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A pilot study to permit Opioid Treatment Program physicians to prescribe methadone through community pharmacies for their stable methadone patients (OTP-Pharmacy Care)

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1. Abstract

The overall objective of this pilot implementation study will focus on exploring a collaborative care model aimed at increasing access to methadone maintenance treatment (MMT). The study aims are to determine the feasibility, acceptability, and satisfaction of patients and opioid treatment program (OTP) providers (e.g., medical staff, nurses, and counselors) and pharmacists with community pharmacy administration and dispensing of methadone for patients with opioid use disorder (OUD).

Approximately 20 adults, aged 18 or older, who have been stabilized on MMT long-term for OUD and who receive between 6- and 13-days of methadone take-home doses will be enrolled in the study. Participants will be recruited from 1-2 OTPs. Morse Clinic of North Raleigh (Raleigh, NC) will serve as the primary OTP site for the study; Morse Clinic of Zebulon (Zebulon, NC) will serve as a backup OTP site for this study. Health Park Pharmacy (Raleigh, NC) will be the study pharmacy site.

Given the pilot study nature and the focus on implementation issues, this study will use a non-randomized, prospective, single group design. After the intake study assessment (baseline), the administration and dispensing of participants' take-home methadone doses will be transferred from the OTP to the pharmacy for 3 months under the supervision of methadone prescriber (medical provider). Each participant will be assessed monthly for 3 months (at 1, 2, and 3 months following intake/baseline) to explore the feasibility of transferring their methadone administration and dispensing to the select community pharmacy.

The operation for the pharmacy administration and dispensing of methadone for OUD treatment will be based on the available treatment guidelines for pharmacy-based medication management and Medication-assisted treatment (MAT) for OUD, including SAMHSA's guidelines to the federal OTP regulations and the guideline for pharmacy-based supervision of methadone consumption from other countries (Adams et al., 2015; Hill, 2014; Ontario Pharmacists Association, 2017; SAMHSA, 2015a, 2015b; SAMHSA, 2018a;). An Operational Care Agreement (OCA) will be used to define the respective roles of the methadone medical provider (supervising care and writing prescriptions) and pharmacist and determine study procedures. The OTP will continue to follow routine care practices and procedures as usual during the study and provide counseling, medical supervision, and urine drug testing. The study pharmacist will administer and dispense methadone according to the OTP provider's prescription.

Participants will be assessed at baseline (following informed consent). Outcome assessments will be conducted at each monthly visit throughout the follow-up phase of the study. Assessments will focus mainly on the feasibility and acceptability of pharmacy-based methadone administration and dispensing in order to inform the development of a future multisite randomized clinical trial. **Primary outcome** will be medication adherence. Measures of adherence will include: (1) adherence to scheduled pharmacy visits for dose administration and take-home pickup and (2) success in methadone call-back (e.g., failed methadone dose call back as an indicator treatment non-adherence). **Secondary outcomes** will include recruitment rate, treatment retention, opioid and other substance use, participant treatment satisfaction, pharmacist and physician treatment satisfaction, and participant safety. Information generated from this pilot study will inform the development of a future randomized controlled trial, which will test the effect of pharmacy-OTP collaborative care model for the management of patients with OUD.

2. Objectives

The overarching goal is to explore the feasibility and acceptability of transferring methadone dose administration and take-home methadone dispensing for OUD treatment for stable patients from OTPs to pharmacies. We will achieve this goal by pursuing the following primary pilot study objectives.

a) Calculate the rate of recruitment, defined as the number of participants enrolled in the study out of the number of MMT patients who are potentially eligible and approached for participation. The average monthly rate of participants starting pharmacy-based methadone dispensing for OUD among enrolled participants 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.
b) Calculate the adherence to methadone treatment defined as (1) the proportion of methadone take-home doses dispensed at the pharmacy out of the total number of take home doses prescribed and (2) the proportion of successful scheduled methadone dose call-back with no signs of methadone diversion.
c) Examine retention in treatment, as determined by the proportion of participants who remain in treatment at the pharmacy during the 3-month follow-up phase.

d) Examine the proportion of positive urine drug screens (UDS) over the study duration.
e) Examine the number of days of self-reported substance use (alcohol intoxication, and other drugs) as collected on Timeline Followback (TLFB) over the study duration (Sobell, 1992; Sobell & Sobell, 2000).
f) Determine indicators of participant satisfaction with treatment delivery measured using the Treatment Satisfaction Survey (adapted from Harland et al., 2005) obtained at each assessment; 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).
g) Determine pharmacist and physician satisfaction with treatment delivery measured using the Treatment Satisfaction Survey at follow-up assessment, and a proportion of physician and pharmacist ratings of satisfied or very satisfied.
h) Examine participant safety, as measured by: (1) Any fatal or non-fatal substance-related overdose measured by medical examiner record or self-report, respectively; and (2) Any substance-related emergency department (ED) visit or hospitalization, measured by self-report.

3. Background and rationale

3.1. Prescription (Rx) opioid and heroin overdose epidemic

The United States is facing a pressing and tragic opioid overdose epidemic that has been escalating for about two decades. It has evolved progressively from an initial rise in prescription opioid overdose deaths, followed by a significant surge in heroin overdose deaths, to the more recent sharp increase in illicitly manufactured fentanyl overdose deaths (Compton et al., 2016; Hedegaard et al., 2018; Seth et al., 2018). The opioid epidemic affects both men and women as well as diverse racial/ethnic groups. Overdose deaths disproportionally affect adults aged 25-54 years (Hedegaard et al., 2018). In 2016, there were an estimated 42,249 opioid-involved overdose deaths in the United States (Centers for Disease Control and Prevention [CDC], 2017). In 2017, the age-adjusted rate of drug overdose deaths in the United States increased by 9.6% over the previous year with heroin and illicit fentanyl as the main drivers (Hedegaard et al., 2018). The total economic burden of opioid overdose and OUD was estimated to be $78.5 billion for calendar year 2013 (Florence et al., 2016). There is an urgent need to identify effective service models to improve access to, and utilization of, evidence-based pharmacotherapy for OUD to reduce morbidity and mortality (Volkow et al., 2014).

