklist		
Organizational Readiness		
Birth Control Assessment		
Buprenorphine Education Feedback Monitor		
Psychosocial Counseling Attendance Form		
Coaching Training Completion (Pharmacists)		
Pregnancy Test		
Liver Function Tests (LFTs)		
VAS Opioid Craving		
Clinical Opioid Withdrawal Scale (COWS)		
Concomitant Medications		
Drug Therapy Problem List		
Vital Signs		
Physical Exam		
Visit 1	x	x		x																	
Visit 1B										x											
Visit 2	x					x	x	x	x	x	x	x	x	x		x					
Visit 3	x						x	x	x		x	x	x	x		x					
Visit 4	x						x	x	x		x	x	x	x		x					
Visit 5	x						x	x	x		x	x	x	x		x					
Visit 6	x						x	x	x		x	x	x	x		x					
Early Termination Visit	x						x	x	x		x	x	x	x		x					

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x		x					x	x	x		x	x	x		x		x			Week 21 (Week 24)	Pharmacy (6 Month)	Visit 7
x		x					x	x	x		x	x	x		x		x				Pharmacy	Early Termination
			x						x	x								x		As needed		

10.2 Research Tasks: General Assessments

***Note**: the visit numbers used in this section follow the order indicated in the Study Assessment Timetable.*

Inclusion/Exclusion Checklist

This form will include each inclusion and exclusion criterion to document eligibility. Eligibility will be assessed continually, as appropriate. Only participants who continue to meet study eligibility criteria will be allowed to continue with the screening process and study intervention.

Locator Form

A locator form is used to obtain information to assist in finding participants during treatment and at follow-up. The information on this form will also be used to contact participants to remind them of upcoming study visits. This form collects the current address, email address, and phone numbers of the participant AND one or more family members/significant other, friends, or counselors designed by the participant to provide participant's attendance of psychosocial interventions. In order to facilitate locating participants if direct contact efforts are unsuccessful, addresses, email adresses and phone numbers of at least one other person (e.g., family members, significant others, friends) who may know how to reach the participant are collected, as well as information such as social security number, driver's license number and other information to aid in searches of public records. This information will be collected at screening, and will be updated at each visit as needed. No information from this form is used in data analyses nor is this information captured in the data capture system.

Demographics

The Substance Abuse and Addiction Collection of the PhenX Toolkit (http://www.phenxtoolkit.org) includes recommended measures that are being adopted across NIDA-funded research (NIDA, 2012). The Demographics form will collect information about demographic characteristics of the participant, including sex, date of birth, ethnicity, race, education, employment pattern, and marital status.

Treatment Satisfaction Survey

Participants, pharmacists and buprenorphine physicians will be asked to rate their overall satisfaction with the quality of the treatment (modified from Harland *et al*., 2015). Participant satisfaction with treatment will be recorded on the Treatment Satisfaction Survey (based on a 5point Likert scale: 0 = very dissatisfied, to 5 = very satisfied) that is completed by study participants at each study visit (1-7), including the Early Termination Visit (if participant discontinues study participation early). Pharmacists and physicians will also be asked to complete the Treatment Satisfaction Survey once per month, beginning the month of the first participant, first visit (FPFV; Visit 1) at their paired site and ending the month of the last participant, last visit (LPLV) at their paired site.

End of Medication Form

This form tracks the participant's status with regard to the study intervention/medication. It will be completed at the pharmacy at the Early Termination Visit (if the participant discontinues study participation early), or at Visit 7 (for participants who complete study participation). Phone interviews may be used to collect study assessments for participants who discontinue study participation early and are unable to return for Early Termination Visit during the specified time period.

Study Completion

This form tracks the participant's status in the study. It will be completed at Visit 7 (for participants who complete the study) or at the Early Termination Visit (for participants who discontinue study participation early). For participants who do not complete a final visit, the Study Completion form will be completed once the Visit 7 visit window elapses. This form will be used in data analyses to address variables such as treatment retention and completion.

Protocol Deviations

Protocol Deviations will be assessed and documented throughout the study.

10.3 Research Tasks: Clinical Assessments

DSM-5 Opioid Use Disorder (OUD) Checklist

The DSM-5 OUD Checklist is a semi-structured, interviewer-administered instrument that provides past-year diagnosis for opioid use disorder based on DSM-5 diagnostic criteria (APA, 2013; Forman *et al*., 2004). The DSM-5 OUD Checklist will be completed at screening to determine eligibility.

Urine Drug Screen (UDS)

Urine drug screens will be collected at Intake/Baseline, at Visits 2 through 7, and/or as needed, based on clinical decision. If the participant discontinues study participation early, UDS will be collected at the Early Termination Visit. However, should the study participant have a medical condition (e.g., being on a catheter) that prevents or affects the proper collection of UDS and its temperature testing, UDS and its temperature testing may not be needed to define the validity of the test. For example, the catheter urine does not have to be subject to temperature testing.

All urine specimens will be collected using FDA-approved one-step temperature-controlled urine drug test cups and all of the manufacturer's recommended procedures will be followed. The commercially available UDS system (Rapid Dip Drug Test,Opiate 2000 ng single strip, and BUP 10 ng single strip) will test for the presence of the following drugs: opiates, oxycodone, barbiturates, benzodiazepines, cocaine, amphetamines, methamphetamines, marijuana, methadone, buprenorphine, phencyclidine, and ecstasy (MDMA). The phencyclidine results will not be entered into the data system or used for data analysis. UDS tests are temperature controlled to avoid tampering, and a further validity check is performed using a commercially available adulterant test strip. In the event that urine specimen tampering is suspected, either based on observation or adulterant test results, study staff should request a second urine sample and may observe the urine collection process according to clinic standard operating procedures.

Urine is recognized as the prime matrix for drug test screening with well-established methods and testing protocols (Allen, 2011). Compared to oral fluid testing, urine drug screening is more sensitive, less expensive, and can detect drug use for several days prior to the date of testing, whereas oral fluid cannot (Allen, 2011). The presence of drug in saliva has been insufficiently tested to be able to offer reliable and scientifically reproducible results; further, the lack of concordance studies examining both urine and oral fluid drug levels and kinetics in the clinical setting is of some concern (Allen, 2011). In addition, instant saliva tests have produced inconsistent results compared with laboratory evaluation (Yacoubian and Wish, 2006), and cannot be reliably used for the purpose of evaluating and adjusting buprenorphine treatment based on the drug testing during the clinical visit.

In this study, urine drug screening results demonstrating ongoing opioid use or other substance use (e.g., cocaine) will be managed in a non-punitive manner. Results demonstrating opioidnegative tests will receive positive reinforcement. Unexpected urine drug screen results provide opportunities for counseling and brief intervention.

Timeline Followback (TLFB)

The Timeline Followback (TLFB), an instrument with high test-retest reliability and validity for the assessment of self-reported substance and alcohol use over a 30-day look-back period (Sobell and Sobell, 1992; Sobell and Sobell, 2000), will be utilized in this study. Participants will be asked to report daily substance and alcohol use since the previous TLFB assessment at the Intake/Baseline Visit and Visits 2 through 7. If the participant discontinues study participation early, TLFB will be collected at the Early Termination Visit.

Substance Abuse and Addiction: PhenX Core Tier 1-2

The PhenX Toolkit provides researchers with well-established and low-burden measures suitable for human subject research (NIDA, 2012; Pan *et al*., 2012). We will use the measures from the Substance Abuse and Addiction PhenX Core Tier 1 to collect information regarding substance use including age of onset, past 30-day quantity and frequency, lifetime use for alcohol, tobacco and other substances; quality of life; and HIV Risk and Status. We will also assess annual family income. The assessments will be completed at Intake/Baseline. The “Quality of Life” and “Tobacco Use History” measures will be also be repeated at visits 2, 3, 4, 5, 6, and 7 (or the Early Termination Visit if the participant discontinues study participation early).

Medical and Psychiatric History and Status – Medical History (MHX), Patient Health Questionnaire (PHQ-9), P4 Screener (P4S), and Suicidal Risk form (SUR)

The MHX, PHQ-9, and P4S case report forms will assess information about medical and psychiatric history, as well as past and present health conditions, to help determine eligibility and to provide baseline information. The **MHX** gathers medical and behavioral history exploring current symptoms, including psychiatric treatments and medications, and will be collected during screening only.

The **PHQ-9** (Spitzer *et al.*, 1999), a validated, self-administered version of the PRIME-MD, contains the mood (PHQ-9) module as covered in the original PRIME-MD. It will be administered at Intake/Baseline and repeated at the Early Termination Visit if the participant discontinues study participation early. Endorsements of suicidality on the PHQ-9 (i.e., if the participant answers Q9 (“Thoughts that you would be better off dead, or of hurting yourself in some way”) as “Several days”, “More than half the days” or “Nearly every day”) will be addressed locally at each site and will trigger the completion of the **Suicidal Risk** form.

The **P4 Screener** (Dube *et al*., 2010) is a brief measure (approximately 5 minutes used for assessing potential suicide risk in primary care. The participant will answer 4 questions regarding past attempts, a plan, probability of completing suicide, and preventive factors at screening to exclude active suicidal ideation at Intake/Baseline. If the participant answers “Yes” to Question 2 of this screener, “Have you thought about how you might actually hurt yourself?”, study staff will ask the participant additional clarifying questions to assess suicidality. During treatment Visits 27, any suicidal ideation investigated and/or reported in the psychological problem section of the Problem List (see below) will prompt the administration of the P4S. If the participant discontinues study participation early, the P4S Screener will be completed at the Early Termination Visit. The completion of the **Suicidal Risk** form requires direct evaluation of the participant for suicide risk

by qualified healthcare individual(s) according to the site's specific SOPs or existing procedures or policy at the site to address such risk. This evaluation will take place immediately following the outcome analysis of the results and prior to the participant leaving the study site. Medical or psychiatric history information collected before study participation may be used with the participant's permission. Information from this form may be used in data analyses.

Physical Exam

The study clinician will complete a physical examination and review of systems at screening to ensure that there are no medical concerns regarding participation and to gather baseline information regarding the participant's physical health. Alternatively, physical exam data may be abstracted from medical records, when available, if conducted within 6 months prior to the date of informed consent. Research staff will record the information on the case report form.

Vital Signs

Study personnel will collect vital signs information (blood pressure, pulse, temperature, height, and weight) at screening to inform overall medical fitness for participation (in combination with data from the physical exam). Alternatively, vital sign data may be abstracted from medical records, when available, if conducted within 1 month prior to the date of informed consent.

Problem List

This form has been in use at community treatment programs (NIDA, 1998) and explores 7 problematic areas in open-ended fashion, including Drugs/Alcohol, Employment/Support, Family, Recreational/Social Psychological, Legal, and Medical. It will be used at the Intake/Baseline Visit and at Visits 2 through 7 (or the Early Termination Visit if the participant discontinues study participation early). Initially, information regarding the previous year will be collected, then changes from the previous visit will be recorded.

Concomitant Medications & Non-Drug Therapy Log

Concomitant medications will be collected on the Concomitant Medications form at the Intake/Baseline Visit (Visit 1). Concomitant medications will be reviewed at every subsequent study visit (including Visit 7 or the Early Termination Visit if the participant discontinues study participation early), and changes will be documented on the Buprenorphine Visit Checklist. If at any point it is indicated that the participant has a need for ongoing opioid analgesic treatment, he or she will be excluded/withdrawn in accordance with study eligibility criteria. Non-drug therapies will be assessed and documented at Intake/Baseline and at each study visit after that, including Visit 7 (or the Early Termination Visit if the participant discontinues study participation early). The study medical clinician may also exclude any participant taking medications or receiving non-drug therapies that could interact adversely with the study drug at his/her clinical discretion.

10.4 Clinical Tasks

Buprenorphine Visit Checklist

The purpose of this document is to provide the buprenorphine prescribing physician with a clinical instrument for coaching, supervising, and monitoring the activities of pharmacists while the pharmacists are involved with patient evaluation and buprenorphine treatment dispensing. In order to fully understand and utilize the checklist, physicians will be asked to become familiar with the instrument and its application. Both the buprenorphine prescribing physician (during the stabilization phase) and the pharmacist (during the maintenance phase) will be asked to adopt the Buprenorphine Visit Checklist and follow a consistent grid of interventions, including the main

evaluation and management actions listed in Section 9.5. The results of this effort will be captured for the Intake/Baseline Visit 1/1B and subsequent Visits 2 through 7 (or Early Termination Visit if the participant discontinues study participation early). Different aspects of treatment compliance, fidelity and replicability are associated with and justify the use of this checklist.

Visual Analog Craving Scale (VAS)

Participants' craving for opioids will be documented on a visual analog scale (VAS) that ranges from 0 (no craving) to 100 (most intense craving possible) (McMillan, Gilmore-Thomas, 1996). Participants will be specifically instructed to indicate the overall intensity of craving experienced. This scale will be completed at the following visits: Intake/Baseline and Visits 2, 3, 4, 5, 6, and 7. If the participant discontinues study participation early, the scale will be completed at the Early Termination Visit. Results from this scale are part of the clinical information the physician will receive and utilize to adjust the buprenorphine treatment as outlined in the study protocol.

Clinical Opioid Withdrawal Scale (COWS)

The presence of withdrawal discomfort will be documented using the COWS (Wesson and Ling, 2003), an 11-item, interviewer-administered questionnaire designed to provide a description of directly observed signs and symptoms of opiate withdrawal (e.g., sweating, runny nose). This scale will be completed at each visit (i.e., Intake/Baseline and Visits 2 through 7). If the participant discontinues study participation early, this scale will be completed at the Early Termination Visit. Results from this scale are part of the clinical information the physician will receive and utilize to adjust the buprenorphine treatment as outlined in the study protocol.

10.5 Research Tasks: Safety Assessments

Laboratory tests

Trained staff will be responsible for collecting and processing biologic specimens. **Local laboratories at participating sites will be used to conduct laboratory tests.** Laboratories must participate in the Clinical Laboratory Improvement Act of 1998 (CLIA) (or provide equivalent evidence of laboratory certification). Laboratories will provide reference ranges and proof of laboratory certification prior to study initiation and as needed throughout the study.

Safety labs: Liver function tests (LFTs, consisting of AST and ALT) will be performed to help determine eligibility at screening. Receipt and review of laboratory test results is necessary before confirming eligibility and beginning the study intervention. Results of laboratory tests conducted within 60 days prior to the Intake/Baseline Visit (Visit 1) (e.g., collected as part of routine care before the induction admission) will be acceptable. Throughout the study, LFTs may be collected as needed for participant safety, per the discretion of the study physician.

Pregnancy and Birth Control Assessment

This form will document the administration of pregnancy tests, test results, childbearing potential, and female participants' self-reports of an acceptable method of birth control. The Pregnancy and Birth Control Assessment, will be collected during screening (Visit 1) to determine eligibility, as well as at Visits 2 through 7.

For females of childbearing potential: a blood pregnancy test will be performed at Visit 1 (or up to 7 days prior to Visit 1B) to confirm participant eligibility. A confirmatory urine pregnancy test will also be completed at the pharmacy following Visit 1, immediately before the participant is dispensed the first dose of study medication. Following initiation of the study intervention. subsequent urine pregnancy tests will be performed at Visits 2 through 7 and as needed

throughout the study. If the participant discontinues study participation early, the birth control assessment and urine pregnancy test will be completed at the Early Termination Visit.

A positive pregnancy test following initiation of the study intervention will result in the cessation of study medication and a referral back to the buprenorphine physician. The site staff will follow the participant until an outcome of the pregnancy is known and reported.

Safety Events

As buprenorphine is an approved drug being prescribed in accordance with the approved usage, there would be no need to capture AEs per se, as the likely AEs are already known. However, in terms of compliance, informing dosing, side effects or monitoring those aspects, a solicited collection of information is relevant. To aid the collection of safety events, a tool in the form of a Safety Event Response Checklist [SERC-75] with solicited symptom information, yes/no responses, and level of severity (mild, moderate, severe) will be developed for addition to the MOP. The checklist will be used by research staff to obtain self-reported information from each participant at the monthly pharmacist visit, which will then be captured electronically in the database. The MOP will specify the process of reporting safety events that may require interventions (such as dosing, side effects, etc.) to participants' physicians and pharmacists, as well as to the Lead Investigators. In this way, open-ended questions that are left up to the determination of the Pharmacists/research staff are avoided and staff members remain within their scope by eliminating the expectation that they will be assessing physical symptoms of a participant. The completion of the checklist will be documented in the progress note for each visit so that the physician is able to review along with the other information provided by the pharmacist from the visit prior to writing the participant's prescription.

For the purposes of this protocol, the following safety events will be collected and reported to inform dosing as well as assist with monitoring of medication compliance: possible side effects of the medication: headache, nausea, vomiting, constipation, insomnia, excessive sweating, increased sensitivity in the mouth, burning sensation in the mouth, sores in the mouth, pain, swelling, and overdoses. In addition, we will collect all ER visits, hospitalizations, and death of any participant who provided written informed consent.

Following informed consent, the protocol-specified safety events will be solicited and recorded at each study visit (including the Early Termination Visit if the participant discontinues study participation early), according to the outlined procedures. If a reportable safety event suggests medical or psychological deterioration, it will be brought to the attention of the study clinician for further evaluation. The safety event will be medically managed, reported, and followed in accordance with applicable regulatory requirements. The participant may need to return to the clinician's office for extra visits in order to adequately manage an identified safety event.

Hospitalizations

Hospitalization for any medical and/or psychiatric reason will be reported accordingly on the Safety Event Response Checklist [SERC-75]. All hospitalizations will be assessed by self-report at visits 1 through 7 (or Early Termination Visit if the participant discontinues study participation early).

Overdoses

Non-fatal overdoses since the last visit will be captured via self-report using the Safety Event Response Checklist at each visit following consent (including the Intake/Baseline Visit) through Visit 7 (or the Early Termination Visit if the participant discontinues study participation early).

Overdose events are sentinel events that are less likely to be prone to recall bias than other events.

Data on fatal overdoses may be collected via medical chart record review, if EHR data is available, at Visit 7 (or the Early Termination Visit if the participant discontinues study participation early). This will be supplemented with information from contact with persons listed on the participant's locator form when participants are lost to follow-up throughout the study. Fatal overdoses will be captured on the Safety Event Response Checklist [SERC-75].

Death

All deaths, regardless of cause, will be captured for this study. These events will be identified through the participants' locator information, or when possible through state medical examiner records, National Death Index, and/or review of medical records. Deaths will be reported using the Safety Event Response Checklist [SERC-75].

10.6 Research Tasks: Treatment Compliance and Feasibility

Recruitment Log

Drawing on the information captured in the Master Enrollment Log, as well as by reviewing the signed consent forms, the Recruitment Log will collect data on the number of potential participants who have been pre-screened for participation in the study and the number of participants who signed the informed consent form. This data will be used monthly to calculate the recruitment rates for each study site during the 6-7 month enrollment phase. Data from this log will be used to project the number of participants and inform the duration of enrollment (i.e., recruitment rate) for a future multi-site clinical trial.

Coaching Training Completion (Pharmacists)

This form will capture the successful completion of training by each single pharmacist and will be completed by the end of the coaching phase. Pharmacists will not be able to see study participants unless they have participated in the expected training and have passed the tests as required.