The escalating rate of opioid overdose deaths also is related closely to the low availability of pharmacotherapy for OUD (Hammarlund et al., 2018; Jones et al., 2015). The majority of people with OUD in the US have not received FDA-approved OUD pharmacotherapy (Wu et al., 2016; Zhu & Wu, 2018). In order to bring effective treatment to scale, it will be important to expand access to all three currently FDA-approved medications, including extended-release naltrexone (XR-NTX), buprenorphine, and methadone. Nonetheless, each of these medications has challenges. Starting XR-NTX is limited by the need for patients to be opioid abstinent for an adequate period of time prior to its injection (Jarvis et al., 2018). Buprenorphine treatment has expanded access to OUD treatment since its 2002 approval by the FDA. However, there is an inadequate number of providers with the federal waiver required to prescribe this medication, and those providers with the waiver, treat on average few patients (SAMHSA, 2018b; Stein et al., 2016). Access to buprenorphine treatment is much more limited in rural areas compared with urban areas (Jones et al., 2015; Stein et al., 2016). Indeed, 60% of rural counties lack a waivered provider (Andrilla et al., 2017). Volkow and colleagues (2014) have called for the use of OUD pharmacotherapy to tackle the opioid overdose epidemic, an approach endorsed by the President's Commission Report on the opioid crisis (Christie et al., 2017).

3.2. Methadone maintenance treatment

Methadone maintenance treatment (MMT) is by far the most studied and longest utilized OUD treatment. MMT has been associated with reduced risks of overdose death, HIV and hepatitis C infections, criminal behavior, and lower healthcare costs (SAMHSA, 2018a). Longer retention in treatment has been associated with superior patient outcomes. For many patients, treatment is long term, often over many years. In the US, federal regulations require MMT to be provided through one of the approximately 1,500 SAMHSA certified OTPs (SAMHSA, 2018b).

The limited number of OTPs and the federal OTP regulations governing methadone administration and dispensing present a barrier to treatment expansion, especially in rural and underserved areas. Early in treatment and during periods of instability, patients must travel to the OTP at least six days/week for dose

administration. Take-home methadone doses for unsupervised consumption are permitted at the discretion of the OTP's medical director within the parameters of tenure and progress in treatment outlined in the federal OTP regulations (Office of the Federal Register, 2001). These regulations permit stable patients who have been successful in treatment for at least one, two, or three years to receive up to 6, 14, and 30 take-home doses, respectively (Office of the Federal Register, 2001). Moreover, OTPs are frequently located in urban or metropolitan areas, with few such programs in non-metropolitan or rural areas. Requiring stable patients to attend the OTP for medication administration places a travel and time burden on the patient, exposes them to other non-stable patients who are using illicit drugs, may discourage them from continuing in treatment which could lead to relapse, and can be associated with stigma. Stable patients also occupy a treatment slot and require nursing time that could otherwise be afforded to out-of-treatment individuals.

A graduated system of methadone treatment was envisioned as early as 1971 by Dole who saw the potential benefit of mainstreaming stable MMT patients into medical practices for continuing treatment. Over recent decades, there have been a number of successful attempts (variously termed medical methadone maintenance or office based opioid treatment [OBOT]) in the US to provide MMT to stable patients beyond the walls of OTPs (Senay et al., 1993). Starting in the 1980s, physician office-based MMT for such patients was provided under Food and Drug Administration (FDA) Investigational New Drug permits (INDs) in New York City (Novick et al., 1998) and Baltimore (Schwartz et al., 1999). Their care was transferred from OTPs to physician offices, where patients received their take-home doses, were seen by the physicians, and provided urine specimens for drug testing. Subsequent randomized trials of this approach found that patients treated in physician offices performed as well as those who remained at their OTP (Fiellin et al., 2001; King et al., 2002). A later demonstration pilot in Seattle found that pharmacists could be deployed to an internal medicine clinic to dispense methadone as part of medical maintenance (Merrill et al., 2005).

3.3. Pharmacist-managed MMT treatment

Another promising collaborative care model to expand access to MMT includes the engagement of pharmacies to dispense or administer methadone. There are approximately 65,000 US pharmacies in the US (Oata et al., 2017). Pharmacy administration and dispensing of methadone for OUD treatment has been part of standard care for decades throughout the world (e.g., Australia, Canada, France, Germany, Netherlands, New Zealand, Switzerland, United Kingdom; Australian Institute of Health and Welfare, 2018; Bonnet et al., 2001; Chaar et al., 2013; Gossop et al., 1991; McCormick et al., 2006; Samitca et al., 2007; Winstock et al., 2010). In Australia, MMT has been provided through community pharmacies since 1985 (Chaar et al., 2013). There were 2,732 dosing points in 2016–2017, serving almost 50,000 patients (Australian Institute of Health and Welfare, 2018). Pharmacies were the most common dosing sites in Australia with an average of 18 patients served per location in 2017 (Australian Institute of Health and Welfare, 2018).

Outside the US, pharmacy delivered methadone treatment has led to an increase in the number of patients served and a reduction in overdose mortality (Matheson et al., 2007; Sheridan et al., 2007; Strang et al., 2010). In the United Kingdom, Sheridan et al., (2007) found a significant increase in the proportion of pharmacies dispensing methadone for OUD (from 51% in 1995 to 63% in 2005). In Scotland, the number of methadone patients treated through pharmacies increased from 3,387 in 1995 to 12,400 in 2006 (Matheson et al., 2007). Strang et al., (2010) found that the introduction of supervised methadone dosing in pharmacies was followed by substantial declines in deaths related to overdose of methadone in both Scotland and England.

In Canada, methadone patients once stabilized at an OTP, are able to receive regularly supervised methadone administration at local pharmacies (Eibl et al., 2015, 2017). Thus, stabilized patients are only required to see their prescribing physician a few times per month. This model is particularly advantageous for patients whose physicians are several hundred miles away (Eibl et al., 2015). As such, patients with OUD living in a rural, remote, or resource-limited region are able to receive methadone for OUD treatment.

Community pharmacists have positive attitudes about delivering methadone treatment. In Australia, Lawrinson et al., (2008) found that pharmacists reported high levels of support for the pharmacy-delivered methadone treatment and nearly all intended to continue providing OUD treatment (Lawrinson et al., 2008). Of note, 64% of all pharmacists, and significantly more rural pharmacists (90%), indicated that they were willing to take on additional patients.

There have been two reports of pharmacy dispensing of methadone treatment in the US. Harris and colleagues (2006), reported on a 5-year follow-up of a methadone medical maintenance program initiated with FDA-approval in 1998. In this retrospective report from the Bronx, 127 stable MMT patients were provided treatment through physician offices and hospital pharmacy dispensing (Harris et al., 2006). The treatment

retention rate was extremely high, there were no failed medication recalls, and extremely low rates of drug positive urine specimens. The second report, was a 12-month prospective pilot study started in 2003 in New Mexico (Tuchman et al., 2006). This was the first trial of pharmacy dispensing of methadone in the US. In this study, 26 stable methadone patients were randomly assigned to remain in the OTP or to receive MMT through pharmacy dispensing, physician visits, and social work counseling in offices outside of the OTP. None of the 13 office-based patients left treatment compared with one patient in the control group. There were no significant between group differences in rates of drug positive tests. Taken together, pharmacy dispensing permitted patients to receive care closer to their home, and to avoid seeing illicit drug users at their OTPs. Methadone treatment, currently delivered only through a limited number of federally certified OTPs, could contribute to increasing access to care and improving the quality of care if scalable pharmacy-based models that have been used for decades internationally could be adapted for use in the US, particularly in rural and resource-limited areas (Australian Institute of Health and Welfare, 2018; Sheridan et al., 2007).

3.4. Clinical and Public Health Impact

The benefits of permitting OTP physicians to prescribe methadone through community pharmacies for their stable patients are many. These include extended operating hours which improve the quality of life for working people. Delivering services closer to the patients' homes, which reduces patient burden and transportation costs. Decrease stigma associated with attending an OTP while reducing interactions between stable and unstable OTP patients. The resulting improved quality of care could reduce the likelihood of stable patients requesting premature discontinuation of treatment due to burdens associated with OTP attendance. Reduced OTP caseloads would permit admitting new patients to replace those treated in pharmacies. It will also significantly increase the professional capacity of pharmacists to provide OUD care, and most importantly, to increase the number of patients in effective treatment (Australian Institute of Health and Welfare, 2018; Chaar et al., 2011; Lawrinson et al., 2008; Matheson et al., 2007; Sheridan et al., 2007). Finally, if this model is proven feasible, acceptable, and effective, it could be expanded to treat patients with shorter periods of stability who would attend the pharmacy for more frequent dose administration.

If this pilot study is successful, the proposed service model that would permit methadone prescribing through OTPs for pharmacy dose administration and dispensing could be tested in a multi-site randomized trial, to provide data that could help to address the opioid epidemic.

4. Study Procedures/Study design

The investigative team will obtain the approvals from the Drug Enforcement Administration (DEA), Substance Abuse and Mental Health Services Administration (SAMHSA), NC State Opioid Treatment Authority (NC Department of Health and Human Services, Division of Mental Health, Developmental Disabilities and Substance Abuse Services), and Duke University Health System institutional review board (IRB) to implement this study protocol.

4.1. Participants.

A total of up to 20 OTP patients will be consented and enrolled in this study over a period of up to 12 weeks (i.e., 3 months). Given the focus on exploring the feasibility for implementation, the sample size is not powered to test for between-group efficacy or hypothesis testing.

Inclusion criteria:

1. Patient aged 18 or older receiving methadone treatment at Morse Clinic in Raleigh or Zebulon, NC.
2. Able to provide informed written consent to participate in the pilot study.
3. Receiving a stable methadone dose between 5 mg and 160 mg.
4. Having all negative drug tests (except for prescribed methadone and ethanol) at the OTP for the past 12 months.
5. No missed call-backs in the past 12 months.
6. No signs/symptoms of a co-occurring major mental illness (i.e., thought disorder, thoughts of harm to self or others, delusions or hallucinations, cognitive impairment compromising informed consent to study procedures and requirements).
7. Meeting the federal and state regulations for eligibility to receive between 6- and 13-days of take-home methadone and receiving this level of take-home doses at the time of study enrollment.
8. If female, using adequate birth control methods.

Exclusion criteria:

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.
2. Have chronic pain requiring ongoing pain management with opioid analgesics.
3. Prisoner status or pending legal action that could prevent participation in study activities
4. Legal order for treatment (e.g., parole, probation, or pre-trial)
5. Pregnant or breastfeeding at the time of screening.

4.2. Informed consent and recruitment.

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 Duke University Health System IRB prior to use. Every study participant is required to sign an IRB-approved study informed consent form (i.e., current version) prior to the initiation of any study related procedures. 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 electronically via RedCAP. Staff members delegated by the Principal Investigator (PI) to obtain informed consent must be listed on the Staff Delegation of Responsibilities and Signature Log and must be approved by the Duke 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. An electronic copy of the informed consent will be given to a prospective participant to review during the consent process. 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. All signed consent forms will be stored electronically via RedCAP as source documents for quality assurance review and regulatory compliance.