Buprenorphine Visit Monitor Form

The Buprenorphine Visit Monitor Form adopts a Complete, Incomplete, or N/A scoring system for each section of the Buprenorphine Visit Checklist. A specific task is defined in each section of the checklist: Complete will be defined a completed task, Incomplete will be assigned if the task was not completed or was missing, and N/A defines tasks that are Not Applicable. An Incomplete score in any section will be discussed between the pharmacist and physician as part of the supervision activity. If more than two Incomplete sections are identified per visit, this will determine a change of course and closer monitoring of visits/notes. If more than two insufficient visits (i.e., with more than 2 Incomplete sections) are identified per pharmacist, or by decision of the LIs, additional training will be assigned. Pharmacist monitoring by physician will be performed during the maintenance phase. Twenty percent (20%) of each pharmacist's progress notes (i.e., the Buprenorphine Visit Checklist), randomly selected, will be scored by the supervising physician using the Buprenorphine Visit Monitor form. Further, random monitoring by the Co-LI (Mannelli) of physician, pharmacist and pharmacist-physician interaction will be performed at each site using the Buprenorphine Visit Monitor form. One or more visits per physician and pharmacist respectively will be monitored in this fashion. The Co-LI will also participate in at least one regular clinical review meeting per physician/pharmacist.

Buprenorphine Education Feedback Questionnaire

We will collect the opinions of pharmacists and buprenorphine physicians about the clarity and utility of the coaching materials, as well as any lack of useful information from the training. The questionnaire will consist of specific questions on each training module to be rated on a 5-point Likert Scale of satisfaction, and will be filled out at the end of the coaching phase and once all participants at each site complete Visit 7 (or the Early Termination Visit, if not Visit 7). The results will be used to structure the coaching education material for a subsequent multi-site clinical trial.

Psychosocial Counseling Attendance Form

Participants' psychosocial counseling attendance will be assessed at each visit (Intake/Baseline Visit and maintenance Visits 2 through 7 (or the Early Termination Visit if the participant discontinues study participation early)). It serves the purpose of monitoring and reporting whether counseling attendance matches what is recommended in the treatment plan at each visit. This will be accomplished through participants' self reports, which may be confirmed by communication with the participant's counselor/therapist or family/significant other. The physician or pharmacist will also assess the participant's attendance of self-help group or other counseling encounters by confirming with their sponsor/significant other. This information will be documented on the Psychosocial Counseling Attendance Form and summarized on the Buprenorphine Visit Checklist.

Process Measures

The pilot study seeks to evaluate the acceptability and feasibility of having pharmacists administer office-based buprenorphine therapy under the supervision of buprenorphine physicians and improve safe access to evidence-based treatment. Patient and physician or pharmacist attitudes, assessed in the pilot study, influence and ultimately determine adoption of new treatment modalities (Rieckmann, Daley *et al*., 2007). The patient, physician or pharmacist, and organizational attitudes are key inputs to adoption of new evidence-based approaches in healthcare settings (Damschrodern *et al*., 2009). In the case of this pilot study, the quality of transfer of the OBBT treatment to a pharmacy environment is crucial and will be adopted as a process measure. Further, we will collaborate with CTN DSC/CCC to conduct two brief surveys of physicians and pharmacists, as well as staff/managers, of participating sites regarding organizational readiness in implementing MAT services (a first survey before the study initiation, a second survey after the completion of the study). Prior to agreeing to complete the survey, survey participants will be asked to read an IRB-approved information sheet that outlines the purpose of the survey and the procedures involved. Survey participants who proceed with the survey after reading the information sheet are considered to have provided informed consent for the survey. The content of the survey will be framed to understand barriers and facilitators of implementing MAT at their facilities (e.g., administrative support, staffing, training, and organizational processes in place). Participants of the Organizational Readiness Survey will be compensated $25 for completion of each survey ($50 total).

The pilot study will assess treatment satisfaction using the Treatment Satisfaction Survey (1-5). Comparing treatment satisfaction between participants, pharmacists and physicians will inform the link between treatment process and outcomes.

11.0 STUDY TREATMENTS

11.1 Study Medication

11.1.1 Study Medication Management

Each research site, including pharmacies, is required to observe local, state, and federal regulations regarding receipt, custody, dispensing, and disposition of all study medications. Each site will maintain an adequate supply of unexpired study medications on site.

Upon receipt of the study medication, the investigator, pharmacist, or authorized designee at each site is responsible for taking inventory of the study drug. A record of this inventory must be kept and usage must be documented. Any unused or expired study drug shall be accounted for.

During the stabilization phase, buprenorphine prescribing clinicians are instructed to provide the study medication as follows: Give total daily dose administered on the previous day. Add an additional 2 to 4 mg as needed (up to 16 mg) based on severity of withdrawal symptoms (e.g., add 2 mg for mild withdrawal or 4 mg for moderate-severe withdrawal as rated by COWS). Criteria for dose increase: Increased opioid craving or withdrawal since last observation. Target Dose will be the dose that results in the optimal relief of objective and subjective opioid withdrawal symptoms and cravings. The expected dose is 16 mg daily, though lower doses such as 8 mg per day may be sufficient and higher doses such as 24 mg may be required. Maximum suggested daily dose is 24 mg (HRSA, 2016).

During the maintenance phase, dose is maintained stable unless recent opioid use and/or increased withdrawal and craving from previous visit suggest adjustment by the study physician.

11.1.2 Medication (Drug) Accountability Records

Appropriately qualified and trained study personnel will maintain accurate and current accounting of all study medication by utilizing drug accountability records which are made available for review by study monitors and other appropriate research personnel.

Accurate drug accountability records:

- Demonstrate that the study drug was dispensed according to standard clinical practice;
- Document receipt of the study medication, date, lot #, expiration date, quantity and dosage;
- Account for unopened, un-dispensed, unused, returned, wasted or broken medication;
- Dosing logs should record participant ID #, date dispensed, drug name, lot # and amount dispensed;
- Temperature logs should show a daily record of medication storage temperature.

11.1.3 Dispensing of Study Medication

All study medications shall be prepared and dispensed by a pharmacist or licensed medical practitioner appropriately trained and authorized to dispense study medications per local regulations.

11.1.4 Study Medication Storage

The medication will be stored at the pharmacy where maintenance visits are conducted at 25°C (77°F), with excursions permitted between 15-30°C (59-86°F). Study medication will be stored in compliance with the Package Insert and all federal, state, and local laws and institutional policy, including the regulations observed with other class III medications dispensed at the pharmacy. Study medication is stored in a secured location, separate from any commercial stock, under the conditions specified by the package insert.

11.1.5 Used/Unused Medication

Study medication returned by a participant may not be re-issued for use. Unused study medication is returned and logged into a perpetual inventory of study medication returned. Damaged, returned, expired or unused study medication is accounted for by the NIDA contract monitor and sent to the central distributor or a reverse distributor for destruction.

11.1.6 Lost Medication

No replacement of study medications is permitted. Exceptions may be made on a case-by-case basis at the request of the site study physician with LI(s) agreement and will be considered a study deviation.

11.1.7 Medication Packaging

Buprenorphine/naloxone sublingual film will be provided at no cost for participants after enrollment and supplied individually for both the 4mg and 8mg films.

Each package has the study drug information. Lot number, medication expiration date, and storage conditions, as well as manufacturer and distributor information, will be included on the kit labels as supplied by the manufacturer.

11.1.8 Provisions for Access to Treatment after Study

Prior to the conclusion of the 24-week treatment phase, the research team will make efforts to arrange for continued treatment with buprenorphine as locally appropriate. In most cases, participants will be returned to the care of referring study physician who will continue to prescribe buprenorphine. Where this is not possible (due to insurance or availability of treatment resources, etc.), alternative treatment referrals (e.g., other buprenorphine physicians, methadone maintenance, intensive outpatient psychosocial aftercare) will be made as appropriate.

12.0 CONCOMITANT THERAPY

12.1 General Considerations

Past research has demonstrated that the metabolism of buprenorphine is mediated by the cytochrome P450 pathway, as it inhibits the activity of both CYP2D6 and CYP3A4 (Picard *et al*., 2005). Further, in vitro studies employing human liver microsomes have demonstrated that the major metabolite of buprenorphine, norbuprenorphine, moderately inhibits the activity of CYP2D6 (Picard *et al*., 2005). Despite these findings, the relatively low plasma concentrations of buprenorphine and norbuprenorphine that results from therapeutic dosing are not expected to raise a concern for significant drug-drug interactions. However, the concomitant use of

buprenorphine with CYP3A4 inhibitors (e.g., azole antifungals such as ketoconazole, macrolide antibiotics such as erythromycin, and HIV protease inhibitors) should be monitored, and may require dose-reduction of one or both agents. The interaction of buprenorphine with CYP3A4 inducers has not been studied; therefore, it is recommended that patients receiving buprenorphine be monitored for signs and symptoms of opioid withdrawal if inducers of CYP3A4 (e.g., efavirenz, phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered. Buprenorphine treatment induction (performed before study screening) and therapy management during the trial are anticipated to greatly decrease the risk of precipitating opioid withdrawal.

12.2 Prohibited Medications

As described in the eligibility criteria, participants will be excluded from the study if there is a need for ongoing opioid analgesic treatment at any point during the study (including screening/baseline or following re-assessment during the trial). The study medical clinician may also exclude any participant taking medications that could interact adversely with the study drug at his/her clinical discretion.

12.3 Medications Allowed During the Study

Participants will be instructed to contact the pharmacist and supervising clinician if they plan on taking any concomitant medications (including prescription, over-the-counter, and herbal supplements) during the course of the study. At intake/baseline (Visit 1), all medications will be captured on the Concomitant Medications form. Changes to conconmitant medications will be recorded on the Buprenorphione Visit Checklist.

12.3.1 Ancillary Medications

No ancillary medications use is expected.

12.3.2 Rescue Medications

In the event a participant experiences opioid withdrawal during the study, this may be managed by adjusting the dose of buprenorphine. In case of prolonged discomfort, with or without concomitant opioid abuse reported by the managing pharmacist, a decision may be made by the supervising physician (in concert with the LIs) to discontinue the participant from the study. Discontinued participants will be asked to complete an Early Termination Visit. These participants will then be returned to physician care and/ or referred to local methadone treatment programs (see MOP for the management of patients receiving pharmacy-based OUD care (**SOP for OCA**)).

13.0 STATISTICAL ANALYSIS

13.1 General Design

13.1.1 Study Hypothesis

This is a feasibility study, and as such there are no *a priori* hypotheses. The main objective is to understand the feasibility regarding the study design features and operational procedures in order to inform the design of a full scale clinical trial (e.g., whether participants can be recruited in a timely fashion, whether the collaboration between OBBT physician and pharmacist can ensure standard buprenorphine maintenance care).

13.1.2 Primary and Secondary Outcomes (Endpoints)

As noted in Section 8.1, the main objective of this pilot study is to assess the feasibility of a full scale trial thus the primary outcome measures are as follows:

- Recruitment rate
- Retention in treatment
- Substance use (self-report and urine drug testing)
- Medication compliance

The secondary outcomes are also itemized in Section 8.2.

13.1.3 Recruitment

Based on the feedback from the local buprenorphine practice, it is anticipated that the clinical sites will each be able to recruit a sufficient number of participants who are stabilized on buprenorphine during the screening and baseline period to enroll 20-30 into the maintenance phase. The main objective of this feasibility study is to assess the recruitment rate, so there will be no specific targeted recruitment rate for assessing clinical site performance. Whatever recruitment rate is observed will inform the results of this feasibility study. Note that it is possible for a consented participant to drop out or be lost to follow-up prior to initiating the maintenance phase of their buprenorphine treatment. The recruitment rate will be calculated using all participants consented, however the number of participants who enroll into the maintenance phase of the study will also be tracked closely versus the number of potential participants that were consented. Additional details on participant recruitment are given in Section 7.3.

13.1.4 Randomization and Factors for Stratification

This is not a randomized study, as the treatment arm is the same for all clinical sites.

13.2 Rationale for Sample Size and Statistical Power

13.2.1 General Approach

As CTN-0075 is a feasibility study, there will be no hypothesis testing and thus performing sample size and/or power calculations are inappropriate. Instead, it is important to evaluate the precision with which primary outcome measures can be estimated. Particularly, we focus on the width of confidence intervals for the following: (1) the marginal odds of a scheduled visit being attended (retention in treatment), (2) the number of days of self-reported opioid use in the 30 days prior to the six month follow-up visit (opioid use), and (3) proportion of participants with an opiate-positive UDS at the six month follow-up visit (opioid use).

13.2.2 Projected Number of Study Sites

The Lead Node and the NIDA CCTN have determined that it is only possible fiscally and timelinewise to utilize approximately 3-4 study sites for the CTN-0075 feasibility pilot study.

13.2.3 Projected Number of Participants per Study Site

Depending on the number of study physicians at a study site, each study site may enroll up to 2030 participants who are stabilized on buprenorphine into the maintenance phase. However, this is an outcome of the study and will not be considered when assessing performance of a study site during this pilot study.

13.2.4 Confidence Interval Estimation for Retention in Treatment

The retention in treatment outcome measure is defined as an indicator of whether each of the six scheduled visits during the six month follow-up phase for each participant. Thus, there are two layers of correlation: visits within participants, and participants within site. To estimate the precision of the probability that any given follow-up was attended, we used simulations. **Appendix C** describes the approach to simulating the data for this outcome measure. For each simulated dataset, proc GLIMMIX (SAS 9.4) was used to model the log-odds of visit attendance and calculate the 95% confidence interval for the corresponding probability. Example code:

```
proc glimmix data=simul; class
        site patid;
        model x(event='1') = / dist=binary link=logit solution;
        random intercept / subject=site; random intercept /
        subject=patid(site); estimate "intercept" intercept 1 /
        ilink cl; run;
```

Generalized estimating equations (Liang and Zeger, 1986) were also considered for the method of analysis, however the coverage probabilities were low and thus that approach is not reported here. Several other approaches (e.g., bootstrap, MCMC) were also considered but suffered from poor coverage as well and thus were dropped from consideration.

The key parameters necessary for this set of simulations are (notation defined in **Appendix C**):

μ = P(visit attended)

γ = independence parameter for visits within a participant α / β = relative

contribution of study site effect to participant effect on μ

As summarized in **Figure 4,** the confidence interval width decreases as the visits within a participant become increasingly independent ("abg(3)" = $\gamma \rightarrow 1$). Further, the confidence interval width also decreases as the ratio of the site effect to the participant decreases (i.e., "rat" = $\alpha / \beta \rightarrow 0$).

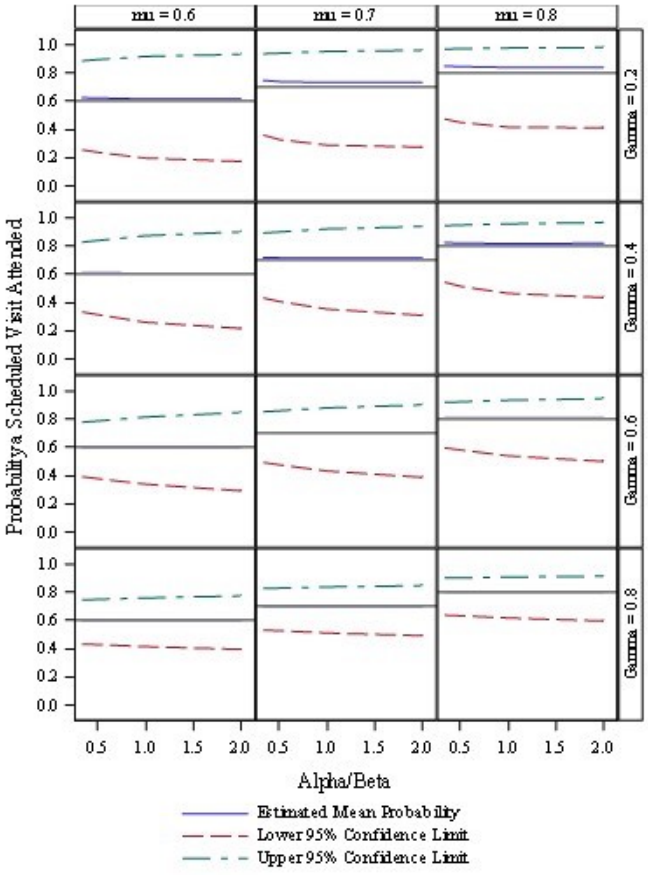

Figure 4. Simulation Results for Precision in the Retention in Treatment Outcome Measure

13.2.5 Confidence Interval Estimation for Opioid Use (self-report and UDS-based)

For the UDS-based opioid use outcome, data were simulated in a similar fashion to that for the retention in treatment except there is only one visit per participant (the six month follow-up visit). It is anticipated that the proportion of participants attending the final six month follow-up visit who will have an opioid-positive UDS ranges from 20-30% (Cunningham *et al*., 2013). **Figure 5** provides a graphical summary of the simulation results.

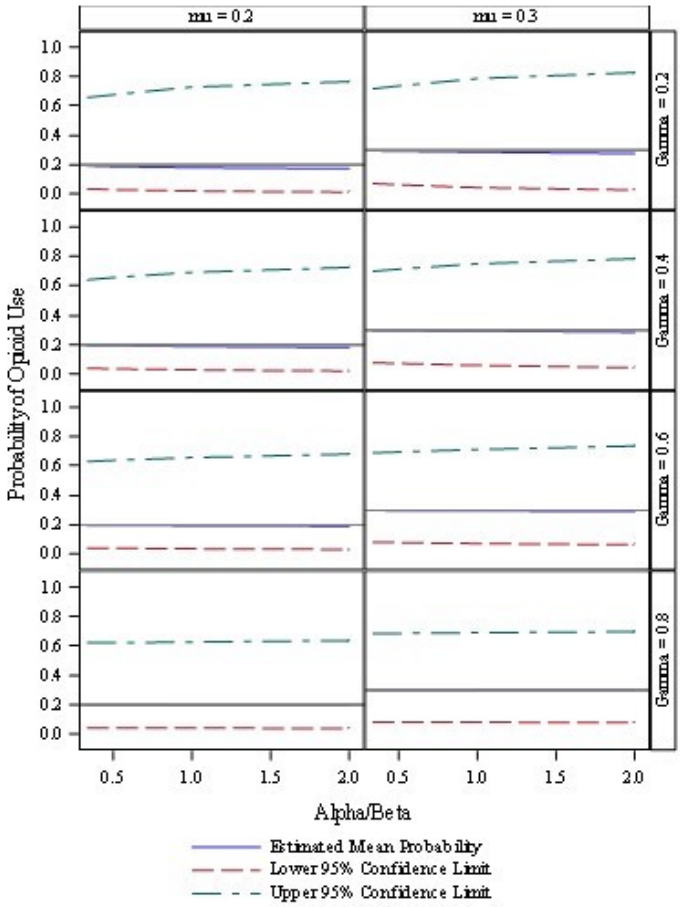

Figure 5. Simulation Results for Precision in the UDS-based Opioid Use Outcome Measure

The opioid use outcome measure based on self-report is the total number of days of opioid use, from TLFB, during the last 30 prior to the six month follow-up visit. The data for the precision simulations were also generated in a manner similar to that for the retention in treatment outcome. In this instance, each day in the evaluation period is considered a "visit", thus the "abg3" = γ parameter captures the relationship between days of self-reported use within a participant. As with the previous simulations, the closer γ is to 0, the greater the degree of correlation of days of use within a participant. **Figure 6** summarizes the results of these precision simulations when the daily opioid use rates varies from 20-40% (Cunningham *et al*., 2013, Rosenthal *et al*., 2016).