Recruitment:

Potentially eligible participants will be screened and recruited from Morse Clinic of North Raleigh, NC. Morse Clinic of Zebulon (Zebulon, NC) will serve as a backup study site for this study if participant recruitment in Raleigh should prove insufficient. Dr. Eric Morse is the medical director and psychiatrist at both OTP clinics and will serve as the Site Principal Investigator (Site PI) to help recruit and enroll participants. Patients' medical records from Dr. Morse's OTP clinics will be used to identify eligible patients to facilitate the recruitment. Additionally, members of the clinic care team will be informed about the study and asked to refer potential participants who are interested in learning more about the study to clinic research staff for pre-screening. Finally, an IRB-recruitment flyer will be available at the OTP for patients to self-refer to the study.

During the pre-screening phase, potential participants will be identified by the site PI through an examination of the take-home schedules of patients enrolled in the OTP. Patients also will be either self-referred (such as via the information from the IRB-approved study flyers) or referred by OTP providers. If a potential study participant is interested in learning more about the study, a study staff member will meet with the participant in-person at the clinic or remotely via phone or a Duke-approved teleconferencing platform for research to discuss the study. Potential participants will have already met clinic criteria for receiving take-home doses of methadone 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 to explain study procedures and the potential risks and benefits of participating in the trial. Potential participants will have to demonstrate an understanding of the study requirements as part of the consent process prior to providing written informed consent (eConsent). Strict ethical guidelines regarding professional conduct and confidentiality will be enforced for all study staff.

It is acknowledged that recruiting participants in clinical settings poses potential challenges to pre-screening and consenting potential participants, including the rapid pace of care, interruptions in clinical workflow, clinic productivity requirements, and space limitations (Berkman et al., 2001; Falcon et al., 2011). To minimize the impact of these challenges, research staff will spend 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. The Site PI will help facilitate negotiation of space and time requirements and serve as a resource to research staff regarding clinic procedures.

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. 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. The informed consent process, screening, and data collection (study assessments) also will occur remotely over the phone or by using a Duke-approved teleconferencing platform for research as needed. If a participant feels ill during the interview, research staff will stop and reschedule the visit. The intake/baseline assessments may take more than 1 visit to complete.

The data collected from the intake/baseline assessments, along with a review of the participant's OTP records, will be primarily utilized to determine each participant's eligibility for continuation to the pharmacy follow-up phase of the study. After the pre-screening 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. 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 will capture the participant's clinical presentation and treatment history, as well as measures of safety (see Study Assessment Timetable, **Table 1**). In total, the intake/baseline assessments will take approximately 60 minutes to complete.

4.3. Pharmacy Procedures

Once a participant is determined to be eligible and enrolled into the study, study participants will go to Health Park Pharmacy, Raleigh, NC, to receive methadone administration and take-home methadone doses for Opioid Use Disorder from the study pharmacist(s) for approximately 3 months. Participants will receive their take-home methadone doses from the pharmacy on a once-a-week or every 2-week schedule, consistent with their methadone take-home schedule at the study OTP program (Morse Clinic of North Raleigh, NC; Morse Clinic of Zebulon, NC). The prescriptions will be written by the site PI (Morse Clinic of North Raleigh, NC; Morse Clinic of Zebulon, NC), Eric Morse, MD, DFAPA, who will have been granted an exception by the DEA to write prescriptions for methadone for the treatment of Opioid Use Disorder. Each prescription will include the OTP's registration number, in addition to the prescriber's DEA number, and indication for Opioid Use Disorder. Prior to dispensing take-home doses to a participant at each pharmacy visit, the study pharmacist will observe ingestion of one dose at each visit. All methadone dispensed by the pharmacy for this study will be from the pharmacy's stock supply. The costs of methadone medication dispensed at the pharmacy for the study will be paid by research funds from the National Institute on Drug Abuse, the National Institutes of Health (NIH).

Participants will complete three follow-up assessments at 1-month, 2-months, and 3-months following the baseline visit. These follow-up assessments will be completed either in-person between the participant and research staff or remotely via phone or a Duke-approved teleconferencing platform for research. Assessments will focus on collecting clinical and safety information since the previous assessment, including substance use data via urine toxicology samples and self-report using the timeline followback (TLFB) assessment, compliance with psychosocial interventions, medication side effects or other safety events, and suicidality risk evaluation. The full list of assessments to be administered is included below (**Table 1**). Based on the convenience of the patient's time and methadone take-home schedule, monthly research assessment may be scheduled to occur on a day that take-home doses are scheduled to be dispensed. Completion of the intake/baseline assessments will take approximately 45-60 minutes. Follow-up research interviews will be briefer, about 30 minutes in duration.

Using the guidance from the pharmacy practice's collaborative practice agreements (CPAs), the role and responsibilities of study pharmacists (Health Park Pharmacy, Raleigh, NC) and study OTP prescriber/physician (Eric Morse, MD), including communication procedures, will be specified by an Operational Care Agreement (OCA) and signed by study pharmacists and Dr. Eric Morse. Throughout the study, participants will continue to receive their usual care at the OTP (e.g., counseling, methadone provider

oversight of dose orders, urine drug screen) and participants will return to their OTP at the end of the study (i.e., 3 months after baseline). The last monthly study assessment (3 months after baseline) will occur remotely (via phone or a Duke-approved teleconferencing platform), at the OTP, or at the pharmacy; however, no methadone will be dispensed at the pharmacy as part of the 3-month assessment.

4.4. Assessments

Study assessments will focus on the feasibility (e.g., recruitment, implementation of the intervention), treatment adherences, and safety measures. A list of assessments by the study visit is summarized in **Table 1**. Assessments are categorized as either general and medical assessments, safety assessments, substance use assessments, or methadone treatment and satisfaction assessments. A detailed description of each assessment is provided following the study assessment timetable.