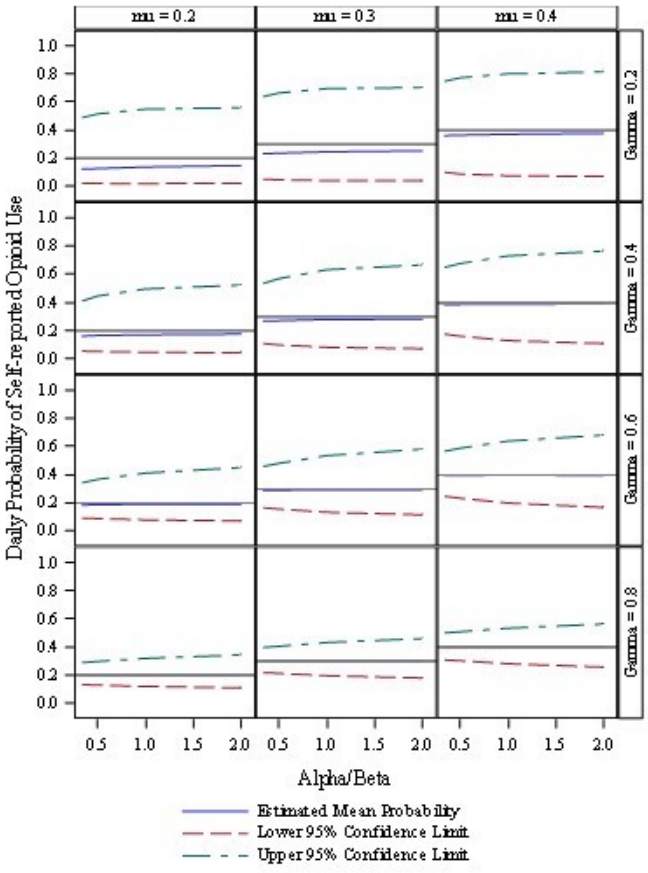

Figure 6. Simulation Results for Precision in the TLFB-based Opioid Use Outcome Measure

13.3 Statistical Methods for Primary and Secondary Outcomes

For the primary outcomes, estimates and 95% confidence intervals will be constructed as described below. As there is only one arm in this pilot feasibility study, no statistical testing will be performed. Descriptive statistics, including measures of spread, will be reported. The remainder of this section provides basic information regarding the primary outcome measures. A separate Statistical Analysis Plan will be developed that provides additional details regarding the statistical methods for both the primary and secondary outcomes.

13.3.1 Recruitment Rate

The recruitment rate will be estimated as the number of participants consented per month during the enrollment period. We will also calculate the number of participants reaching the maintenance phase on a per-month basis. These rates will also be calculated by site.

13.3.2 Retention in Treatment

For a particular participant, this outcome measure is captured by a vector of length six, denoted by $\boldsymbol{r}$ (r_1, … r_6), where each element of the vector is an indicator of whether the participant attended

the *i*th visit (*i*=1, ..., 6) during the maintenance phase. This is outcome measure involves hierarchical clustering as follows: visits within participant, and participants within study site. Given the target effective sample size (e.g., study completers) of 45 participants, asymptotic confidence intervals will be constructed. Based on the poor coverage findings from the simulation studies presented in Section 13.2, a random effects model will be used to construct these intervals while adjusting for the two levels of clustering.

13.3.3 Substance Use

Primary interest lies in opioid (licit and illicit) and heroin use. Both biological assessment of use, as well as self-reported use will be considered. For biological assessment, urine drug testing will be used for all substances . While we will focus on the six month follow-up visit, as has been done in other studies, we will also estimate substance use over all six visits during the maintenance phase. For self-reported use, the main outcome measure of interest is quantified as the number of days of use of opioids/heroin in the 30 days prior to the six month follow-up visit. In addition, we will also examine daily use rates and evaluate patterns over time. Similar to the analyses described in Section 13.2.2, a random effects model will be used to construct the 95% confidence intervals while adjusting for the two levels of clustering.

13.3.4 Medication Compliance

The operational definition of this outcome measure is the proportion of expected buprenorphine use in relation to actual use. The expected dose will be based on the number of milligrams expected based on the dispensed dose during the maintenance phase. The expected dose will accommodate adjustments to dosing made during the maintenance phase. The Statistical Analysis Plan will describe how compliance is calculated for early study terminations.

13.4 Significance Testing

Significance testing will not be conducted in this pilot study of feasibility. Section 13.3 describes the statistics and analytic approaches that will be used to summarize the data.

13.5 Interim Analysis

No interim analyses for efficacy or futility are planned for this study. Safety and data quality reports will be prepared for the Data and Safety Monitoring Board, and they may request interim analyses at any time during the trial.

13.6 Exploratory Analysis

Given the small sample size and the limited scope of this trial, every effort will be made to minimize any *post hoc* exploration of the data entered into Advantage eClinical.

13.7 Missing Data and Dropouts

For simplicity in this small pilot study, all missing data will be handled as follows for the four primary outcome measures:

1. Recruitment rate – no missing data
2. Retention in treatment – no missing data

3. Substance use

    a. Any day with missing self-reported substance use during the last 30 days of the 24 week follow-up period will be imputed as non-abstinent

    b. A missing UDS at the six month follow-up visit, for any reason, will be imputed positive

4. Medication compliance – no missing data

Should there be a substantial amount of missing data for the substance use outcomes, a sensitivity analysis may be implemented to see how the estimated outcome measures are impacted by deviations from the imputation schemes specified above.

13.8 Demographic and Baseline Characteristics

Baseline demographic and clinical variables will be summarized for participants enrolled in the maintenance phase. Descriptive summaries of the distribution of continuous baseline variables will be presented with percentiles (median, 25th and 75th percentiles), and with mean and standard deviation. Categorical variables will be summarized in terms of frequencies and percentages. The NIH requires subgroup analyses by gender, race and ethnicity (NIH, 2016). Given the scope of this study, all primary outcome measures will be summarized by these three factors but there will be no testing for differences across the demographic groups.

13.9 Safety Analysis

All protocol-defined safety events reported on the SERC-75 will be coded for body system and preferred term using MedDRA codes (per The Medical Dictionary for Regulatory Activities). Safety events on the SERC-75 will be summarized by frequency in the screening phase and maintenance phase. Listings of emergency department visits, hospitalizations, overdoses, and deaths will include system organ class (SOC) and preferred term (PT). Suicide risk from the P4 Screener will be assessed and presented in a listing.

14.0 REGULATORY COMPLIANCE AND SAFETY

14.1 Regulatory Compliance

This study will comply with all applicable rules and regulations. These include requirements of having received federal funding and the HIPAA requirements for data.

14.2 Statement of Compliance

This trial will be conducted in compliance with the appropriate protocol, current Good Clinical Practice (GCP), the principles of the Declaration of Helsinki, and all other applicable regulatory requirements. Participating sites must obtain written approval of the study protocol, consent form, other supporting documents, and any advertising for participant recruitment from the Institutional Review Board (IRB) of Record in order to participate in the study. Prior to study initiation, the protocol and the informed consent document(s) will be reviewed and approved by an appropriate Ethics Review Committee (ERC) or IRB. Any amendments to the protocol or consent materials must be approved before they are implemented. Annual progress reports and local Serious Adverse Event (SAE) reports will be submitted to the IRB, according to its usual procedures.

14.3 Institutional Review Board Approval

Prior to initiating the study, the Lead Node will obtain written IRB approval to conduct the study from a single IRB. Further, each site investigator will be required to set up a written IRB Reliance (Authorization) Agreement to name the single IRB as the IRB of Record for the study. The reliance agreement will also contain information about how communication between the participating site and the single IRB will take place. Should changes to the study protocol become necessary, protocol amendments will be submitted in writing by the Lead Node for IRB approval from the single IRB prior to implementation. In addition, the IRB will approve all consent forms, recruitment materials, and any materials given to the participant. Annual reports and progress reports will be submitted to the IRB annually or at a frequency requested by the IRB so that continuous study approval is maintained without lapse. Lead Investigators (LIs) will be responsible for maintaining in their research files copies of all performance site(s) current IRB/IEC approval notice(s), IRBapproved consent document(s), including approval for all protocol modifications. These materials must be received by LIs prior to the initiation of research activities at a given site, and must be available at any time for audit.

14.4 Informed Consent

The informed consent process is a means of providing study information to each prospective participant and allows for an informed decision about participation in the study. The informed consent form will include all of the required elements of informed consent. The study informed consent (and any updates made to the consent form throughout the trial) will be approved by the IRB prior to use. A copy of the IRB-approved consent, along with the IRB study approval, must be sent to the Clinical Coordinating Center (CCC) and the Lead Node (LN) (as needed) prior to the site initiation visit and with each subsequent consent revision. Every study participant is required to sign a valid, IRB-approved current version of the study informed consent form prior to the initiation of any study related procedures. The site must maintain the original signed informed consent for every participant in a locked, secure location that is in compliance with the IRB and any applicable institutional policies and that is accessible to the study monitors. Every study participant should be given a copy of the signed consent form.

Prior to informed consent, research staff will explain the study to the potential participant and provide a copy of the consent to read. If the participant is interested in participating in the study, a staff member will review each section of the informed consent form in detail and answer any questions the participant may pose. The participant will consent by signing and dating the consent document. The person obtaining consent and a witness, if required by the IRB, will also sign and date the consent document. It is strongly recommended that another research staff member review the consent after it is signed to ensure that the consent is properly executed and complete. Staff members delegated by the PI to obtain informed consent must be listed on the Site Staff Delegation of Responsibilities and Signature Log and must be approved by the IRB, if required. All persons obtaining consent must have completed appropriate training.

The informed consent form must be updated or revised whenever important new safety information is available, or whenever the protocol is amended in a way that may affect participants' participation in the trial. A copy of the informed consent will be given to a prospective participant to review during the consent process and to keep for reference. The participant will be informed that their participation is voluntary and they may withdraw from the study at any time, for any reason without penalty. Individuals who refuse to participate or who withdraw from the study will be treated without prejudice. Study sites will be responsible for maintaining signed consent forms as source documents for quality assurance review and regulatory compliance.

14.5 Confidentiality

Confidentiality will be maintained in accordance with all applicable federal regulations and/or state/Commonwealth law and regulations. By signing the protocol signature page, the investigator affirms that information furnished to the investigator by NIDA will be maintained in confidence and such information will be divulged to the IRB, Ethical Review Committee, or similar expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. The lead investigator will obtain a federal Certificate of Confidentiality (CoC), protecting participants against disclosure of sensitive information (e.g., substance use), and will distribute it to all sites when received. If applicable, the NIH office that issues the CoC will be advised of changes in the CoC application information. Participating sites will be notified if CoC revision is necessary. Participant records will be held confidential by the use of study codes for identifying participants on CRFs, secure storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data.

There is the potential risk of loss of confidentiality. Every effort will be made to keep participants' information confidential; however, this cannot be guaranteed.

14.5.1 Health Insurance Portability and Accountability Act (HIPAA)

Study sites may be required by their institutions to obtain authorization from participants for use of protected health information. Sites will be responsible for communicating with their IRBs or Privacy Boards and obtaining the appropriate approvals or waivers to be in regulatory compliance. Releases of participant identifying information that are permitted by the HIPAA regulations, but which are prohibited by other applicable federal regulations and/or state/Commonwealth law and regulation, are prohibited.

14.6 Investigator Assurances

Each research site must file (or have previously filed) a Federal Wide Assurance (FWA) with the HHS Office for Human Research Protection setting forth the commitment of the organization to establish appropriate policies and procedures for the protection of human research subjects, with documentation sent to NIDA or its designee. Research covered by these regulations cannot proceed in any manner prior to NIDA receipt of certification that the research has been reviewed and approved by the IRB provided for in the assurance (45 CFR 46.103(b) and (f)). Prior to initiating the study, the Principal Investigator at each study site will sign a protocol signature page, providing assurances that the study will be performed according to the standards stipulated therein.

14.6.1 Financial Disclosure

All investigators will comply with the requirements of 42 CFR Part 50, Subpart F to ensure that the design, conduct, and reporting of the research will not be biased by any conflicting financial interest. Everyone with decision-making responsibilities regarding the protocol will confirm to the sponsor annually that they have met their institutional financial disclosure requirements.

14.6.2 DEA Registration

All DEA requirements must be met, including registration, inspection if required, and certification, as applicable. Additionally, dispensing any controlled substance requires a DEA registration unless exempt by federal or state law or pursuant to CFR Sections 1301.22-1301.26.

Buprenorphine physicians and pharmacists will operate with their own buprenorphine DEA numbers.

14.7 Clinical Monitoring

Investigators will host periodic visits by NIDA contract monitors who will examine whether study procedures are conducted appropriately and that study data are generated, documented and reported in compliance with the protocol, GCP, and applicable regulations. These monitors will audit, at mutually agreed upon times, regulatory documents, case report forms (CRFs), informed consent forms and corresponding source documents for each participant. Monitors will have the opportunity and ability to review any study-associated document or file.

NIDA-contracted monitors will assess whether submitted data are accurate and in agreement with source documentation and will also review regulatory/essential documents such as correspondence with the IRB. Areas of particular concern will be participant informed consent forms, protocol adherence, reported safety events and corresponding assessments, and Principal Investigator oversight and involvement in the trial. Reports will be prepared following the visit and forwarded to the site Principal Investigator, the Lead Investigator and NIDA CCTN.

Qualified node personnel and NIDA CCTN CCC staff will provide site management for each site during the trial. Node and CCC staff will audit source documentation, including informed consent forms and HIPAA forms. This will take place as specified by the local protocol team, node PI or lead team, and will occur as often as needed, and is feasible, to help prevent, detect, and correct problems at the study sites. Node and CCC personnel will verify that study procedures are properly followed and that site personnel are trained and able to conduct the protocol appropriately. If the node personnel or CCC's review of study documentation indicates that additional training of site study personnel is needed, node and/or CCC personnel will undertake or arrange for that training. Details regarding monitoring are found in the study monitoring plan.

14.8 Inclusion of Women and Minorities

The study sites should aim and take steps to enroll a diverse study population. If difficulty is encountered in recruiting an adequate number of women and/or minorities, the difficulties involved in recruitment will be discussed in national conference calls and/or face-to-face meetings, encouraging such strategies as linkages with medical sites and/or treatment programs that serve a large number of women and/or minorities, advertising in newspapers or radio stations with a high female/minority readership/listening audience, etc.

Female-Specific Risks

Being a part of this study while pregnant may expose the unborn child to significant risks, some of which may be currently unforeseeable. Therefore, pregnant women will be excluded from the study. Women of childbearing potential will have a serum pregnancy test completed during screening (using 1 teaspoon of blood drawn from a vein by needle-stick). The pregnancy test must yield a negative result before the participant can continue in the study. If sexually active, women who consent to the study and are of childbearing potential must agree to use appropriate contraceptive measures while participating in the study. Medically acceptable contraceptives include: (1) surgical sterilization (hysterectomy or bilateral oophorectomy, NOT tubal litigation/cauterization or vasectomy of male partner), (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable

methods for routine use. In addition to the confirmatory urine pregnancy test conducted at the pharmacy following Visit 1, immediately prior to dispensation of the first dose of study medication, urine pregnancy tests will be performed at study visits 2 through 7. Women are asked to inform the study pharmacist and physician immediately if they become pregnant during this study or have unprotected sex.

14.9 Regulatory Files

The regulatory files should contain all required regulatory documents, study-specific documents, and all important communications. Regulatory files will be checked at each participating site for regulatory document compliance prior to study initiation, throughout the study, as well as at study closure.

14.10 Records Retention and Requirements

Research records for all study participants (e.g., case report forms, source documents, signed consent forms, and regulatory files) are to be maintained by the investigator in a secure location for a minimum of 3 years after the study is completed and closed. These records are also to be maintained in compliance with IRB, state and federal requirements, whichever is longest. The sponsor and Lead Investigator must be notified in writing and acknowledgment must be received by the site prior to the destruction or relocation of research records.

14.11 Reporting to Sponsor

The site Principal Investigator agrees to submit accurate, complete, legible and timely reports to the Sponsor, as required. These include, but are not limited to, reports of any changes that significantly affect the conduct or outcome of the trial or increase risk to study participants. Safey event reporting will occur as previously described. At the completion of the trial, the Lead Investigator will provide a final report to the Sponsor.

14.12 Audits

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

14.13 Study Documentation

Study documentation includes all case report forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence, signed protocol and amendments, Ethics Review Committee or Institutional Review Committee correspondence and approved consent form and signed participant consent forms.

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Whenever possible, the original recording of an observation should be retained as the source

document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

14.14 Protocol Deviations

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

All protocol deviations will be recorded in the Electronic Data Capture (EDC) system via the Protocol Deviation CRF. The CCC, DSC and the Lead Investigator must be contacted immediately if an unqualified or ineligible participant is consented and enrolled into the study.

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

14.15 Safety Monitoring

14.15.1 Safety Events

All protocol-defined safety events (medical and/or psychiatric) occurring during the course of the study will be assessed, documented, and reported. Safety events occurring during the course of the clinical trial will be collected, documented, and reported by the Principal Investigator or subinvestigators according to the specific instructions detailed in this section of the protocol. Appropriately qualified and trained personnel will elicit participant reporting of safety events at each study visit designated to collect safety events (i.e., the first visit following informed consent and at every study visit thereafter).

A study medical clinician (MD, DO, PA, or NP) will review or provide consultation for each safety event as necessary. The study medical clinician and site Principal Investigator (if different) will also make decisions to exclude, refer, or withdraw participants as required. The study staff will be trained to monitor for and report safety events.

14.15.2 Reportable Safety Events

For the purposes of this protocol, the following safety events will be collected and reported: headache, nausea, vomiting, constipation, insomnia, excessive sweating, increased sensitivity in the mouth, burning sensation in the mouth, sores in the mouth, pain, swelling, overdoses, ED visits, hospitalizations, and death of any participant who provides informed consent in this study.

The local site is responsible for the reporting of safety events to their local IRB and/or the IRB of Record per applicable IRB guidelines.

14.15.3 Medical Monitor and Safety Monitor

Under the supervision of the NIDA-assigned Medical Monitor, the study Safety Monitor will be responsible for overseeing safety and for evaluating all safety events. The Safety Monitor will review all reported safety events on a regular basis. The Medical Monitor will review events regularly and will be available at all times for consultation. Where further information is needed, the Safety Monitor will discuss the event with the site. It is the responsibility of the site Principal Investigator to provide this information to the Safety Monitor. It is also the site Principal Investigators' responsibility to inform the IRB per IRB guidelines.

The Medical Monitor will independently review the safety data, present it to the DSMB for periodic review, and provide PIs a Safety Letter when necessary for submission to the IRB for regulatory compliance. The Medical Monitor will determine which safety events require expedited reporting to NIDA, the DSMB, pharmaceutical/distributors, and regulatory authorities. This will include events that are serious, related, and unexpected (SUSAR).