Table 1: Study Assessment Timetable

Study visit number	**Visit 1**	**Visit 2*_**	**Visit 3**	**Visit 4**	**Visit 5**	**Early termination**	
Visit location**	**OTP/remote**	**Pharmacy**	**OTP, Pharmacy, remote**	**OTP, Pharmacy, remote**	**OTP, Pharmacy, remote**	**OTP, Pharmacy, remote**	
Assessment/Activity	**Screening/ Baseline**	**Methadone dosing and dispensing**	**1 Month After Visit 2**	**2 Months After Visit 2**	**3 Months After Visit 2**		**As needed**
General and Medical Assessments							
Recruitment Log	x						
Prisoner Status Assessment	x		x	x	x		x
Informed Consent/HIPAA/ Medical Release Form	x						x
Master Enrollment Log	x						
Inclusion/Exclusion Checklist +	x						
Locator Form	x		x	x	x		x
Demographics	x						
Medical History	x						
Substance use history	x						
Charlson Comorbidity Index	x						
Concomitant Medications	x		x	x	x		x
Study Completion					x	x	
Protocol Deviations							x
Missed Visit							x
Safety Assessments							
Patient Health Questionnaire (PHQ-9)	x		x	x	x	x	
P4 suicide screener (P4 screener) (Follow-up assessment will be triggered by the PHQ-9 result) ++	x		see ++	see ++	see ++		x
Safety Event Response Checklist	x		x	x	x		x
Pregnancy and birth control assessment	x		x	x	x		x
Substance Use Assessments							
Urine Drug Screen (UDS) (the OTP records)	x		x	x	x		x
Timeline Followback (TLFB)	x		x	x	x	x	
Methadone Treatment and Satisfaction Assessments							
Methadone Call Back (once)			see +++	see +++	see +++		x+++

Study visit number	Visit 1	Visit 2*_	Visit 3	Visit 4	Visit 5	Early termination	
Visit location**	**OTP/remote**	**Pharmacy**	**OTP, Pharmacy, remote**	**OTP, Pharmacy, remote**	**OTP, Pharmacy, remote**	**OTP, Pharmacy, remote**	
Assessment/Activity	**Screening/ Baseline**	**Methadone dosing and dispensing**	**1 Month After Visit 2**	**2 Months After Visit 2**	**3 Months After Visit 2**		**As needed**
(the OTP records)+++							
OTP's Psychosocial Counseling Attendance Form (the OTP records)	x		x	x	x	x	
Methadone Visit Checklist++++		x	x	x	x		x
End of Methadone Medication Form					x	x	
Treatment Satisfaction Survey	x		x	x	x	x	

* Visit 2 refers to the pharmacy visit for the **first** methadone dose administration. The timing of the subsequent follow-up visits are anchored at visit 2.
** Remote pre-screening and screening, remote consenting (eConsent), and remote data collection (study assessments) by phone or the Duke-approved teleconferencing platform for research also will be used.
+ Inclusion/exclusion criteria: Medical record data at the OTP will be used to determine study eligibility status.
++ P4 Screener: Follow-up assessment for suicide risk by P4 Screener will be triggered by the PHQ-9 result. 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 trigger the completion of the P4 Screener form. A positive finding will be reported promptly to Site PI for further medical evaluation and clinical decision.
+++ Methadone Call Back: At least one random methadone call-back visit will occur during the study period (i.e., after the first methadone dispensing at the pharmacy).
++++ Methadone Visit Checklist: Methadone for Opioid Use Disorder will be administered and dispensed by study pharmacist(s) at Visit 2 (after enrollment into the study) and subsequently according to the length of time prescribed by the OTP physician for a total of 3 months. This form will be completed by the study pharmacist at each pharmacy visit. The number of pharmacy visits will be based on each participant's methadone take-home doses and treatment schedule.

4.4.1. General and Medical Assessments (Note: The visit numbers used in this section follow the order indicated in the Study Assessment Timetable.)

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. These data will be used monthly to calculate the recruitment rates during the 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.

Prisoner Status Assessment: The Prisoner Status Assessment will be administered at the intake/baseline visit (Visit 1) and at the beginning of each monthly study visit to determine whether a participant is incarcerated/detained in a correctional facility, pending trial, or otherwise meets the definition of a prisoner as delineated in 45 CFR 46.303(c) as adopted by the Office for Human Research Protections (OHRP). Prisoner status is an exclusion criterion. Participants who meet the OHRP definition of a prisoner at any point during the follow-up phase of the study will be withdrawn from further participation.

Inclusion/Exclusion Checklist: This form will include each inclusion and exclusion criterion to document eligibility. It will gather data from the study screening visit as well as OTP record review prior to enrollment. The record review will include looking for evidence for meeting study eligibility (e.g. receiving specified number of methadone take-home doses, and being treated within the specified methadone dose range). 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 current address, email address, and phone numbers of the participant AND one or more family members/significant other, or friends. In order to facilitate locating participants if direct contact efforts are unsuccessful, addresses, email addresses and phone numbers of at least one other person (e.g., family members, significant others, friends) who may know how to reach the participant will be collected. 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 (RedCAP).

Demographics: Demographics form will collect information about demographic characteristics of the participant, including sex, date of birth, ethnicity, race, education, employment pattern, insurance status, and marital status.

Medical History and Charlson Comorbidity Index forms: Medical History form and Charlson Comorbidity Index form will obtain a medical and psychiatric history from the participant covering past and present health conditions to help determine eligibility and to provide baseline information (Austin et al., 2015). These data will be collected during screening only.

Psychosocial Counseling Attendance Form: Participants' psychosocial counseling attendance will be assessed at each visit (Intake/Baseline Visit and follow-up visits 2 through 4, or the Early Termination Visit if 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 the data from the OTP records.

Concomitant Medications: 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 visits (including Visit 4, or the Early Termination Visit if the participant discontinues study participation early), and changes will be documented on the form. The study medical clinician may exclude any participant taking medications that could interact adversely with methadone at his/her clinical discretion.

Study Completion: This form tracks the participant's status in the study. It will be completed at the last research visit (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 4 research 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. This form will document a description of the deviation, how it occurred, the corrective action taken to resolve the specific deviation, as well as a description of the plan implemented to prevent future occurrences of similar deviations.

Missed Study Assessment Visit: This form is designed to capture the reason a study visit was missed. Once the visit window closes without completion of the visit, this assessment will be completed directly in the electronic data capture system. Completing this form will remove the requirement for all assessments scheduled for that visit. Active tracking and follow-up should be performed for all missed visits.

4.4.2. Safety Assessments

Patient Health Questionnaire (PHQ-9): The PHQ-9 (Spitzer et al., 1999) is 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 each follow-up visit and the Early Termination Visit if 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 trigger the completion of the P4 Screener form and an immediate report to the study's physician and PI.

P4 Screener for suicide risk: 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 P4 Screener, "Have you thought about how you might actually hurt yourself?", research staff will ask the participant additional clarifying questions to assess suicidality (Suicidal Risk form). A safety standard operating procedure will be indicated in the Manual of Operating Procedures (MOP), including the decision tree, assessment processes and documentation, and procedures to contact the study physician, study pharmacist, and the designated on-site crisis responder for assessment of the participant's intent to harm and disposition.

Pregnancy and Birth Control Assessment: This form will document childbearing potential, and female participants' self-reported pregnancy status and use of an acceptable method of birth control. The Pregnancy and Birth Control Assessment will be collected during screening (Visit 1) to determine eligibility. For females of childbearing potential: Self-reported contraceptive use and pregnancy status will be performed at Visit 1 to confirm participant eligibility. Birth Control assessment and self-reported pregnancy question will also be administered at Visits 2 through 4. Pregnancy occurring during the study will be reported to Site PI for additional clinical monitoring, referral to pre-natal care (as needed), and the participant will be withdrawn from the study.

Safety Event Response Checklist: As methadone is an approved medication being prescribed in accordance with the approved usage, there would be no need to capture Adverse Events (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 with solicited symptom information, yes/no responses, and level of severity (mild, moderate, severe) will be developed for addition to the Manual of Operating Procedures (MOP). The checklist will be used by research staff to obtain self-reported information from each participant at each research visit. The MOP will specify the process of reporting safety events that may require interventions (such as side effects, reported loss of medication, call-back failure) to study physician (Site PI) and pharmacists, as well as to the Study PI.

For the purposes of this protocol, the following safety events will be collected and reported to assist with monitoring of methadone treatment and compliance. Side effects of the medication may include but are not limited to: headache, nausea, vomiting, constipation, excessive sleeping/insomnia, excessive sweating, pain, swelling, and overdoses.

In addition, we will collect all failure to respond to random call-back or to return the appropriate amount of medication, reported loss of medication, ED 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 monthly research 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 or lack of responsible handling of methadone, 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 OTP for extra visits or termination from the study with a return to the OTP for methadone administration and dispensing and changes in take-home levels 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. All hospitalizations will be assessed by self-report at each monthly research visit or Early Termination Visit if 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 monthly research visit following consent. Research staff will report overdose events to PI who will arrange with the site PI to terminate the participant from the study and return the participant to the OTP for medication administration, change in take home regimen, and other appropriate

intervention. Data on fatal overdoses may be collected via medical chart record review, if medical records data is available, or during participant tracking for follow-up interviews. Information from records will be supplemented with information from contacts 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.

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 using state medical examiner records, National Death Index, and/or review of medical records. Deaths will be reported using the Safety Event Response Checklist.

4.4.3. Substance Use Assessments

Urine Drug Screen (UDS): Urine drug screens will be performed once a month at the OTP as part of usual care for each participant during the study. The monthly urine specimens collected at the OTP are screened via enzyme immunoassay (EIA) and liquid chromatography-mass spectrometry (LCMS) is used for result confirmation to test for the following drugs: opiates, oxycodone, fentanyl, barbiturates, benzodiazepines, cocaine, amphetamine, methamphetamine, marijuana (THC), methadone, and ecstasy (MDMA). Monthly UDS data collected at the OTP will be documented into the UDS CRF at each monthly study visit via medical record review. Any UDS results demonstrating ongoing opioid use or other illicit/nonmedical substance use (e.g., cocaine) will be reported to the site PI to determine whether the participant should continue in the study.

Timeline Followback (TLFB): The Timeline Followback (TLFB) assessment will be used to collect self-reported information on substance and alcohol use over a 30-day look-back period, for which it has shown high test-retest reliability and validity (Sobell and Sobell 1992; Sobell and Sobell 2000). Participants will be asked to report daily substance and alcohol use since the previous TLFB assessment at the Intake/Baseline Visit and each monthly research visit. If a participant discontinues study participation early, the TLFB assessment also will be administered at the Early Termination Visit.

4.4.4. Methadone Treatment Assessments

Methadone Visit Checklist: This form will be completed by the study pharmacists to document all study medication administered and dispensed at each Pharmacy visit, including the daily prescribed dose of methadone and the lot number and expiration date of administered/dispensed medication. This form also will be used to document pharmacist-provided care, such as (1) performing methadone prescription reconciliation, (2) providing patient education (e.g., safe storage, medication side effects); (3) checking and recording the patient's controlled medications prescription status using the NC Controlled Substances Reporting System [CSRS]); (4) monitoring and recording safety related events/concerns and communicating with the OTP medical physician or staff promptly regarding the event/concern; and (5) administering one methadone dose at the pharmacy and dispensing methadone according to the prescription of the OTP physician and applicable federal/state guideline for methadone treatment for opioid use disorder. Communications between the study pharmacist and the OTP medical physician or staff will be documented on the form, such as reasons for changes in methadone doses and/or take-home schedule.

Methadone Call-Back: The OTP medical staff (e.g., nurse) will implement the call back procedure. This form will collect the written results provided from the OTP medical staff to document the outcome of each random methadone call-back visit during the study period (i.e., at least once for every study participant after the first methadone dispensing by study pharmacist(s)), including the amount of used and unused medication returned. Failure to successfully complete call back result in termination from the study and return of the participant to the OTP for further assessment and ongoing treatment. This Methadone Call-Back form will include questions assessing whether a random methadone call-back visit is completed, its date, and the outcome of the call back (e.g., brought back all does or not). The OTP staff is required to sign and date the form that a call back was done and its results (e.g., brought back all doses or not).