14.15.4 Data and Safety Monitoring Board (DSMB)

This study will utilize the CTN DSMB to oversee ongoing trial progress and examine accumulating data to assure protection of participants' safety while the study's scientific goals are being met. The purpose of this board is to determine whether risks emerge during the conduct of the trial that make continuation unethical. This process is intended to assure the IRBs, the sponsor, and investigators that participants are provided with an accurate and ongoing risk evaluation when participating in CTN research trials. It will determine whether there is support for continuation of the trial, evidence that study procedures should be changed, or if the trial should be halted, for reasons relating to the safety of the study participants, the efficacy of the treatment under study, or inadequate trial performance (e.g., poor recruitment). Safety monitoring begins with the initial review of the protocol during the study development process. The CTN DSMB is responsible for conducting periodic reviews of accumulating safety and efficacy data. The DSMB will meet at least annually. Recommendations from these reviews will be distributed to site investigators and submitted to the IRB.

14.15.5 Known Potential Toxicities of Study Drug

Refer to package insert in **Appendix B**.

14.15.6 Potential Events Related to the Underlying Clinical Condition and/or Study Populations

Each of the participating research sites have established practices for managing medical and psychiatric emergencies, and the study staff will continue to utilize these procedures. Participants at each research site will be referred for medical care in the event of possible clinical deterioration or other problems, and for implementing appropriate courses of action.

14.15.7 Additional Study-Specific Risks

Buprenorphine Side Effects

Side effects commonly observed with the administration of BUP-NX sublingual (under the tongue) film include sore mouth, partial loss of sensation of touch, headache, nausea, vomiting, constipation, signs and symptoms of withdrawal, insomnia, pain, and swelling of the limbs. The long-term side effects of BUP-NX are unknown at the present time.

It is also possible that a patient may have a hypersensitivity or allergic reaction to BUP-NX. The most common signs and symptoms of having an allergic reaction include rashes, hives, and itching. More serious, but less common occurrences include those related to anaphylactic shock such as difficulty breathing. To minimize the risk of hypersensitivity or allergic reaction, the study doctor will ask each participant if he or she has taken buprenorphine/naloxone prior to entering the study to see if he or she has had a previous allergic reaction or increased sensitivity to the medication or any of its components.

BUP-NX itself causes physical dependence and can result in withdrawal symptoms when BUPNX is stopped. BUP-NX can also cause drowsiness and breathing that is slow and shallow.

A number of deaths have been reported in people who abuse BUP-NX in combination with benzodiazepines, such as Valium or sleeping pills. Combining BUP-NX with alcohol or other drugs may be hazardous. Patients must not drink alcohol-containing beverages or take other drugs including benzodiazepines, like Valium or sleeping pills, or narcotic pain relievers, while using BUP-NX. Patients who are receiving benzodiazepine treatment by another physician will only be able to participate in the study if his or her doctor monitors their prescriptions during the study.

Patients should not inject (“shoot-up”) BUP-NX. Injecting BUP-NX may cause serious withdrawal symptoms such as pain, cramps, vomiting, diarrhea, anxiety, sleep problems, and cravings.

BUP-NX may also impair mental or physical abilities involved in such activities as driving or operating machinery. Patients are advised not to engage in such activities for at least 6 hours after taking the first dose of BUP-NX. The researchers will be happy to discuss alternative methods of transportation with patients, such as getting a ride from a family member or friend, or taking a taxi or bus.

Risks of Buprenorphine Misuse

As buprenorphine is a partial opioid agonist medication, missing one or more doses during treatment could result in opioid withdrawal. Use of full opioid agents (e.g., heroin or prescription opioid medications) during treatment may result in lack of effects or trigger opioid withdrawal discomfort. Administering a large amount of exogenous opioids to overcome such symptoms could result in potentially life-threatening opioid intoxication and overdose. Use of sedative substances (e.g., alcohol and benzodiazepines) in addition to buprenorphine could lead to excessive sedation and respiratory depression. Patients are advised to discuss these risks with the study pharmacist and doctor if they so choose.

Risks of Drawing Blood

Risks associated with drawing blood from the arm include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although unlikely.

Drug Interactions

For the participant's safety, participants must tell the study pharmacist, doctor, and staff about all of the prescribed medical foods and drugs, herbal products, over-the-counter (OTC) drugs, vitamins, natural remedies, and alcohol that he or she is taking before starting the study. Participants must also tell the study pharmacist, doctor, and staff before starting to take any of these products while enrolled in the study.

Other Risks

Some of the questions the researchers will ask participants as part of this study may make participants feel uncomfortable. Participants may decline to answer any of the questions and participants may take a break at any time during the study visits. Participants may stop their participation in this study at any time.

There may be risks, discomforts, drug interactions or side effects that are not yet known.

15.0 DATA MANAGEMENT AND PROCEDURES

15.1 Design and Development

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

15.2 Site Responsibilities

The data management responsibilities of each site will be specified by the Lead Node and the DSC.

15.3 Data Center Responsibilities

The DSC will 1) develop and apply data management procedures to ensure the collection of accurate and good-quality data, 2) provide final Case Report Forms (CRFs) and electronic CRFs (eCRFs) for the collection of all data required by the study, 3) develop data dictionaries for each CRF that will comprehensively define each data element, 4) prepare instructions for the use of Advantage eClinical and for the completion of CRFs, 5) conduct ongoing data validation and cleaning activities on study data collected from all study sites, and 6) perform data validation and cleaning activities prior to any interim analyses and prior to the final study database lock.

15.4 Data Acquisition and Entry

Data will be collected at the study sites on source documents and entered by the site into eCRFs in Advantage eClinical, or will be collected via direct entry into the eCRF. In the event that Advantage eClinical is not available, the DSC will provide the sites with paper CRF source documents and completion instructions. Data will be entered into Advantage eClinical in accordance with the instructions provided during protocol-specific training and guidelines

established by the DSC. Data entry into the eCRFs shall be performed by authorized individuals. Selected eCRFs may also require the investigator's electronic signature.

The Principal Investigator at each site is responsible for maintaining accurate, complete and upto-date research records. In addition, the investigator is responsible for ensuring the timely completion of eCRFs for each research participant.

15.5 Data Editing

Data will be entered into the DSC automated data acquisition and management system (Advantage eClinical). eCRFs will be monitored for completeness and accuracy throughout the study. Dynamic reports listing missing values and forms are available to sites at all times in Advantage eClinical. These reports will be monitored regularly by the DSC. In addition, the DSC will identify inconsistencies within eCRFs and between eCRFs and post data clarification requests or queries in Advantage eClinical on a scheduled basis. Sites will resolve data inconsistencies and errors by entering all corrections and changes directly into Advantage eClinical.

The CCC will conduct regular on-site and remote visits, during which audits comparing source documents to the data entered on the eCRF will be performed. Any discrepancies identified between the source document and the eCRF will be corrected by the site.

Trial progress and data status reports, which provide information on recruitment, availability of primary outcome, treatment exposure, regulatory status, and data quality, will be generated daily and posted to a secure website. These reports are available to the site, the corresponding node, the lead node, the coordinating centers, and NIDA to monitor study progress overall and at each individual participating site.

15.6 Data Transfer/Lock

At the conclusion of data collection for the study, the DSC will perform final cleaning activities and will "lock" the study database from further modification. The final analysis datasets will be transferred to the Lead Investigator and to NIDA, as requested, for storage and archiving.

15.7 Data Training

The training plan for site staff includes provisions for training on assessments, eCRF completion guidelines, data management procedures, and the use of Advantage eClinical.

15.8 Data Quality Assurance

To address the issue of data entry quality, the DSC will follow a standard data monitoring plan. An acceptable quality level prior to study lock or closeout will be established as a part of the data management plan. Data quality summaries will be made available during the course of the protocol.

16.0 TRAINING REQUIREMENTS

The study staff will be trained as specified in the study Training Plan. Required training will include Human Subjects Protection (HSP) and Good Clinical Practice (GCP), as well as protocol-specific training as needed (e.g., assessments, study interventions, fidelity to protocol, safety procedures, data management and collection, and other research procedures). Attention will be given to provide the study clinic staff physicians and pharmacists training in management of OUD,

buprenorphine induction and maintenance, and to familiarize study personnel with study procedures. Support mechanisms are identified (e.g., who to contact for aid, questions, resources), as well as re-training procedures. All study staff will also be required to complete any training requirements per their study site and IRB requirements.

Training in study-specific assessments will be provided as specified in a comprehensive training plan that will be developed by the Lead Node, the CCC, and the DSC. All non-intervention training is expected to be delivered via conference call, webinar and self-study. Research staff (and all other study personnel) will receive HSP and GCP training through the web-based system currently in use. The CTN-0075 Training Plan will provide a detailed description of training, supervision, and fidelity monitoring procedures.

17.0 PUBLICATIONS AND OTHER RIGHTS

Per NIH policy, the results of the proposed trial are to be made available to the research community and to the public at large. The planning, preparation, and submission of publications will follow the policies of the Publications Committee of the CTN.

18.0 SIGNATURES

SPONSOR – CCTN SCIENTIFIC OFFICER OR DESIGNEE

Printed Name	Signature	Date

ACKNOWLEDGEMENT BY INVESTIGATOR:

- I am in receipt of version 7.0 of the protocol and agree to conduct this clinical study in accordance with the design and provisions specified therein.
- I agree to follow the protocol as written except in cases where necessary to protect the safety, rights, or welfare of a participant, an alteration is required, and the sponsor and IRB have been notified prior to the action.
- I will ensure that the requirements relating to obtaining informed consent and institutional review board (IRB) review and approval in 45 CFR 46 are met.
- I agree to personally conduct or supervise this investigation at this site and to ensure that all site staff assisting in the conduct of this study are adequately and appropriately trained to implement this version of the protocol and that they are qualified to meet the responsibilities to which they have been assigned.
- I agree to comply with all the applicable federal, state, and local regulations regarding the obligations of clinical investigators as required by the Department of Health and Human Services (HHS), the state, and the IRB.

SITE'S PRINCIPAL INVESTIGATOR

Printed Name	Signature	Date

Site Name _____

Node Affiliation _____

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20.0 APPENDIX A: Data and Safety Monitoring Plan

20.1 Brief Study Overview

The primary goal of the CTN-0075 study is to determine the acceptability and feasibility of shifting the outpatient buprenorphine based treatment (OBBT) of OUD from physician to pharmacist care. Secondary objectives are to generate point estimates for treatment fidelity and satisfaction, participant safety, and use of PDMP and the EHRs.

20.2 Oversight of Clinical Responsibilities

A. Site Principal Investigator

Each participating site's Principal Investigator (PI) is responsible for study oversight, including ensuring human research subject protection by designating appropriately qualified, trained research staff and medical clinicians to assess, report, and monitor safety events.

All protocol-defined reportable safety events occurring during the course of the clinical trial will be collected, documented, and reported by the investigator or sub-investigators according to the protocol.

The occurrence of safety events will be assessed at each visit during the study.

Reportable safety events are required to be entered into the data system within 48 hoursof the site staff becoming aware of the event by completing the checklist. Deaths are required to be entered into the data system within 24 hours of the site's knowledge of the event.

B. CCC Medical Monitor

The NIDA CTN Clinical Coordinating Center's (CCC) Medical Monitor or designee is responsible for reviewing all safety events reported. Where further information is needed the Medical Monitor or designee will discuss the event with the site staff. All safety events are reviewed on a regular basis to observe trends or unusual events.

Voluntary Regulatory Reporting in non-IND Trials:

For non-IND trials, if an event meets expedited reporting criteria (serious, related and unexpected) the CCC Medical Monitor or designee will voluntarily report to FDA/Regulatory Authorities using the MedWatch Form 3500 or similar.

C. Data and Safety Monitoring Board (DSMB)

The NIDA CTN DSMB affiliated with this trial will be responsible for conducting periodic reviews of accumulating safety, trial performance, and outcome data. Reports will be generated and presented for Data and Safety Monitoring Board (DSMB) meetings. The DSMB will receive listings of safety events and summary reports of all deaths at a frequency requested by the DSMB, but at least annually. Furthermore, the DSMB will be informed of expedited reports of safety events. The DSMB will make recommendations to NIDA CCTN as to whether there is sufficient support for continuation of the trial, evidence that study procedures should be changed, or evidence that the trial (or a specific site) should be halted for reasons relating to safety of the study participants or inadequate trial performance (e.g., poor recruitment).

Following each DSMB meeting, the NIDA CCTN will communicate the outcomes of the meeting, based on DSMB recommendations, in writing to the study Lead Investigator. This communication summarizing study safety information will be submitted to participating IRBs.

D. Quality Assurance (QA) Monitoring

The monitoring of the study sites will be conducted on a regular basis by the NIDA CTN CCC. Investigators will host periodic visits for the NIDA CTN CCC monitors. The purpose of these visits is to assess compliance with GCP requirements and to document the integrity of the trial progress. Areas of particular concern will be the review of inclusion/exclusion criteria, participant Informed Consent Forms, protocol adherence, safety monitoring, IRB reviews and approvals, regulatory

documents, participant records, study drug accountability, and Principal Investigator supervision and involvement in the trial. The monitors will interact with the site staff to identify issues and retrain the site as needed to enhance research quality.

Site Visit Reports will be prepared by the NIDA CCC monitors following each site visit. These reports will be sent to the site Principal Investigator, the study Lead Investigator and NIDA CCTN.

E. Management of Risks to Participants Confidentiality

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

Information Meeting Reporting Requirements

The consent form will specifically state the types of information that are required for reporting and that the information will be reported as required. These include suspected or known sexual or physical abuse of a child or elders, or threatened violence to self and/or others.

Participant Protection

The site's study clinician will evaluate all pertinent screening and baseline assessments prior to commencing the study intervention to ensure that the participant is eligible and safe to enter the study. Safety events and concomitant medications will be assessed and documented at each clinic visit. Individuals who experience a safety event that compromises safe participation in the study will be discontinued from further medication administration and provided referrals for other treatment or to specialized care. Study personnel will request that the participant complete an Early Termination Visit to assure safety and to document end-of-medication outcomes.

21.0 APPENDIX B: SUBOXONE® Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SUBOXONE sublingual film safely and effectively. See full prescribing information for SUBOXONE sublingual film.

SUBOXONE® (buprenorphine and naloxone) sublingual film, for sublingual or buccal use CIII
Initial U.S. Approval: 2002

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.2, 2.3, 2.5, 2.8)	09/2017
Warnings and Precautions (5.2, 5.3)	02/2018

----------INDICATIONS AND USAGE----------

SUBOXONE® sublingual film contains buprenorphine, a partial-opioid agonist, and naloxone, an opioid antagonist, and is indicated for treatment of opioid dependence. (1)

SUBOXONE sublingual film should be used as part of a complete treatment plan that includes counseling and psychosocial support. (1)

----------DOSAGE AND ADMINISTRATION----------

- Prescription use of this product is limited under the Drug Addiction Treatment Act. (2.1)
- Administer SUBOXONE sublingual film as a single daily dose. (2.2)
- To avoid precipitating withdrawal, induction with SUBOXONE sublingual film should be undertaken when objective and clear signs of withdrawal are evident and SUBOXONE sublingual film should be administered in divided doses when used as initial treatment. (2.3)
- For patients dependent on short-acting opioid products who are in opioid withdrawal; on Day 1, administer up to 8 mg/2 mg SUBOXONE sublingual film (in divided doses). On Day 2, administer up to 16 mg/4 mg of SUBOXONE sublingual film as a single dose. (2.3)
- For patients dependent on methadone or long-acting opioid products, induction onto sublingual buprenorphine monotherapy is recommended on Days 1 and 2 of treatment. (2.3)
- For maintenance treatment, the target dosage of SUBOXONE sublingual film is usually 16 mg/4 mg as a single daily dose. (2.4)
- Sublingual Administration: Place one film under the tongue, close to the base on the left or right side, and allow to completely dissolve.
  Buccal Administration: Place one film on the inside of the left or right cheek and allow to completely dissolve. (2.5)
- SUBOXONE sublingual film must be administered whole. Do not cut, chew, or swallow SUBOXONE sublingual film (2.5)
- When discontinuing treatment, gradually taper to avoid signs and symptoms of withdrawal. (2.8)

----------DOSAGE FORMS AND STRENGTHS----------

Sublingual film:

- buprenorphine 2 mg/ naloxone 0.5 mg,
- buprenorphine 4 mg/ naloxone 1 mg,
- buprenorphine 8 mg/ naloxone 2 mgand
- buprenorphine 12 mg/ naloxone 3 mg. (3)

----------CONTRAINDICATIONS----------

Hypersensitivity to buprenorphine or naloxone. (4)

----------WARNINGS AND PRECAUTIONS----------

- Addiction, Abuse, and Misuse: Buprenorphine can be abused in a similar manner to other opioids. Monitor patients for conditions indicative of diversion or progression of opioid dependence and addictive behaviors. Multiple refills should not be prescribed early in treatment or without appropriate patient follow-up visits. (5.1)
- Respiratory Depression: Life-threatening respiratory depression and death have occurred in association with buprenorphine use. Warn patients of the potential danger of self-administration of benzodiazepines or other CNS depressants while under treatment with SUBOXONE sublingual film. (5.2, 5.3)
- Unintentional Pediatric Exposure: Store SUBOXONE sublingual film safely out of the sight and reach of children. Buprenorphine can cause severe, possibly fatal, respiratory depression in children. (5.4)
- Neonatal Opioid Withdrawal Syndrome: Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy (5.5)
- Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid. (5.6)
- Risk of Opioid Withdrawal with Abrupt Discontinuation: If treatment is temporarily interrupted or discontinued, monitor patients for withdrawal and treat appropriately. (5.7)
- Risk of Hepatitis, Hepatic Events: Monitor liver function tests prior to initiation and during treatment and evaluate suspected hepatic events. (5.8)
- Precipitation of Opioid Withdrawal Signs and Symptoms: An opioid withdrawal syndrome is likely to occur with parenteral misuse of SUBOXONE sublingual film by individuals physically dependent on full opioid agonists, or by sublingual or buccal administration before the agonist effects of other opioids have subsided. (5.10)
- Risk of Overdose in Opioid-Naïve Patients: SUBOXONE sublingual film is not appropriate as an analgesic. There have been reported deaths of opioid naïve individuals who received a 2 mg sublingual dose. (5.11)

----------ADVERSE REACTIONS----------

Adverse events commonly observed with the sublingual/buccal administration of the SUBOXONE sublingual film are oral hypoesthesia, glossodynia, oral mucosal erythema, headache, nausea, vomiting, hyperhidrosis, constipation, signs and symptoms of withdrawal, insomnia, pain, and peripheral edema. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Indivior Inc. at 1-877-782-6966 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Benzodiazepines: Use caution in prescribing SUBOXONE sublingual film for patients receiving benzodiazepines or other CNS depressants and warn patients against concomitant self-administration/misuse. (7)
- CYP3A4Inhibitors and Inducers: Monitor patients starting or ending CYP3A4 inhibitors or inducers for potential over- or under- dosing. (7)
- Antiretrovirals: Patients who are on chronic buprenorphine treatment should have their dose monitored if NNRTIs are added to their treatment regimen. Monitor patients taking buprenorphine and atazanavir with and without ritonavir. Dose reduction of buprenorphine may be warranted (7).
- Serotonergic Drugs: Concomitant use may result in serotonin syndrome. Discontinue SUBOXONE sublingual film if serotonin syndrome is suspected. (7)

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Buprenorphine passes into mother's milk. (8.2)
- Geriatric Patients: Monitor for sedation and respiratory depression. (8.5)
- Moderate or Severe Hepatic Impairment: Buprenorphine/naloxone products are not recommended in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 02/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SUBOXONE sublingual film is indicated for treatment of opioid dependence. SUBOXONE sublingual film should be used as part of a complete treatment plan that includes counseling and psychosocial support.

2 DOSAGE AND ADMINISTRATION

2.1 Drug Addiction and Treatment Act

Under the Drug Addiction Treatment Act (DATA) codified at 21 U.S.C. 823(g), prescription use of this product in the treatment of opioid dependence is limited to healthcare providers who meet certain qualifying requirements, and who have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription.

2.2 Important Dosage and Administration Information

SUBOXONE sublingual film is administered sublingually or buccally as a single daily dose.

Medication should be prescribed in consideration of the frequency of visits. Provision of multiple refills is not advised early in treatment or without appropriate patient follow-up visits.

2.3 Induction

Prior to induction, consideration should be given to the type of opioid dependence (i.e., long- or short-acting opioid products), the time since last opioid use, and the degree or level of opioid dependence.

Patients dependent on heroin or other short-acting opioid products

Patients dependent on heroin or other short-acting opioid products may be inducted with either SUBOXONE sublingual film or with sublingual buprenorphine monotherapy. At treatment initiation, the first dose of SUBOXONE sublingual film should be administered when objective signs of moderate opioid withdrawal appear, not less than six hours after the patient last used opioids.

It is recommended that an adequate treatment dose, titrated to clinical effectiveness, be achieved as rapidly as possible. In some studies, a too-gradual induction over several days led to a high rate of drop-out of buprenorphine patients during the induction period.

On Day 1, an induction dosage of up to 8 mg/2 mg SUBOXONE sublingual film is recommended. Clinicians should start with an initial dose of 2 mg/0.5 mg or 4 mg/1 mg buprenorphine/naloxone and may titrate upwards in 2 or 4 mg increments of buprenorphine, at approximately 2-hour intervals, under supervision, to 8 mg/2 mg buprenorphine/naloxone based on the control of acute withdrawal symptoms.

On Day 2, a single daily dose of up to 16 mg/4 mg SUBOXONE sublingual film is recommended.

Because the exposure to naloxone is somewhat higher after buccal than after sublingual administration, it is recommended that the sublingual site of administration be used during induction to minimize exposure to naloxone, to reduce the risk of precipitated withdrawal.

Patients dependent on methadone or long-acting opioid products

Patients dependent upon methadone or long-acting opioid products may be more susceptible to precipitated and prolonged withdrawal during induction than those on short-acting opioid products.

Buprenorphine/naloxone combination products have not been evaluated in adequate and well-controlled studies for induction in patients who are physically dependent on long-acting opioid products, and the naloxone in these combination products is absorbed in small amounts by the sublingual route and could cause worse precipitated and prolonged withdrawal. For this reason, buprenorphine monotherapy is recommended

in patients taking long-acting opioids when used according to approved administration instructions. Following induction, the patient may then be transitioned to once-daily SUBOXONE sublingual film.

2.4 Maintenance

- For maintenance, SUBOXONE sublingual film may be administered buccally or sublingually.
- The dosage of SUBOXONE sublingual film from Day 3 onwards should be progressively adjusted in increments/decrements of 2 mg/0.5 mg or 4 mg/1 mg buprenorphine/naloxone to a level that holds the patient in treatment and suppresses opioid withdrawal signs and symptoms.
- After treatment induction and stabilization, the maintenance dose of SUBOXONE sublingual film is generally in the range of 4 mg/1 mg buprenorphine/naloxone to 24 mg/6 mg buprenorphine/naloxone per day depending on the individual patient and clinical response. The recommended target dosage of SUBOXONE sublingual film during maintenance is 16 mg/4 mg buprenorphine/naloxone/day as a single daily dose. Dosages higher than 24 mg/6 mg daily have not been demonstrated to provide a clinical advantage.
- When determining the prescription quantity for unsupervised administration, consider the patient's level of stability, the security of his or her home situation, and other factors likely to affect the ability to manage supplies of take-home medication.
- There is no maximum recommended duration of maintenance treatment. Patients may require treatment indefinitely and should continue for as long as patients are benefiting and the use of SUBOXONE sublingual film contributes to the intended treatment goals.

2.5 Method of Administration

SUBOXONE sublingual film must be administered whole. Do not cut, chew, or swallow SUBOXONE sublingual film. Advise patients not to eat or drink anything until the film is completely dissolved.

Sublingual Administration

Place one film under the tongue, close to the base on the left or right side. If an additional film is necessary to achieve the prescribed dose, place an additional film sublingually on the opposite side from the first film. Place the film in a manner to minimize overlapping as much as possible. The film must be kept under the tongue until the film is completely dissolved. If a third film is necessary to achieve the prescribed dose, place it under the tongue on either side after the first 2 films have dissolved.

Buccal Administration

Place one film on the inside of the right or left cheek. If an additional film is necessary to achieve the prescribed dose, place an additional film on the inside of the opposite cheek. The film must be kept on the inside of the cheek until the film is completely dissolved. If a third film is necessary to achieve the prescribed dose, place it on the inside of the right or left cheek after the first two films have dissolved.

SUBOXONE sublingual film should NOT be moved after placement.

To ensure consistency in bioavailability, patients should follow the same manner of dosing with continued use of the product. Proper administration technique should be demonstrated to the patient.

2.6 Clinical Supervision

Treatment should be initiated with supervised administration, progressing to unsupervised administration as the patient's clinical stability permits. SUBOXONE sublingual film is subject to diversion and abuse. When determining the prescription quantity for unsupervised administration, consider the patient's level of stability, the security of his or her home situation, and other factors likely to affect the ability to manage supplies of take-home medication.

Ideally patients should be seen at reasonable intervals (e.g., at least weekly during the first month of treatment) based upon the individual circumstances of the patient. Medication should be prescribed in consideration of the frequency of visits. Provision of multiple refills is not advised early in treatment or without appropriate patient follow-up visits. Periodic assessment is necessary to determine compliance with the dosing regimen, effectiveness of the treatment plan, and overall patient progress.

Once a stable dosage has been achieved and patient assessment (e.g., urine drug screening) does not indicate illicit drug use, less frequent follow-up visits may be appropriate. A once-monthly visit schedule may be reasonable for patients on a stable dosage of medication who are making progress toward their treatment objectives. Continuation or modification of pharmacotherapy should be based on the healthcare provider's evaluation of treatment outcomes and objectives such as:

1. Absence of medication toxicity.
2. Absence of medical or behavioral adverse effects.
3. Responsible handling of medications by the patient.
4. Patient's compliance with all elements of the treatment plan (including recovery-oriented activities, psychotherapy, and/or other psychosocial modalities).
5. Abstinence from illicit drug use (including problematic alcohol and/or benzodiazepine use).

If treatment goals are not being achieved, the healthcare provider should re-evaluate the appropriateness of continuing the current treatment.

2.7 Unstable Patients

Healthcare providers will need to decide when they cannot appropriately provide further management for particular patients. For example, some patients may be abusing or dependent on various drugs, or unresponsive to psychosocial intervention such that the healthcare provider does not feel that he/she has the expertise to manage the patient. In such cases, the healthcare provider may want to assess whether to refer the patient to a specialist or more intensive behavioral treatment environment. Decisions should be based on a treatment plan established and agreed upon with the patient at the beginning of treatment.

Patients who continue to misuse, abuse, or divert buprenorphine products or other opioids should be provided with, or referred to, more intensive and structured treatment.

2.8 Discontinuing Treatment

The decision to discontinue therapy with SUBOXONE sublingual film after a period of maintenance should be made as part of a comprehensive treatment plan. Advise patients of the potential to relapse to illicit drug use following discontinuation of opioid agonist/partial agonist medication-assisted treatment. Taper patients to reduce the occurrence of opioid withdrawal signs and symptoms *[See Warnings and Precautions (5.7)]*.

2.9 Switching Between Buprenorphine or Buprenorphine and Naloxone Sublingual Tablets and SUBOXONE Sublingual Film

Patients being switched between buprenorphine and naloxone or buprenorphine only sublingual tablets and SUBOXONE sublingual film should be started on the same dosage of the previously administered product. However, dosage adjustments may be necessary when switching between buprenorphine products. Not all strengths and combinations of the SUBOXONE sublingual films are bioequivalent to SUBOXONE® sublingual tablets as observed in pharmacokinetic studies *[see Clinical Pharmacology (12.3)]*. Therefore, systemic exposures of buprenorphine and naloxone may be different when patients are switched from tablets to film or vice-versa. Patients should be monitored for symptoms related to over-dosing or under-dosing.

2.10 Switching Between SUBOXONE Sublingual Film Strengths

As indicated in Table 1, the sizes and the compositions of the four units of SUBOXONE sublingual films, i.e.,

2 mg/0.5 mg, 4 mg/1 mg, 8 mg/2 mg and the 12 mg/3 mg units, are different from one another. If patients switch between various combinations of lower and higher strength units of SUBOXONE sublingual films to obtain the same total dose, (e.g., from three 4 mg/1 mg units to a single 12 mg/3 mg unit, or vice-versa), systemic exposures of buprenorphine and naloxone may be different and patients should be monitored for over-dosing or under-dosing. For this reason, pharmacist should not substitute one or more film strengths for another without approval of the prescriber.

Table 1. Comparison of Available SUBOXONE Sublingual Film Strengths by Dimensions and Drug Concentrations.

SUBOXONE sublingual film unit strength (buprenorphine/naloxone)	SUBOXONE sublingual film unit dimensions	Buprenorphine Concentration % (w/w)	Naloxone Concentration % (w/w)
2 mg/0.5 mg	22.0 mm x 12.8 mm	5.4	1.53
4 mg/1 mg (2 times the length of the 2 mg/0.5 mg unit)	22.0 mm x 25.6 mm	5.4	1.53
8 mg/2 mg	22.0 mm x 12.8 mm	17.2	4.88
12 mg/3 mg (1.5 times the length of the 8 mg/2 mg unit)	22.0 mm X 19.2 mm	17.2	4.88

2.11 Switching Between Sublingual and Buccal Sites of Administration

The systemic exposure of buprenorphine between buccal and sublingual administration of SUBOXONE sublingual film is similar. Therefore, once induction is complete, patients can switch between buccal and sublingual administration without significant risk of under or overdosing.

3 DOSAGE FORMS AND STRENGTHS

SUBOXONE sublingual film is supplied as an orange rectangular film with a white printed logo in four dosage strengths:

- Buprenorphine 2 mg/naloxone 0.5 mg,
- Buprenorphine 4 mg/naloxone 1 mg,
- Buprenorphine 8 mg/naloxone 2 mg and
- Buprenorphine 12 mg/naloxone 3 mg

4 CONTRAINDICATIONS

SUBOXONE sublingual film is contraindicated in patients with a history of hypersensitivity to buprenorphine or naloxone as serious adverse reactions, including anaphylactic shock, have been reported *[see Warnings and Precautions (5.9)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

SUBOXONE sublingual film contains buprenorphine, a schedule III controlled substance that can be abused in a manner similar to other opioids, legal or illicit. Prescribe and dispense buprenorphine with appropriate

precautions to minimize risk of misuse, abuse, or diversion, and ensure appropriate protection from theft, including in the home. Clinical monitoring appropriate to the patient's level of stability is essential. Multiple refills should not be prescribed early in treatment or without appropriate patient follow-up visits *[see Drug Abuse and Dependence (9.2)]*.

5.2 Risk of Respiratory and Central Nervous System (CNS) Depression

Buprenorphine has been associated with life-threatening respiratory depression and death. Many, but not all, post-marketing reports regarding coma and death involved misuse by self-injection or were associated with the concomitant use of buprenorphine and benzodiazepines or other CNS depressants, including alcohol. Warn patients of the potential danger of self-administration of benzodiazepines or other CNS depressants while under treatment with SUBOXONE sublingual film *[see Warnings and Precautions (5.3), Drug Interactions (7)]*.

Use SUBOXONE sublingual film with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression).

5.3 Managing Risks from Concomitant Use of Benzodiazepines or Other CNS Depressants

Concomitant use of buprenorphine and benzodiazepines or other CNS depressants increases the risk of adverse reactions including overdose and death. Medication-assisted treatment of opioid use disorder, however, should not be categorically denied to patients taking these drugs. Prohibiting or creating barriers to treatment can pose an even greater risk of morbidity and mortality due to the opioid use disorder alone.

As a routine part of orientation to buprenorphine treatment, educate patients about the risks of concomitant use of benzodiazepines, sedatives, opioid analgesics, and alcohol.

Develop strategies to manage use of prescribed or illicit benzodiazepines or other CNS depressants at initiation of buprenorphine treatment, or if it emerges as a concern during treatment. Adjustments to induction procedures and additional monitoring may be required. There is no evidence to support dose limitations or arbitrary caps of buprenorphine as a strategy to address benzodiazepine use in buprenorphine-treated patients. However, if a patient is sedated at the time of buprenorphine dosing, delay or omit the buprenorphine dose if appropriate.

Cessation of benzodiazepines or other CNS depressants is preferred in most cases of concomitant use. In some cases, monitoring in a higher level of care for taper may be appropriate. In others, gradually tapering a patient off of a prescribed benzodiazepine or other CNS depressant or decreasing to the lowest effective dose may be appropriate.

For patients in buprenorphine treatment, benzodiazepines are not the treatment of choice for anxiety or insomnia. Before co-prescribing benzodiazepines, ensure that patients are appropriately diagnosed and consider alternative medications and non-pharmacologic treatments to address anxiety or insomnia. Ensure that other healthcare providers prescribing benzodiazepines or other CNS depressants are aware of the patient's buprenorphine treatment and coordinate care to minimize the risks associated with concomitant use.

In addition, take measures to confirm that patients are taking their medications as prescribed and are not diverting or supplementing with illicit drugs. Toxicology screening should test for prescribed and illicit benzodiazepines *[see Drug Interactions (7)]*.

5.4 Unintentional Pediatric Exposure

Buprenorphine can cause severe, possibly fatal, respiratory depression in children who are accidentally exposed to it. Store buprenorphine-containing medications safely out of the sight and reach of children and destroy any unused medication appropriately [see *Patient Counseling Information (17)*].

5.5 Neonatal Opioid Withdrawal Syndrome

Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy, whether that use is medically-authorized or illicit. Unlike opioid withdrawal syndrome in adults, NOWS may be life-threatening if not recognized and treated in the neonate. Healthcare professionals should observe newborns for signs of NOWS and manage accordingly *[see Use in Specific Populations (8.1)]*.

Advise pregnant women receiving opioid addiction treatment with SUBOXONE sublingual film of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Use in Specific Populations (8.1)]*. This risk must be balanced against the risk of untreated opioid addiction which often results in continued or relapsing illicit opioid use and is associated with poor pregnancy outcomes. Therefore, prescribers should discuss the importance and benefits of management of opioid addiction throughout pregnancy.

5.6 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.7 Risk of Opioid Withdrawal with Abrupt Discontinuation

Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces physical dependence of the opioid type, characterized by withdrawal signs and symptoms upon abrupt discontinuation or rapid taper. The withdrawal syndrome is typically milder than seen with full agonists and may be delayed in onset *[see Drug Abuse and Dependence (9.3)]*. When discontinuing SUBOXONE sublingual film, gradually taper the dosage *[see Dosage and Administration (2.8)]*.

5.8 Risk of Hepatitis, Hepatic Events

Cases of cytolytic hepatitis and hepatitis with jaundice have been observed in individuals receiving buprenorphine in clinical trials and through post-marketing adverse event reports. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of death, hepatic failure, hepatic necrosis, hepatorenal syndrome, and hepatic encephalopathy. In many cases, the presence of pre-existing liver enzyme abnormalities, infection with hepatitis B or hepatitis C virus, concomitant usage of other potentially hepatotoxic drugs, and ongoing injecting drug use may have played a causative or contributory role. In other cases, insufficient data were available to determine the etiology of the abnormality. Withdrawal of buprenorphine has resulted in amelioration of acute hepatitis in some cases; however, in other cases no dose reduction was necessary. The possibility exists that buprenorphine had a causative or contributory role in the development of the hepatic abnormality in some cases. Liver function tests, prior to initiation of treatment, are recommended to establish a baseline. Periodic monitoring of liver function during treatment is also recommended. A biological and etiological evaluation is recommended when a hepatic event is suspected. Depending on the case, SUBOXONE sublingual film may need to be carefully

discontinued to prevent withdrawal signs and symptoms and a return by the patient to illicit drug use, and strict monitoring of the patient should be initiated.

5.9 Hypersensitivity Reactions

Cases of hypersensitivity to buprenorphine and naloxone containing products have been reported both in clinical trials and in the post-marketing experience. Cases of bronchospasm, angioneurotic edema, and anaphylactic shock have been reported. The most common signs and symptoms include rashes, hives, and pruritus. A history of hypersensitivity to buprenorphine or naloxone is a contraindication to the use of SUBOXONE sublingual film.

5.10 Precipitation of Opioid Withdrawal Signs and Symptoms

Because it contains naloxone, SUBOXONE sublingual film is likely to produce withdrawal signs and symptoms if misused parenterally by individuals dependent on full opioid agonists such as heroin, morphine, or methadone. Because of the partial agonist properties of buprenorphine, SUBOXONE sublingual film may precipitate opioid withdrawal signs and symptoms in such persons if administered before the agonist effects of the opioid have subsided.

5.11 Risk of Overdose in Opioid Naïve Patients

There have been reported deaths of opioid-naïve individuals who received a 2 mg dose of buprenorphine as a sublingual tablet for analgesia. SUBOXONE sublingual film is not appropriate as an analgesic.

5.12 Use in Patients With Impaired Hepatic Function

Buprenorphine/naloxone products are not recommended in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment. The doses of buprenorphine and naloxone in this fixed-dose combination product cannot be individually titrated, and hepatic impairment results in a reduced clearance of naloxone to a much greater extent than buprenorphine. Therefore, patients with severe hepatic impairment will be exposed to substantially higher levels of naloxone than patients with normal hepatic function. This may result in an increased risk of precipitated withdrawal at the beginning of treatment (induction) and may interfere with buprenorphine's efficacy throughout treatment. In patients with moderate hepatic impairment, the differential reduction of naloxone clearance compared to buprenorphine clearance is not as great as in subjects with severe hepatic impairment. However, buprenorphine/naloxone products are not recommended for initiation of treatment (induction) in patients with moderate hepatic impairment due to the increased risk of precipitated withdrawal. Buprenorphine/naloxone products may be used with caution for maintenance treatment in patients with moderate hepatic impairment who have initiated treatment on a buprenorphine product without naloxone. However, patients should be carefully monitored and consideration given to the possibility of naloxone interfering with buprenorphine's efficacy *[see Use in Specific Populations (8.6)]*.

5.13 Impairment of Ability to Drive or Operate Machinery

SUBOXONE sublingual film may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery, especially during treatment induction and dose adjustment. Caution patients about driving or operating hazardous machinery until they are reasonably certain that SUBOXONE sublingual film therapy does not adversely affect his or her ability to engage in such activities.

5.14 Orthostatic Hypotension

Like other opioids, SUBOXONE sublingual film may produce orthostatic hypotension in ambulatory patients.