Treatment Satisfaction Survey: Participants, pharmacists and methadone treatment 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 5-point Likert scale: 0 = very dissatisfied, to 5 = very satisfied) that is completed by study participants at each study visit (1-4), 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 Methadone 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 participant discontinues study participation early), or at the LAST visit at the pharmacy for methadone administration and dispensing, which will occur about 3 months after the first pharmacy visit. Remote/virtual interviews by phone or the Duke-approved teleconferencing platform for research 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.

Methadone Treatment Education Feedback Questionnaire: We will collect the opinions of pharmacists and OTP physicians about the clarity and utility of the study training materials, as well as any lack of useful information from the training. The questionnaire will consist of specific questions on the training modules to be rated on a 5-point Likert Scale of satisfaction, and will be filled out at the end of the training phase and once all participants have completed the study. The results will be used to structure training materials for a subsequent clinical trial.

4.4.5. Process measures (qualitative interviews)

The pilot study seeks to evaluate the acceptability and feasibility of having pharmacists administer methadone therapy under the supervision of OTP physicians to 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 OTP treatment to a pharmacy environment is crucial and will be adopted as a process measure. The Treatment Satisfaction Survey administered during the study to participants, pharmacists, and physicians will inform the link between treatment process and outcomes.

Additionally, at the end of the pilot study, we will conduct a qualitative interview of participating OTP's staff (e.g., physicians/medical staff, nurses, counselors), pharmacists, and study participants at the end of the study about barriers and facilitators of implementing this pilot program of pharmacy-based dispensing of methadone for the OUD maintenance care. The information will be critical to informing the future designs of the pharmacy-based dispensing and supervised methadone consumption program, including its multisite clinical trials. These interviews may be completed in-person at the OTP/pharmacy or remotely via phone or a Duke-approved teleconferencing platform.

4.5. Methadone diversion policy and prevention for diversion risk

4.5.1. OTP programs: Study participants will follow the OTP program's routine methadone diversion policy (Morse Clinic of North Raleigh, NC; Morse Clinic of Zebulon, NC), which requires patients to have active working phone numbers that the medical staff (e.g., nurse) will call when Methasoft randomly selects patients whose dispensed take-home doses have been recalled. All recalled doses must be returned to the program within 24 hours for staff inspection.

- For this study, each study participant must have at least one Methadone Call-Back selected at random after the first methadone dispensing at the pharmacy.

4.5.2. Community pharmacy: The pharmacy (Health Park Pharmacy, Raleigh, NC) will adhere to the following procedures to avoid any possible confusion and to reduce the chance of diversion.

- Prior to participating in this research study, the pharmacy will brief all employees regarding the nature of the study, its purpose, and each participant's role in the study. This will include all new employees hired during the course of this study.

- Prior to the start of this research study, the pharmacy will obtain documentation from the participating prescribing practitioners confirming each has been granted an exception by DEA to 21 C.F.R. §§ 1306.07(a)and 1306.04(c)), thereby allowing these practitioners to issue prescriptions for methadone to the patients of the study for the purpose of opioid maintenance.

- Health Park Pharmacy will consult with their local DEA field office to determine what additional physical and alarm security, if any, will be necessary for participating in this study.

- When the pharmacy receives a prescription as part of this study, the dispensing pharmacist will review each prescription to ensure it contains all required information as outlined in 21 C.F.R. § 1306, and will not fill such prescriptions if the required information is lacking. The prescription will include both the prescribing practitioner's DEA registration number and the DEA registration number of the participating OTP.

- Pursuant to 21 C.F.R. § 1301.71(a), the dispensing pharmacist will confirm the patient's identity prior to dispensing methadone in response to each such prescription, and will confirm the patient remains part of the research study. The OTP will also notify the participating pharmacies each time a patient is removed from the research study and returned to routine care at the OTP.

- Pharmacy staff will direct all patients who present in the pharmacy earlier or later than the scheduled visit date to the OTP for evaluation and medication. The Pharmacy staff will also contact the OTP to inform them of this development.

- The pharmacist will provide patient education regarding dose administration and safe storage of methadone.

- The pharmacist who dispenses the methadone will review and confirm what is dispensed, and will observe the patient take the first dose prior to the patient's departure from the pharmacy.

- Methadone will be dispensed in child-proof bottles that are properly labelled.

- The pharmacy will communicate with the participating OTP and make them aware of any concerns they note during the course of this study. Any indication of drug misuse or diversion will prompt the pharmacy to direct the patient to the participating OTP for evaluation and medication.

- Pursuant to 21 C.F.R. § 1301.74(c) the pharmacy will notify their local DEA field office within one (1) business day of discovery of any theft or significant loss of methadone for this study.

- The practitioners in this research study have been advised that the exception granted to them will end twenty-four (24) months from the date of their letter, or sooner if the research study ends prior to that date.

5. Study duration and number of study visits required of research participants.

Study participation includes the baseline assessment and three monthly follow-up research assessments. As noted above, participants will be asked to complete study specific assessments at baseline and months 1 through 3 following the administration of the first methadone dose at the pharmacy.

6. Blinding, including justification for blinding or not blinding the trial, if applicable.

This is a pilot demonstration study. All participants will be assigned to the same treatment condition.

7. Justification of why participants will not receive routine care or will have current therapy stopped.

The enrolled participants will receive their methadone under the supervision of study pharmacist during the study period. All other aspects of routine care will remain the same. Study participants will attend the pharmacy the same number of times/week as required at the OTP at the time of study enrollment for methadone administration and dispensing of take-home doses. Study participants will continue to receive their usual care at the OTP (e.g., counseling, prescription orders, urine drug screen), and they will return to their OTP at the end of the study. Study participants will also be able to, alternatively, withdraw from participating in the study at any point during the study period.