5.15 Elevation of Cerebrospinal Fluid Pressure

Buprenorphine, like other opioids, may elevate cerebrospinal fluid pressure and should be used with caution in patients with head injury, intracranial lesions, and other circumstances when cerebrospinal pressure may be

increased. Buprenorphine can produce miosis and changes in the level of consciousness that may interfere with patient evaluation.

5.16 Elevation of Intracholedochal Pressure

Buprenorphine has been shown to increase intracholedochal pressure, as do other opioids, and thus should be administered with caution to patients with dysfunction of the biliary tract.

5.17 Effects in Acute Abdominal Conditions

As with other opioids, buprenorphine may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Addiction, Abuse, and Misuse [*see Warnings and Precautions (5.1)*]
- Respiratory and CNS Depression *[see Warnings and Precautions (5.2), (5.3)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.5)]*
- Adrenal Insufficiency *[see Warnings and Precautions (5.6)]*
- Opioid Withdrawal *[see Warnings and Precautions (5.7, 5.10)]*
- Hepatitis, Hepatic Events *[see Warnings and Precautions (5.8)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.9)]*
- Orthostatic Hypotension *[see Warnings and Precautions (5.14)]*
- Elevation of Cerebrospinal Fluid Pressure *[see Warnings and Precautions (5.15)]*
- Elevation of Intracholedochal Pressure *[see Warnings and Precautions (5.16)*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of SUBOXONE sublingual film is supported by clinical trials using SUBUTEX® (buprenorphine) sublingual tablets and SUBOXONE (buprenorphine and naloxone) sublingual tablets, and other trials using buprenorphine sublingual solutions, as well as an open-label study in 194 patients treated with SUBOXONE sublingual film administered sublingually and 188 patients treated with the film administered buccally. In total, safety data from clinical studies are available from over 3000 opioid-dependent subjects exposed to buprenorphine at doses in the range used in the treatment of opioid dependence. Few differences in the adverse event profile were noted with regard to sublingually and bucally administered SUBOXONE sublingual film, SUBOXONE sublingual tablets, SUBUTEX sublingual tablets and a buprenorphine ethanolic sublingual solution.

The most common adverse event (>1%) associated with the sublingual administration of the SUBOXONE sublingual film was oral hypoesthesia. Other adverse events were constipation, glossodynia, oral mucosal erythema, vomiting, intoxication, disturbance in attention, palpitations, insomnia, withdrawal syndrome, hyperhidrosis, and blurred vision.

The most common adverse events associated with the buccal administration were similar to those observed with sublingual administration of the film.

Other adverse event data were derived from larger, controlled studies of SUBOXONE sublingual tablets and SUBUTEX sublingual tablets and of buprenorphine sublingual solution. In a comparative study of SUBOXONE sublingual tablets and SUBUTEX sublingual tablets, adverse event profiles were similar for subjects treated with 16 mg/4 mg SUBOXONE sublingual tablets or 16 mg SUBUTEX sublingual tablets. The following adverse events were reported to occur by at least 5% of patients in a 4 week study of SUBOXONE sublingual tablets and

SUBUTEX sublingual tablets.

Table 2. Adverse Events (≥5%) by Body System and Treatment Group in a 4 Week Study

Body System/ Adverse Event (COSTART Terminology)	SUBOXONE sublingual tablets 16 mg/4 mg/day N=107 n (%)	SUBUTEX sublingual tablets 16 mg/day N=103 n (%)	Placebo N=107 n (%)
Body as a Whole			
Asthenia	7 (6.5%)	5 (4.9%)	7 (6.5%)
Chills	8 (7.5%)	8 (7.8%)	8 (7.5%)
Headache	39 (36.4%)	30 (29.1%)	24 (22.4%)
Infection	6 (5.6%)	12 (11.7%)	7 (6.5%)
Pain	24 (22.4%)	19 (18.4%)	20 (18.7%)
Pain abdomen	12 (11.2%)	12 (11.7%)	7 (6.5%)
Pain back	4 (3.7%)	8 (7.8%)	12 (11.2%)
Withdrawal syndrome	27 (25.2%)	19 (18.4%)	40 (37.4%)
Cardiovascular System			
Vasodilation	10 (9.3%)	4 (3.9%)	7 (6.5%)
Digestive System			
Constipation	13 (12.1%)	8 (7.8%)	3 (2.8%)
Diarrhea	4 (3.7%)	5 (4.9%)	16 (15.0%)
Nausea	16 (15.0%)	14 (13.6%)	12 (11.2%)
Vomiting	8 (7.5%)	8 (7.8%)	5 (4.7%)
Nervous System			
Insomnia	15 (14.0%)	22 (21.4%)	17 (15.9%)
Respiratory System			
Rhinitis	5 (4.7%)	10 (9.7%)	14 (13.1%)
Skin And Appendages			

Sweating	15 (14.0%)	13 (12.6%)	11 (10.3%)

Abbreviations: COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms.

The adverse event profile of buprenorphine was also characterized in the dose-controlled study of a buprenorphine ethanolic solution, over a range of doses in four months of treatment. Table 3 shows adverse events reported by at least 5% of subjects in any dose group in the dose-controlled trial.

Table 3. Adverse Events (≥5%) by Body System and Treatment Group in a 16 Week Study

Body System/ Adverse Event (COSTART Terminology)	**Buprenorphine Dose**				
	Very Low* **N=184** **n (%)**	**Low*** **N=180** **n (%)**	**Moderate*** **N=186** **n (%)**	**High*** **N=181** **n (%)**	**Total*** **N=731** **n (%)**
Body as a Whole					
Abscess	9 (5%)	2 (1%)	3 (2%)	2 (1%)	16 (2%)
Asthenia	26 (14%)	28 (16%)	26 (14%)	24 (13%)	104 (14%)
Chills	11 (6%)	12 (7%)	9 (5%)	10 (6%)	42 (6%)
Fever	7 (4%)	2 (1%)	2 (1%)	10 (6%)	21 (3%)
Flu syndrome	4 (2%)	13 (7%)	19 (10%)	8 (4%)	44 (6%)
Headache	51 (28%)	62 (34%)	54 (29%)	53 (29%)	220 (30%)
Infection	32 (17%)	39 (22%)	38 (20%)	40 (22%)	149 (20%)
Injury accidental	5 (3%)	10 (6%)	5 (3%)	5 (3%)	25 (3%)
Pain	47 (26%)	37 (21%)	49 (26%)	44 (24%)	177 (24%)
Pain back	18 (10%)	29 (16%)	28 (15%)	27 (15%)	102 (14%)
Withdrawal syndrome	45 (24%)	40 (22%)	41 (22%)	36 (20%)	162 (22%)
Digestive System					
Constipation	10 (5%)	23 (13%)	23 (12%)	26 (14%)	82 (11%)
Diarrhea	19 (10%)	8 (4%)	9 (5%)	4 (2%)	40 (5%)
Dyspepsia	6 (3%)	10 (6%)	4 (2%)	4 (2%)	24 (3%)
Nausea	12 (7%)	22 (12%)	23 (12%)	18 (10%)	75 (10%)

Vomiting	8 (4%)	6 (3%)	10 (5%)	14 (8%)	38 (5%)
Nervous System					
Anxiety	22 (12%)	24 (13%)	20 (11%)	25 (14%)	91 (12%)
Depression	24 (13%)	16 (9%)	25 (13%)	18 (10%)	83 (11%)
Dizziness	4 (2%)	9 (5%)	7 (4%)	11 (6%)	31 (4%)
Insomnia	42 (23%)	50 (28%)	43 (23%)	51 (28%)	186 (25%)
Nervousness	12 (7%)	11 (6%)	10 (5%)	13 (7%)	46 (6%)
Somnolence	5 (3%)	13 (7%)	9 (5%)	11 (6%)	38 (5%)
Respiratory System					
Cough increase	5 (3%)	11 (6%)	6 (3%)	4 (2%)	26 (4%)
Pharyngitis	6 (3%)	7 (4%)	6 (3%)	9 (5%)	28 (4%)
Rhinitis	27 (15%)	16 (9%)	15 (8%)	21 (12%)	79 (11%)
Skin and Appendages					
Sweat	23 (13%)	21 (12%)	20 (11%)	23 (13%)	87 (12%)
Special Senses					
Runny eyes	13 (7%)	9 (5%)	6 (3%)	6 (3%)	34 (5%)

*Sublingual solution. Doses in this table cannot necessarily be delivered in tablet form, but for comparison purposes:

"Very low" dose (1 mg solution) would be less than a tablet dose of 2 mg
"Low" dose (4 mg solution) approximates a 6 mg tablet dose
"Moderate" dose (8 mg solution) approximates a 12 mg tablet dose
"High" dose (16 mg solution) approximates a 24 mg tablet dose

The safety of SUBOXONE sublingual film during treatment induction is supported by a clinical trial using 16 patients treated with SUBOXONE sublingual film and 18 treated with a buprenorphine-only sublingual film. Few differences in the adverse event profiles were noted between SUBOXONE sublingual film and the buprenorphine-only sublingual film.

The most common adverse event occurring during treatment induction and the 3 days following induction using SUBOXONE sublingual film was restlessness. Other adverse events were anxiety, piloerection, stomach discomfort, irritability, headache, rhinorrhea, cold sweat, arthralgia, and lacrimation increased.

Four subjects left the study early on the first day of sublingual film administration. However, there was no evidence to suggest that any of the four subjects experienced precipitated withdrawal secondary to the administration of buprenorphine or buprenorphine/naloxone sublingual films.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of SUBOXONE sublingual film. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The most frequently reported postmarketing adverse events were peripheral edema, stomatitis, glossitis, and blistering and ulceration of the mouth or tongue.

Serotonin syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in SUBOXONE sublingual film.

Androgen deficiency: Cases of androgen deficiency have occurred with chronic use of opioids *[see Clinical Pharmacology (12.2)]*.

Local reactions: glossodynia, glossitis, oral mucosal erythema, oral hypoesthesia, and stomatitis

7 DRUG INTERACTIONS

Table 4 Includes clinically significant drug interactions with SUBOXONE.

Table 4. Clinically Significant Drug Interactions

Benzodiazepines and Other Central Nervous System (CNS) Depressants	
Clinical Impact:	Due to additive pharmacologic effects, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, increases the risk of respiratory depression, profound sedation, coma, and death.
Intervention:	Cessation of benzodiazepines or other CNS depressants is preferred in most cases of concomitant use. In some cases, monitoring in a higher level of care for taper may be appropriate. In others, gradually tapering a patient off of a prescribed benzodiazepine or other CNS depressant or decreasing to the lowest effective dose may be appropriate. Before co-prescribing benzodiazepines for anxiety or insomnia, ensure that patients are appropriately diagnosed and consider alternative medications and non-pharmacologic treatments *[see Warnings and Precautions (5.2, 5.3)]*.
Examples:	Alcohol, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, and other opioids.
Inhibitors of CYP3A4	
Clinical Impact:	The concomitant use of buprenorphine and CYP3A4 inhibitors can increase the plasma concentration of buprenorphine, resulting in increased or prolonged opioid effects, particularly when an inhibitor is added after a stable dose of SUBOXONE sublingual film is achieved.

	After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the buprenorphine plasma concentration will decrease *[see Clinical Pharmacology (12.3)]*, potentially resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to buprenorphine.
Intervention:	If concomitant use is necessary, consider dosage reduction of SUBOXONE sublingual film until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider increasing the SUBOXONE sublingual film dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal.
Examples:	Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir)
CYP3A4 Inducers	
Clinical Impact:	The concomitant use of buprenorphine and CYP3A4 inducers can decrease the plasma concentration of buprenorphine *[see Clinical Pharmacology (12.3)]*, potentially resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to buprenorphine. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the buprenorphine plasma concentration will increase *[see Clinical Pharmacology (12.3)]*, which could increase or prolong both therapeutic effects and adverse reactions and may cause serious respiratory depression.
Intervention:	If concomitant use is necessary, consider increasing the SUBOXONE sublingual film dosage until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is discontinued, consider SUBOXONE sublingual film dosage reduction and monitor for signs of respiratory depression.
Examples:	Rifampin, carbamazepine, phenytoin
Antiretrovirals: Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	
Clinical Impact:	Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are metabolized principally by CYP3A4. Efavirenz, nevirapine, and etravirine are known CYP3A inducers, whereas delavirdine is a CYP3A inhibitor. Significant pharmacokinetic interactions between NNRTIs (e.g., efavirenz and delavirdine) and buprenorphine have been shown in clinical studies, but these pharmacokinetic interactions did not result in any significant pharmacodynamic effects.

Intervention:	Patients who are on chronic SUBOXONE sublingual film treatment should have their dose monitored if NNRTIs are added to their treatment regimen.
Examples:	efavirenz, nevirapine, etravirine, delavirdine
Antiretrovirals: Protease inhibitors (PIs)	
Clinical Impact:	Studies have shown some antiretroviral protease inhibitors (PIs) with CYP3A4 inhibitory activity (nelfinavir, lopinavir/ritonavir, ritonavir) have little effect on buprenorphine pharmacokinetic and no significant pharmacodynamic effects. Other PIs with CYP3A4 inhibitory activity (atazanavir and atazanavir/ritonavir) resulted in elevated levels of buprenorphine and norbuprenorphine, and patients in one study reported increased sedation. Symptoms of opioid excess have been found in post-marketing reports of patients receiving buprenorphine and atazanavir with and without ritonavir concomitantly.
Intervention:	Monitor patients taking SUBOXONE sublingual film and atazanavir with and without ritonavir, and reduce dose of SUBOXONE sublingual film if warranted.
Examples:	atazanavir, ritonavir
Antiretrovirals: Nucleoside reverse transcriptase inhibitors (NRTIs)	
Clinical Impact:	Nucleoside reverse transcriptase inhibitors (NRTIs) do not appear to induce or inhibit the P450 enzyme pathway, thus no interactions with buprenorphine are expected.
Intervention:	None
Serotonergic Drugs	
Clinical Impact:	The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome.
Intervention:	If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue SUBOXONE sublingual film sublingual film if serotonin syndrome is suspected.
Examples:	Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical Impact:	MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma).

Intervention:	The use of SUBOXONE sublingual film is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.
Examples:	phenelzine, tranylcypromine, linezolid
Muscle Relaxants	
Clinical Impact:	Buprenorphine may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
Intervention:	Monitor patients receiving muscle relaxants and SUBOXONE sublingual film for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of SUBOXONE sublingual film and/or the muscle relaxant as necessary.
Diuretics	
Clinical Impact:	Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.
Intervention:	Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs	
Clinical Impact:	The concomitant use of anticholinergic drugs may increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.
Intervention:	Monitor patients for signs of urinary retention or reduced gastric motility when SUBOXONE sublingual film is used concomitantly with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The data on use of buprenorphine, one of the active ingredients in SUBOXONE sublingual film, in pregnancy, are limited; however, these data do not indicate an increased risk of major malformations specifically due to buprenorphine exposure. There are limited data from randomized clinical trials in women maintained on buprenorphine that were not designed appropriately to assess the risk of major malformations *[see Data]*. Observational studies have reported on congenital malformations among buprenorphine-exposed pregnancies, but were also not designed appropriately to assess the risk of congenital malformations specifically due to buprenorphine exposure [*see Data*]. The extremely limited data on sublingual naloxone exposure in pregnancy are not sufficient to evaluate a drug-associated risk.

Reproductive and developmental studies in rats and rabbits identified adverse events at clinically relevant and higher doses. Embryofetal death was observed in both rats and rabbits administered buprenorphine during the period of organogenesis at doses approximately 6 and 0.3 times, respectively, the human sublingual dose of 16 mg/day of buprenorphine. Pre-and postnatal development studies in rats demonstrated increased neonatal deaths at 0.3 times and above and dystocia at approximately 3 times the human sublingual dose of 16 mg/day of buprenorphine. No clear teratogenic effects were seen when buprenorphine was administered during

organogenesis with a range of doses equivalent to or greater than the human sublingual dose of 16 mg/day of buprenorphine. However, increases in skeletal abnormalities were noted in rats and rabbits administered buprenorphine daily during organogenesis at doses approximately 0.6 and approximately equal to the human sublingual dose of 16 mg/day of buprenorphine, respectively. In a few studies, some events such as acephalus and omphalocele were also observed but these findings were not clearly treatment-related *[see Data]*. Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and embryo-fetal risk

Untreated opioid addiction in pregnancy is associated with adverse obstetrical outcomes such as low birth weight, preterm birth, and fetal death. In addition, untreated opioid addiction often results in continued or relapsing illicit opioid use.

Dose Adjustment during Pregnancy and the Postpartum Period

Dosage adjustments of buprenorphine may be required during pregnancy, even if the patient was maintained on a stable dose prior to pregnancy. Withdrawal signs and symptoms should be monitored closely and the dose adjusted as necessary.

Fetal/neonatal adverse reactions

Neonatal opioid withdrawal syndrome may occur in newborn infants of mothers who are receiving treatment with SUBOXONE sublingual film.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, and/or failure to gain weight. Signs of neonatal withdrawal usually occur in the first days after birth. The duration and severity of neonatal opioid withdrawal syndrome may vary. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly *[see Warnings and Precautions (5.5)]*.

Labor or Delivery

Opioid-dependent women on buprenorphine maintenance therapy may require additional analgesia during labor.

Data

Human Data

Studies have been conducted to evaluate neonatal outcomes in women exposed to buprenorphine during pregnancy. Limited data on malformations from trials, observational studies, case series, and case reports on buprenorphine use in pregnancy do not indicate an increased risk of major malformations specifically due to buprenorphine. Several factors may complicate the interpretation of investigations of the children of women who take buprenorphine during pregnancy, including maternal use of illicit drugs, late presentation for prenatal care, infection, poor compliance, poor nutrition, and psychosocial circumstances. Interpretation of data is complicated further by the lack of information on untreated opioid-dependent pregnant women, who would be the most appropriate group for comparison. Rather, women on another form of opioid medication-assisted treatment, or women in the general population are generally used as the comparison group. However, women in these comparison groups may be different from women prescribed buprenorphine-containing products with respect to maternal factors that may lead to poor pregnancy outcomes.

In a multicenter, double-blind, randomized, controlled trial [Maternal Opioid Treatment: Human Experimental Research (MOTHER)] designed primarily to assess neonatal opioid withdrawal effects, opioid-dependent pregnant women were randomized to buprenorphine (n=86) or methadone (n=89) treatment, with enrollment at an average gestational age of 18.7 weeks in both groups. A total of 28 of the 86 women in the buprenorphine group (33%) and 16 of the 89 women in the methadone group (18%) discontinued treatment before the end of pregnancy.

Among women who remained in treatment until delivery, there was no difference between buprenorphine-treated and methadone-treated groups in the number of neonates requiring NOWS treatment or in the peak severity of NOWS. Buprenorphine-exposed neonates required less morphine (mean total dose, 1.1 mg vs. 10.4 mg), had shorter hospital stays (10.0 days vs. 17.5 days), and shorter duration of treatment for NOWS (4.1 days vs. 9.9 days) compared to the methadone-exposed group. There were no differences between groups in other primary outcomes (neonatal head circumference,) or secondary outcomes (weight and length at birth, preterm birth, gestational age at delivery, and 1-minute and 5-minute Apgar scores), or in the rates of maternal or neonatal adverse events. The outcomes among mothers who discontinued treatment before delivery and may have relapsed to illicit opioid use are not known. Because of the imbalance in discontinuation rates between the buprenorphine and methadone groups, the study findings are difficult to interpret.

Animal Data

The exposure margins listed below are based on body surface area comparisons (mg/m^2) to the human sublingual dose of 16 mg buprenorphine via SUBOXONE sublingual tablets.

Effects on embryo-fetal development were studied in Sprague-Dawley rats and Russian white rabbits following oral (1:1) and intramuscular (IM) (3:2) administration of mixtures of buprenorphine and naloxone during the period of organogenesis. Following oral administration to rats no teratogenic effects were observed at buprenorphine doses up to 250 mg/kg/day (estimated exposure approximately 150 times the human sublingual dose of 16 mg) in the presence of maternal toxicity (mortality). Following oral administration to rabbits, no teratogenic effects were observed at buprenorphine doses up to 40 mg/kg/day (estimated exposure approximately 50 times, the human sublingual dose of 16 mg) in the absence of clear maternal toxicity.

No definitive drug-related teratogenic effects were observed in rats and rabbits at IM doses up to 30 mg/kg/day (estimated exposure approximately 20 times and 35 times, respectively, the human sublingual dose of 16 mg). Maternal toxicity resulting in mortality was noted in these studies in both rats and rabbits. Acephalus was observed in one rabbit fetus from the low-dose group and omphalocele was observed in two rabbit fetuses from the same litter in the mid-dose group; no findings were observed in fetuses from the high-dose group. Maternal toxicity was seen in the high-dose group but not at the lower doses where the findings were observed. Following oral administration of buprenorphine to rats, dose-related post-implantation losses, evidenced by increases in the numbers of early resorptions with consequent reductions in the numbers of fetuses, were observed at doses of 10 mg/kg/day or greater (estimated exposure approximately 6 times the human sublingual dose of 16 mg). In the rabbit, increased post-implantation losses occurred at an oral dose of 40 mg/kg/day. Following IM administration in the rat and the rabbit, post-implantation losses, as evidenced by decreases in live fetuses and increases in resorptions, occurred at 30 mg/kg/day.

Buprenorphine was not teratogenic in rats or rabbits after IM or subcutaneous (SC) doses up to 5 mg/kg/day (estimated exposure was approximately 3 and 6 times, respectively, the human sublingual dose of 16 mg), after IV doses up to 0.8 mg/kg/day (estimated exposure was approximately 0.5 times and equal to, respectively, the human sublingual dose of 16 mg), or after oral doses up to 160 mg/kg/day in rats (estimated exposure was approximately 95 times the human sublingual dose of 16 mg) and 25 mg/kg/day in rabbits (estimated exposure was approximately 30 times the human daily sublingual dose of 16 mg). Significant increases in skeletal abnormalities (e.g., extra thoracic vertebra or thoraco-lumbar ribs) were noted in rats after SC administration of 1 mg/kg/day and up (estimated exposure was approximately 0.6 times the human sublingual dose of 16 mg), but were not observed at oral doses up to 160 mg/kg/day. Increases in skeletal abnormalities in rabbits after

IM administration of 5 mg/kg/day (estimated exposure was approximately 6 times the human daily sublingual dose of 16 mg) in the absence of maternal toxicity or oral administration of 1 mg/kg/day or greater (estimated exposure was approximately equal to the human sublingual dose of 16 mg) were not statistically significant.

In rabbits, buprenorphine produced statistically significant pre-implantation losses at oral doses of 1 mg/kg/day or greater and post-implantation losses that were statistically significant at IV doses of 0.2 mg/kg/day or greater (estimated exposure approximately 0.3 times the human daily sublingual dose of 16 mg). No maternal toxicity was noted at doses causing post-implantation loss in this study.

Dystocia was noted in pregnant rats treated intramuscularly with buprenorphine from Gestation Day 14 through Lactation Day 21 at 5 mg/kg/day (approximately 3 times the human sublingual dose of 16 mg). Fertility, pre- and post-natal development studies with buprenorphine in rats indicated increases in neonatal mortality after oral doses of 0.8 mg/kg/day and up (approximately 0.5 times the human daily sublingual dose of 16 mg), after IM doses of 0.5 mg/kg/day and up (approximately 0.3 times the human sublingual dose of 16 mg), and after SC doses of 0.1 mg/kg/day and up (approximately 0.06 times the human sublingual dose of 16 mg). An apparent lack of milk production during these studies likely contributed to the decreased pup viability and lactation indices. Delays in the occurrence of righting reflex and startle response were noted in rat pups at an oral dose of 80 mg/kg/day (approximately 50 times the human sublingual dose of 16 mg).

8.2 Lactation

Risk Summary

Based on two studies in 13 lactating women maintained on buprenorphine treatment, buprenorphine and its metabolite norbuprenorphine were present in low levels in human milk and infant urine. Available data have not shown adverse reactions in breastfed infants. There are no data on the combination product buprenorphine/naloxone in breastfeeding, however oral absorption of naloxone is limited. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SUBOXONE sublingual film and any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

Clinical Considerations

Advise breastfeeding women taking buprenorphine products to monitor the infant for increased drowsiness and breathing difficulties.

Data

Data were consistent from two studies (N=13) of breastfeeding infants whose mothers were maintained on sublingual doses of buprenorphine ranging from 2.4 to 24 mg/day, showing that the infants were exposed to less than 1% of the maternal daily dose.

In a study of six lactating women who were taking a median sublingual buprenorphine dose of 0.29 mg/kg/day 5 to 8 days after delivery, breast milk provided a median infant dose of 0.42 mcg/kg/day of buprenorphine and 0.33 mcg/kg/day of norbuprenorphine, equal to 0.2% and 0.12%, respectively, of the maternal weight-adjusted dose (relative dose/kg (%) of norbuprenorphine was calculated from the assumption that buprenorphine and norbuprenorphine are equipotent).

Data from a study of seven lactating women who were taking a median sublingual buprenorphine dose of 7 mg/day an average of 1.12 months after delivery indicated that the mean milk concentrations (C_{avg}) of buprenorphine and norbuprenorphine were 3.65 mcg/L and 1.94 mcg/L respectively. Based on the study data, and assuming milk consumption of 150 mL/kg/day, an exclusively breastfed infant would receive an estimated mean absolute infant dose (AID) of 0.55 mcg/kg/day of buprenorphine and 0.29 mcg/kg/day of norbuprenorphine, or a mean relative infant dose (RID) of 0.38% and 0.18%, respectively, of the maternal weight-adjusted dose

8.3 Females and Males of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible *[see Adverse Reactions (6.2), Clinical Pharmacology (12.2), Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

The safety and effectiveness of SUBOXONE sublingual film have not been established in pediatric patients. This product is not appropriate for the treatment of neonatal abstinence syndrome in neonates, because it contains naloxone, an opioid antagonist.

8.5 Geriatric Use

Clinical studies of SUBOXONE sublingual film, SUBOXONE sublingual tablets, or SUBUTEX sublingual tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Due to possible decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy in geriatric patients, the decision to prescribe SUBOXONE sublingual film should be made cautiously in individuals 65 years of age or older and these patients should be monitored for signs and symptoms of toxicity or overdose.

8.6 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of buprenorphine and naloxone has been evaluated in a pharmacokinetic study. Both drugs are extensively metabolized in the liver. While no clinically significant changes have been observed in subjects with mild hepatic impairment; the plasma levels have been shown to be higher and half-life values have been shown to be longer for both buprenorphine and naloxone in subjects with moderate and severe hepatic impairment. The magnitude of the effects on naloxone are greater than that on buprenorphine in both moderately and severely impaired subjects. The difference in magnitude of the effects on naloxone and buprenorphine are greater in subjects with severe hepatic impairment than in subjects with moderate hepatic impairment, and therefore the clinical impact of these effects is likely to be greater in patients with severe hepatic impairment than in patients with moderate hepatic impairment. Buprenorphine/naloxone products should be avoided in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment *[see Warnings and Precautions (5.12), Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

No differences in buprenorphine pharmacokinetics were observed between 9 dialysis-dependent and 6 normal patients following IV administration of 0.3 mg buprenorphine. The effects of renal failure on naloxone pharmacokinetics are unknown.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

SUBOXONE sublingual film contains buprenorphine, a Schedule III controlled substance under the Controlled Substances Act.

Under the Drug Addiction Treatment Act (DATA) codified at 21 U.S.C. 823(g), prescription use of this product in the treatment of opioid dependence is limited to healthcare providers who meet certain qualifying requirements, and who have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription.

9.2 Abuse

Buprenorphine, like morphine and other opioids, has the potential for being abused and is subject to criminal diversion. This should be considered when prescribing or dispensing buprenorphine in situations when the clinician is concerned about an increased risk of misuse, abuse, or diversion. Healthcare professionals should contact their state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

Patients who continue to misuse, abuse, or divert buprenorphine products or other opioids should be provided with or referred for more intensive and structured treatment.

Abuse of buprenorphine poses a risk of overdose and death. This risk is increased with the abuse of buprenorphine and alcohol and other substances, especially benzodiazepines.

The healthcare provider may be able to more easily detect misuse or diversion by maintaining records of medication prescribed including date, dose, quantity, frequency of refills, and renewal requests of medication prescribed.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper handling and storage of the medication are appropriate measures that help to limit abuse of opioid drugs.

9.3 Dependence

Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces physical dependence of the opioid type, characterized by moderate withdrawal signs and symptoms upon abrupt discontinuation or rapid taper. The withdrawal syndrome is typically milder than seen with full agonists and may be delayed in onset *[see Warnings and Precautions (5.7)]*.

Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy *[see Warnings and Precautions (5.5)]*.

10 OVERDOSAGE

Clinical Presentation

The manifestations of acute overdose include pinpoint pupils, sedation, hypotension, respiratory depression, and death.

Treatment of Overdose

In the event of overdose, the respiratory and cardiac status of the patient should be monitored carefully. When respiratory or cardiac functions are depressed, primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Oxygen, IV fluids, vasopressors, and other supportive measures should be employed as indicated.

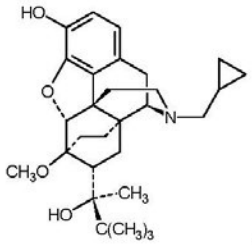
In the case of overdose, the primary management should be the re-establishment of adequate ventilation with mechanical assistance of respiration, if required. Naloxone may be of value for the management of buprenorphine overdose. Higher than normal doses and repeated administration may be necessary. The long duration of action of SUBOXONE sublingual film should be taken into consideration when determining the length of treatment and medical surveillance needed to reverse the effects of an overdose. Insufficient duration of monitoring may put patients at risk.

11 DESCRIPTION

SUBOXONE® (buprenorphine and naloxone) sublingual film is an orange film, imprinted with a logo identifying the product and strength in white ink. It contains buprenorphine HCl, a mu-opioid receptor partial agonist, and a kappa-

opioid receptor antagonist, and naloxone HCl dihydrate, an opioid antagonist, at a ratio of 4:1 (ratio of free bases). It is intended for sublingual or buccal administration and is available in four dosage strengths, 2 mg buprenorphine with 0.5 mg naloxone, 4 mg buprenorphine with 1 mg naloxone, 8 mg buprenorphine with 2 mg naloxone and 12 mg buprenorphine with 3 mg naloxone. Each film also contains polyethylene oxide, hydroxypropyl methylcellulose, maltitol, acesulfame potassium, lime flavor, citric acid, sodium citrate, FD&C yellow #6, and white ink.

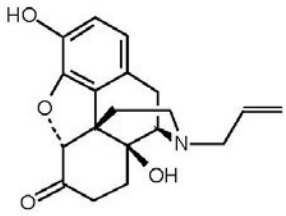
Chemically, buprenorphine HCl is (2S)-2-[17-Cyclopropylmethyl-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol hydrochloride. It has the following chemical structure:



• HCl

Buprenorphine HCl has the molecular formula $C_{29}H_{41}NO_4 \bullet HCl$ and the molecular weight is 504.10. It is a white or off-white crystalline powder, sparingly soluble in water, freely soluble in methanol, soluble in alcohol, and practically insoluble in cyclohexane.

Chemically, naloxone HCl dihydrate is 17-Allyl-4,5 α -epoxy-3, 14-dihydroxymorphinan-6-one hydrochloride dihydrate. It has the following chemical structure:



$HCl \bullet 2H_2O$

Naloxone hydrochloride dihydrate has the molecular formula $C_{19}H_{21}NO_4 \bullet HCl \bullet 2H_2O$ and the molecular weight is 399.87. It is a white to slightly off-white powder and is freely soluble in water, soluble in alcohol, and practically insoluble in toluene and ether.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

SUBOXONE sublingual film contains buprenorphine and naloxone. Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Naloxone is a potent antagonist at mu opioid receptors and produces opioid withdrawal signs and symptoms in individuals physically dependent on full opioid agonists when administered parenterally.

12.2 Pharmacodynamics

Subjective Effects

Comparisons of buprenorphine to full opioid agonists such as methadone and hydromorphone suggest that sublingual buprenorphine produces typical opioid agonist effects which are limited by a ceiling effect.

In opioid-experienced subjects who were not physically dependent, acute sublingual doses of buprenorphine/naloxone tablets produced opioid agonist effects which reached a maximum between doses of 8 mg/2 mg and 16 mg/4 mg buprenorphine/naloxone.

Opioid agonist ceiling-effects were also observed in a double-blind, parallel group, dose-ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg), placebo and a full agonist control at various doses. The treatments were given in ascending dose order at intervals of at least one week to 16 opioid-experienced subjects who were not physically dependent. Both active drugs produced typical opioid agonist effects. For all measures for which the drugs produced an effect, buprenorphine produced a dose-related response. However, in each case, there was a dose that produced no further effect. In contrast, the highest dose of the full agonist control always produced the greatest effects. Agonist objective rating scores remained elevated for the higher doses of buprenorphine (8 mg to 32 mg) longer than for the lower doses and did not return to baseline until 48 hours after drug administration. The onset of effects appeared more rapidly with buprenorphine than with the full agonist control, with most doses nearing peak effect after 100 minutes for buprenorphine compared to 150 minutes for the full agonist control.

Physiologic Effects

Buprenorphine in IV (2, 4, 8, 12 and 16 mg) and sublingual (12 mg) doses has been administered to opioid-experienced subjects who were not physically dependent to examine cardiovascular, respiratory, and subjective effects at doses comparable to those used for treatment of opioid dependence. Compared to placebo, there were no statistically significant differences among any of the treatment conditions for blood pressure, heart rate, respiratory rate, O_2 saturation, or skin temperature across time. Systolic BP was higher in the 8 mg group than placebo (3 hour AUC values). Minimum and maximum effects were similar across all treatments. Subjects remained responsive to low voice and responded to computer prompts. Some subjects showed irritability, but no other changes were observed.

The respiratory effects of sublingual buprenorphine were compared with the effects of methadone in a double-blind, parallel group, dose ranging comparison of single doses of buprenorphine sublingual solution (1, 2, 4, 8, 16, or 32 mg) and oral methadone (15, 30, 45, or 60 mg) in non-dependent, opioid-experienced volunteers. In this study, hypoventilation not requiring medical intervention was reported more frequently after buprenorphine doses of 4 mg and higher than after methadone. Both drugs decreased O_2 saturation to the same degree.

Effect of Naloxone

Physiologic and subjective effects following acute sublingual administration of buprenorphine tablets and buprenorphine/naloxone tablets were similar at equivalent dose levels of buprenorphine. Naloxone had no clinically significant effect when administered by the sublingual route, although blood levels of the drug were measurable. Buprenorphine/naloxone, when administered sublingually to an opioid-dependent cohort, was recognized as an opioid agonist, whereas when administered intramuscularly, combinations of buprenorphine with naloxone produced opioid antagonist actions similar to naloxone. This finding suggests that the naloxone in buprenorphine/naloxone tablets may deter injection of buprenorphine/naloxone tablets by persons with active substantial heroin or other full mu-opioid dependence. However, clinicians should be aware that some opioid-dependent persons, particularly those with a low level of full mu-opioid physical dependence or those whose opioid physical dependence is predominantly to buprenorphine, abuse buprenorphine/naloxone combinations by the intravenous or intranasal route. In methadone-maintained patients and heroin-dependent subjects, IV administration of buprenorphine/naloxone combinations precipitated opioid withdrawal signs and symptoms and was perceived as unpleasant and dysphoric. In morphine-stabilized subjects, intravenously administered combinations of buprenorphine with naloxone produced opioid antagonist and withdrawal signs and symptoms that were ratio-dependent; the most intense withdrawal signs and symptoms were produced by 2:1 and 4:1 ratios, less intense by an 8:1 ratio.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans *[see Adverse Reactions (6.2)]*. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

12.3 Pharmacokinetics

Absorption

In several pharmacokinetic studies following the administration of different dosages, a dose of one or two of the 2 mg/0.5 mg SUBOXONE sublingual films administered sublingually or buccally showed comparable relative bioavailability to the same total dose of SUBOXONE sublingual tablets. In contrast, one 8 mg/2 mg and one 12 mg/3 mg SUBOXONE sublingual films administered sublingually or buccally showed higher relative bioavailability for both buprenorphine and naloxone compared to the same total dose of SUBOXONE sublingual tablets. A combination of one 8 mg/2 mg and two 2 mg/0.5 mg SUBOXONE sublingual films (total dose of 12 mg/ 3 mg) administered sublingually showed comparable relative bioavailability to the same total dose of SUBOXONE sublingual tablets, while buccally administered SUBOXONE sublingual films showed higher relative bioavailability. Table 5, below, illustrates the relative increase in exposure to buprenorphine and naloxone associated with SUBOXONE sublingual films compared to SUBOXONE sublingual tablets, and shows the effect of route of administration [*see Dosage and Administration (2.9, 2.10)*].

Across relevant pharmacokinetic studies, the pharmacokinetic parameters and exposures derived from the buccal and sublingual administrations of SUBOXONE sublingual film were comparable to one another.

Table 5. Changes in Pharmacokinetic Parameters for SUBOXONE Sublingual Film Administered Sublingually or Buccally in Comparison to SUBOXONE Sublingual Tablet

Dosage	PK Parameter	Increase in Buprenorphine			PK Parameter	Increase in Naloxone		
		Film Sublingual Compared to Tablet Sublingual	Film Buccal Compared to Tablet Sublingual	Film Buccal Compared to Film Sublingual		Film Sublingual Compared to Tablet Sublingual	Film Buccal Compared to Tablet Sublingual	Film Buccal Compared to Film Sublingual
1 x 2 3mg/0.5 mg	C_{max}	22%	25%	-	C_{max}	-	-	-
	$AUC_{0\text{-last}}$	-	19%	-	$AUC_{0\text{-last}}$	-	-	-
2 x 2 mg/0.5 mg	C_{max}	-	21%	21%	C_{max}	-	17%	21%
	$AUC_{0\text{-last}}$	-	23%	16%	$AUC_{0\text{-last}}$	-	22%	24%
1 x 8 mg/2 mg	C_{max}	28%	34%	-	C_{max}	41%	54%	-
	$AUC_{0\text{-last}}$	20%	25%	-	$AUC_{0\text{-last}}$	30%	43%	-
1 x 12 mg/3 mg	C_{max}	37%	47%	-	C_{max}	57%	72%	9%
	$AUC_{0\text{-last}}$	21%	29%	-	$AUC_{0\text{-last}}$	45%	57%	-
1 x 8 mg/2 mg plus 2 x 2 mg/0.5 mg	C_{max}	-	27%	13%	C_{max}	17%	38%	19%
	$AUC_{0\text{-last}}$	-	23%	-	$AUC_{0\text{-last}}$	-	30%	19%
1 x 16 mg/4 mg film	C_{max}	34%	29%	7%	C_{max}	44%	46%	9%
	$AUC_{0\text{-last}}$	32%	-	-	$AUC_{0\text{-last}}$	49%	36%	3%

Note: 1. the 16 mg/4 mg strength film is not marketed; it is compositionally proportional to the 8 mg/2 mg strength film and has the same size of 2 x 8 mg/2 mg film. 2. – represents no change when the 90% confidence intervals for the geometric mean ratios of the Cmax and AUC0-last values are within the 80% to 125% limit. 3. There are no data for the 4 mg/1 mg strength film; it is compositionally proportional to 2 mg/0.5 mg strength film and has the same size of 2 x 2 mg/0.5 mg film strength.

Distribution

Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin.

Naloxone is approximately 45% protein bound, primarily to albumin.

Elimination

Buprenorphine is metabolized and eliminated in urine and feces. Naloxone undergoes metabolism as well. When SUBOXONE sublingual film is administered sublingually or buccally, buprenorphine has a mean elimination half-life ranging from 24 to 42 hours and naloxone has a mean elimination half-life ranging from 2 to 12 hours.

Metabolism

Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated primarily by the CYP3A4. Norbuprenorphine, the major metabolite, can further undergo glucuronidation. Norbuprenorphine has been found to bind opioid receptors *in vitro;* however, it has not been

studied clinically for opioid-like activity. Naloxone undergoes direct glucuronidation to naloxone-3-glucuronide as well as N-dealkylation, and reduction of the 6-oxo group.

Excretion

A mass balance study of buprenorphine showed complete recovery of radiolabel in urine (30%) and feces (69%) collected up to 11 days after dosing. Almost all of the dose was accounted for in terms of buprenorphine, norbuprenorphine, and two unidentified buprenorphine metabolites. In urine, most of buprenorphine and norbuprenorphine was conjugated (buprenorphine, 1% free and 9.4% conjugated; norbuprenorphine, 2.7% free and 11% conjugated). In feces, almost all of the buprenorphine and norbuprenorphine were free (buprenorphine, 33% free and 5% conjugated; norbuprenorphine, 21% free and 2% conjugated). Based on all studies performed with sublingually and buccally administered SUBOXONE sublingual film, buprenorphine has a mean elimination half-life from plasma ranging from 24 to 42 hours and naloxone has a mean elimination half-life from plasma ranging from 2 to 12 hours.

Drug Interactions Studies

CYP3A4 Inhibitors and Inducers

Buprenorphine has been found to be a CYP2D6 and CYP3A4 inhibitor and its major metabolite, norbuprenorphine, has been found to be a moderate CYP2D6 inhibitor in *in vitro* studies employing human liver microsomes. However, the relatively low plasma concentrations of buprenorphine and norbuprenorphine resulting from therapeutic doses are not expected to raise significant drug-drug interaction concerns *[see Drug Interactions (7)]*.

Specific Populations

Hepatic Impairment

In a pharmacokinetic study, the disposition of buprenorphine and naloxone were determined after administering a 2.0/0.5 mg SUBOXONE sublingual tablet in subjects with varied degrees of hepatic impairment as indicated by Child-Pugh criteria. The disposition of buprenorphine and naloxone in patients with hepatic impairment were compared to disposition in subjects with normal hepatic function.

In subjects with mild hepatic impairment, the changes in mean C_{max}, $AUC_{0\text{-}last}$, and half-life values of both buprenorphine and naloxone were not clinically significant. No dosing adjustment is needed in patients with mild hepatic impairment.

For subjects with moderate and severe hepatic impairment, mean C_{max}, $AUC_{0\text{-}last}$, and half-life values of both buprenorphine and naloxone were increased; the effects on naloxone are greater than that on buprenorphine (Table 6).

Table 6. Changes in Pharmacokinetic Parameters in Subjects With Moderate and Severe Hepatic Impairment

Hepatic Impairment	PK Parameters	Increase in buprenorphine compared to healthy subjects	Increase in naloxone compared to healthy subjects
Moderate	C_{max}	8%	170%
	$AUC_{0\text{-}last}$	64%	218%
	Half-life	35%	165%
Severe	C_{max}	72%	1030%

	$AUC_{0\text{-last}}$	181%	1302%
	Half-life	57%	122%

The difference in magnitude of the effects on naloxone and buprenorphine are greater in subjects with severe hepatic impairment than subjects with moderate hepatic impairment *[see Warnings and Precautions (5.12), Use in Specific Populations (8.6)]*.

HCV infection

In subjects with HCV infection but no sign of hepatic impairment, the changes in the mean C_{max}, $AUC_{0\text{-last}}$, and half-life values of buprenorphine and naloxone were not clinically significant in comparison to healthy subjects without HCV infection.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

Carcinogenicity data on SUBOXONE sublingual film are not available.

A carcinogenicity study of buprenorphine/naloxone (4:1 ratio of the free bases) was performed in Alderley Park rats. Buprenorphine/naloxone was administered in the diet at doses of approximately 7, 31, and 123 mg/kg/day for 104 weeks (estimated exposure was approximately 4, 18, and 44 times the recommended human sublingual dose of 16 mg/4 mg buprenorphine/naloxone based on buprenorphine AUC comparisons). A statistically significant increase in Leydig cell adenomas was observed in all dose groups. No other drug-related tumors were noted.

Carcinogenicity studies of buprenorphine were conducted in Sprague-Dawley rats and CD-1 mice. Buprenorphine was administered in the diet to rats at doses of 0.6, 5.5, and 56 mg/kg/day (estimated exposure was approximately 0.4, 3, and 35 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) for 27 months. As in the buprenorphine/naloxone carcinogenicity study in rats, statistically significant dose-related increases in Leydig cell tumors occurred. In an 86 week study in CD-1 mice, buprenorphine was not carcinogenic at dietary doses up to 100 mg/kg/day (estimated exposure was approximately 30 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis).

Mutagenicity

The 4:1 combination of buprenorphine and naloxone was not mutagenic in a bacterial mutation assay (Ames test) using four strains of *S. typhimurium* and two strains of *E. coli.* The combination was not clastogenic in an *in vitro* cytogenetic assay in human lymphocytes or in an IV micronucleus test in the rat.

Buprenorphine was studied in a series of tests utilizing gene, chromosome, and DNA interactions in both prokaryotic and eukaryotic systems. Results were negative in yeast (*S. cerevisiae)* for recombinant, gene convertant, or forward mutations; negative in *Bacillus subtilis* "rec" assay, negative for clastogenicity in CHO cells, Chinese hamster bone marrow and spermatogonia cells, and negative in the mouse lymphoma L5178Y assay.

Results were equivocal in the Ames test: negative in studies in two laboratories, but positive for frame shift mutation at a high dose (5 mg/plate) in a third study. Results were positive in the Green-Tweets (*E. coli*) survival test, positive in a DNA synthesis inhibition (DSI) test with testicular tissue from mice, for both *in vivo* and *in vitro* incorporation of [^{3}H]thymidine, and positive in unscheduled DNA synthesis (UDS) test using testicular cells from mice.

Impairment of Fertility

Dietary administration of buprenorphine in the rat at dose levels of 500 ppm or greater (equivalent to approximately 47 mg/kg/day or greater; estimated exposure approximately 28 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) produced a reduction in fertility demonstrated by reduced female conception rates. A dietary dose of 100 ppm (equivalent to approximately 10 mg/kg/day; estimated exposure approximately 6 times the recommended human daily sublingual dose of 16 mg on a mg/m^2 basis) had no adverse effect on fertility.

16 HOW SUPPLIED / STORAGE AND HANDLING

SUBOXONE sublingual film is supplied as an orange rectangular film with a white printed logo in child-resistant polyester/foil laminated pouches:

- NDC 12496-1202-3 (buprenorphine 2 mg/naloxone 0.5 mg/film; content expressed in terms of free base, equivalent to 2.16 mg buprenorphine hydrochloride USP and 0.61 mg naloxone hydrochloride dihydrate USP) - 30 films per carton
- NDC 12496-1204-3 (buprenorphine 4 mg/naloxone 1 mg/film; content expressed in terms of free base, equivalent to 4.32 mg buprenorphine hydrochloride USP and 1.22 mg naloxone hydrochloride dihydrate USP) - 30 films per carton
- NDC 12496-1208-3 (buprenorphine 8 mg/naloxone 2 mg/film; content expressed in terms of free base, equivalent to 8.64 mg buprenorphine hydrochloride USP and 2.44 mg naloxone hydrochloride dihydrate USP) - 30 films per carton
- NDC 12496-1212-3 (buprenorphine 12 mg/naloxone 3 mg/film; content expressed in terms of free base, equivalent to 12.96 mg buprenorphine hydrochloride USP and 3.66 mg naloxone hydrochloride dihydrate USP) - 30 films per carton

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Advise patients to store buprenorphine-containing medications safely and out of sight and reach of children and to destroy any unused medication appropriately *[see Patient Counseling Information (17)]*.

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Medication Guide).

Safe Use

Before initiating treatment with SUBOXONE sublingual film, explain the points listed below to caregivers and patients. Instruct patients to read the Medication Guide each time SUBOXONE sublingual film is dispensed because new information may be available.

- SUBOXONE sublingual film must be administered whole. Advise patients not to cut, chew, or swallow SUBOXONE sublingual film.
- Inform patients and caregivers that potentially fatal additive effects may occur if SUBOXONE sublingual film is used with benzodiazepines or other CNS depressants, including alcohol. Counsel patients that such medications should not be used concomitantly unless supervised by a health care provider *[see Warnings and Precautions (5.2, 5.3), Drug Interactions (7)]*.
- Advise patients that SUBOXONE sublingual film contains an opioid that can be a target for people who abuse prescription medications or street drugs. Caution patients to keep their films in a safe place, and to protect them from theft.
- Instruct patients to keep SUBOXONE sublingual film in a secure place, out of the sight and reach of children. Accidental or deliberate ingestion by a child may cause respiratory depression that can result in

death. Advise patients to seek medical attention immediately if a child is exposed to SUBOXONE sublingual film.

- Inform patients that opioids could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their healthcare providers if they are taking, or plan to take serotonergic medications *[see Drug Interactions (7)]*.
- Inform patients that opioids could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms *[see Warnings and Precautions (5.6)]*.
- Advise patients to never give SUBOXONE sublingual film to anyone else, even if he or she has the same signs and symptoms. It may cause harm or death.
- Advise patients that selling or giving away this medication is against the law.
- Caution patients that SUBOXONE sublingual film may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving or operating machinery. Caution should be taken especially during drug induction and dose adjustment and until individuals are reasonably certain that buprenorphine therapy does not adversely affect their ability to engage in such activities *[see Warnings and Precautions (5.13)]*.
- Advise patients not to change the dosage of SUBOXONE sublingual film without consulting their healthcare provider.
- Advise patients to take SUBOXONE sublingual film once a day.
- Advise patients that if they miss a dose of SUBOXONE sublingual film they should take it as soon as they remember. If it is almost time for the next dose, they should skip the missed dose and take the next dose at the regular time.
- Inform patients that SUBOXONE sublingual film can cause drug dependence and that withdrawal signs and symptoms may occur when the medication is discontinued.
- Advise patients seeking to discontinue treatment with buprenorphine for opioid dependence to work closely with their healthcare provider on a tapering schedule and inform them of the potential to relapse to illicit drug use associated with discontinuation of opioid agonist/partial agonist medication-assisted treatment.
- Advise patients that, like other opioids, SUBOXONE sublingual film may produce orthostatic hypotension in ambulatory individuals *[see Warnings and Precautions (5.14)]*.
- Advise patients to inform their healthcare provider if any other prescription medications, over-the-counter medications, or herbal preparations are prescribed or currently being used *[see Drug Interactions (7)]*.
- Advise women that if they are pregnant while being treated with SUBOXONE sublingual film, the baby may have signs of withdrawal at birth and that withdrawal is treatable *[see Warnings and Precautions (5.5), Use in Specific Populations (8.1)]*.
- Advise women who are breastfeeding to monitor the infant for drowsiness and difficulty breathing *[see Use in Specific Populations (8.2)]*.
- Inform patients that chronic use of opioids may cause reduced fertility. It is not known whether these effects on fertility are reversible *[see Use in Specific Populations (8.3)]*.

- Advise patients to inform their family members that, in the event of emergency, the treating healthcare provider or emergency room staff should be informed that the patient is physically dependent on an opioid and that the patient is being treated with SUBOXONE sublingual film.

Disposal of Unused SUBOXONE Sublingual Films

Unused SUBOXONE sublingual films should be disposed of as soon as they are no longer needed. Unused films should be flushed down the toilet.

Manufactured for Indivior Inc.

North Chesterfield, VA 23235 by:

Aquestive Therapeutics,

Warren, NJ 07059

Distributed by:

Indivior Inc.

North Chesterfield, VA 23235

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22.0 APPENDIX C: Simulation of Data for Precision Analyses

To give some idea of the precision of the estimate of the probability of success, we performed a simulation with various scenarios. Each scenario had 10,000 iterations. The scenarios were defined by the following parameters:

1. $\mu\mu$= the probability of a positive response at a given time, for a given patient, in a given site. That is, we assumed that this probability would be constant across all study sites, patients, and times.

2. $(\alpha\alpha, \beta\beta, \gamma\gamma)$, where all terms are positive and $\alpha\alpha + \beta\beta + \gamma\gamma = 1$. These parameters, which control the correlation structure of the outcomes, have the following intuitive explanations:

   a. $\gamma\gamma$ is the "independence" parameter. The closer $\gamma\gamma$ is to 1, the more independent all the outcomes are from each other.

   b. $\alpha\alpha$ is the "site importance" parameter. For a given $\gamma\gamma$, the larger $\alpha\alpha$ is, the bigger the influence of the study site (in comparison to the influence of the patient), upon the correlation between observations.

   c. $\beta\beta$ is the "patient importance" parameter. For a given $\gamma\gamma$, the larger $\beta\beta$ is, the bigger the influence of the patient (in comparison to the influence of the study site), upon the correlation between observations.

We assume that all the observations of a given patient have a compound-symmetric correlation structure. From the point of view of estimating the probability of success, this is a more pessimistic assumption than assuming the observations of a given patient have an AR(1) or other time series correlation structure. So we assume that the precision results of our simulation will be conservative with respect to real life data.

We explored the effect of the simulation parameters on the width of the 95% confidence interval of the probability of success.

For each iteration of the simulation:

1. Flip S independent coins, one for each of the S study sites, and also SP independent coins, one for each of the P patients at each site, and also TSP coins, one for each of the T time points for each patient at each site. All these coins have P(heads) = $\mu\mu$. Name the study site outcomes $ZZ_1, \ldots, ZZ_{SS}$, the patient outcomes $ZZ_{11}, \ldots, ZZ_{PPSS}$, and the time outcomes $ZZ_{111}, \ldots ZZ_{TTPPSS}$. Each ZZ will be 1 or 0, depending on whether the corresponding coin-flip was Heads or Tails, and is a latent random variable in the simulation.

2. For each time t for patient p at study site s, calculate $\theta\theta_{tttttt} = \alpha\alpha ZZ_{tt} + \beta\beta ZZ_{tttt} + \gamma\gamma ZZ_{tttttt}$. The $\theta\theta'$s are also latent random variables.

3. For each patient p at study site s, time t, calculate his observed (i.e., non-latent) outcome XX_{tttttt} by flipping an independent coin with P(heads) = $\theta\theta_{tttttt}$. Each XX will be 1 or 0, depending on whether the corresponding coin flip was either Heads or Tails.

It is shown below that $EE(XX_{TTPPSS}) = \mu\mu$, $VV(XX_{TTPPSS}) = \mu\mu(1 - \mu\mu)$, and the X's have the following correlation structure:

$$0 \qquad \text{if } SS \neq SS'$$

$$\text{corr}(XX_{TTPPSS}, XX_{TT'PP'SS'}) = \alpha\alpha_2\alpha\alpha + {}_2\beta\beta_2 \text{if } SS \text{ if} = SSSS =', PPSS =' \text{ and } PP', \text{and} PP \neq TTPP \neq' TT'$$

1 if $SS = SS'$, $PP = PP'$, and $TT =$

TT' The algebra to demonstrate these moments follows.

Theorem – Let $EE\,\theta\theta_{\tau\tau} = \mu\mu_{\mu\mu}$ $\theta\theta_{\tau\tau} = \sigma\sigma^{\sigma\sigma}{}_{\theta\theta^{\theta\theta 2}{}_{,\tau\tau}}$ $\sigma\sigma_{\sigma\sigma^{\theta\theta}{}_{\tau\tau 2',\tau\tau}}$, $XX \sim \text{Bernoulli}(\theta\theta)$, and $YY \sim \text{Bernoulli}(\tau\tau)$. Note that XX , VV

and YY are independent, conditional on $\theta\theta, \tau\tau$. Then:

1. $EE(XX) = EE(YY) = \mu\mu$
2. $VV(XX) = VV(YY) = \mu\mu(1 - \mu\mu)$
3. $cccccc(XX, YY) = \sigma\sigma_{\theta\theta,\tau\tau}$

Proof: (1) follows using conditional expected values. (2) follows because X and Y are (0,1) random variables for which (1) is true. (3) follows using the law of total covariance, i.e.:

$$cccccc(XX, YY) = EE_{\theta\theta,\tau\tau}[cccccc(XX, YY|\theta\theta, \tau\tau)] + cccccc_{\theta\theta,\tau\tau}[EE(XX|\theta\theta), EE(YY|\tau\tau)]$$

$$= 0 + cccccc(\theta\theta, \tau\tau) = \sigma\sigma_{\theta\theta,\tau\tau}$$

Now, let

$$\theta\theta = \sum \alpha\alpha_{ii} ZZ_{ii}$$

$$\tau\tau = \sum \beta\beta_{ii} ZZ_{ii}$$

where $\sum \alpha\alpha_{ii} = \sum \beta\beta_{ii} = 1$, all $(\alpha\alpha, \beta\beta)$ are non-negative, and each $ZZ_{ii} \sim \text{Bernoulli}(\mu\mu)$. Note that $\theta\theta$ and $\tau\tau$ meet the conditions of the Theorem. This means that $EE(XX) = EE(YY) = \mu\mu$, $VV(XX) = VV(YY) = \mu\mu(1 - \mu\mu)$, and:

$$cccccc(XX, YY) = cccccc(\theta\theta, \tau\tau) = \mu\mu(1 - \mu\mu) \sum \alpha\alpha_{ii} \beta\beta_{ii}$$

from which $cccccccc(XX, YY) = \sum \alpha\alpha_{ii} \beta\beta_{ii}$.

The statement above about $\text{corr}(XX_{TTPPSS}, XX_{TT'PP'SS'})$ follows on choosing $\alpha\alpha, \beta\beta, \gamma\gamma, \mu\mu$, and the Z's as given in the description of the simulation.