8. Justification for inclusion of a placebo or non-treatment group.

There is no placebo or non-treatment group in this study.

9. Handling of missed visits and substance use

Although the study participants will be stable patients, it is possible that they relapse to illicit drug use which may be manifested by missing appointments. It is also the possibility that scheduling conflicts may occur during the study, which will be addressed as described below.

- **If a participant presents to the pharmacy for take-home methadone administration/dispensing earlier or later than their scheduled visit date**, pharmacy staff will contact the prescribing physician (Site PI) before any medication is administered/dispensed to determine the course of action. Participants will be directed to the OTP for evaluation and medication administration/dispensing for that visit. Pharmacy staff will contact the OTP and the site PI to inform them of this development and document the event in the **Methadone Visit Checklist**. Possible outcomes of this evaluation may include:
  - (1) return to pharmacy dispensing condition,
  - (2) return to routine OTP methadone dispensing, or
  - (3) loss of some or all of take-home methadone privileges for up to 6-months**.**

  The outcome of the evaluation will be communicated the pharmacy and research staff as soon as possible.

- **If the participant fails the OTP program's routine methadone take-home recall procedure during the study or any tampering/diversion is suspected**, the participant will be discontinued from the study and returned to the OTP for methadone dosing and adjustment of their take home schedule as determined by the OTP provider.

- **If illicit or non-prescribed opioid use is reported, found on drug testing, 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 and referred to the study physician for an assessment and to determine whether the participant should continue in the study.

- **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 will result in early termination from the study and return to the OTP for methadone dosing and possible adjustment of the take home schedule.

Missing monthly research assessment visits and the rule for early study termination

- If the participant misses a scheduled monthly research assessment visit, alternative visits will be scheduled to collect the data.

- Missed visits will be documented using the Missed Visit Form. Remote/virtual interviews by phone or a Duke-approved teleconferencing platform for research may be used to collect study assessments for missed visits.

10. Participant Discontinuation

All participants will be followed for the duration of the study (approximately 3 months for pharmacy OUD maintenance) unless they withdraw consent, stop the methadone medication for OUD, die, or the investigator or sponsor decides to discontinue their enrollment for any reason. In addition to what is

described previously (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 early termination of the study for safety reasons. Of note, participants who discontinue methadone 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.

11. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

Following the end of participation in the study, either at 3-months following the first pharmacy dose or sooner for cause, participants will continue to receive all available routine care, with dispensing of methadone within the Morse Clinic OTP program.

12. Drugs/Substances/Devices

- **The rationale for choosing the drug and dose or for choosing the device to be used:**
  The study is investigating the feasibility of administering and dispensing methadone to opioid-dependent patients in a pharmacy setting, and its acceptability to participants, pharmacists and OTP treatment staff.

  The study will **not** evaluate a device.

- **Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed:**
  Not Applicable.

- **Justification and safety information if non-FDA approved drugs without an IND will be administered:**
  Not Applicable.

13. Study Statistics

13.1. Primary outcome variable

- **Treatment adherence:** Adherence to medication is defined as the proportion of participants receiving their scheduled methadone dose administration and methadone dispensed at the pharmacy pickup out of the methadone prescribed. Treatment adherence will also be checked randomly by a methadone dose call-back (at least once during the study period). Failure to attend the random methadone dose call-back visit will be considered as an indicator of non-adherence.

13.2. Secondary Outcome Measures

- **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 pharmacy follow-up 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.
- **Treatment retention in follow-up assessments:** Retention in follow-up assessments is defined as the proportion of study assessments completed (three follow-up assessments).
- **Opioid and other substance use:** The prevalence and frequency of opioid/heroin use and other substance use over the study duration will be examined.
- **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.

- **Participant safety, as measured by:**
  a) Any fatal or non-fatal substance use-related overdose measured by self-report.
  b) Any substance use-related ED visit or hospitalization measured by self-report.

13.3. Statistical plan and data analysis.

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 the OTP and pharmacist can ensure standard methadone treatment for Opioid Use Disorder).

Because this is a non-randomized pilot study with a small sample size, descriptive analyses will be conducted to describe distributions of primary and secondary outcome measures. Generalized estimating equation (GEE) models will be considered and used to assess outcomes that are measured repeatedly throughout the study follow-up phase.

14. Early stopping rules.

The study may be modified, suspended, or terminated at the recommendation of the Study PI or the Duke IRB. This might occur if the community pharmacy experiences unexpected difficulties in administering and/or dispensing methadone. At the very least, new enrollment in the study would likely be suspended until this unanticipated outcome was fully reviewed by the investigator team and the Duke IRB, in consultation with the NIDA Program Official (as needed).

15. Risks

15.1. Medical risks, listing all procedures, their major and minor risks and expected frequency.

This small pilot study will recruit clinically stable and well-functioning patients that receive up to 13 take-home methadone doses at one time. Medical risk as well as the methadone diversion risks are low.

15.2. Steps taken to minimize the medical and diversion risks.

(1.) As mentioned in the section 4.3, this study includes **several safety assessments** to collect the safety information or indicators from each participant monthly in order to identify and address safety issues timely. Safety assessments include Patient Health Questionnaire (PHQ-9, depression screen), P4 Screener (suicide risk screen), Pregnancy and Birth Control Assessment, and Safety Event Response Checklist.

As methadone is an approved medication being prescribed in accordance with the approved usage, there would be no need to capture Adverse Events (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 with solicited symptom information, yes/no responses, and level of severity (mild, moderate, severe) will be developed. The checklist will be used by research staff to obtain self-reported information from each participant at each monthly research visit. The data will be captured electronically in the database. The Manual of Operating Procedures (MOP) will specify the process of reporting safety events that may require interventions (such as dosing, side effects, etc.) to study physician (Site PI) and pharmacists, as well as to Study PI.

- 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 methadone compliance. Side effects of the medication

may include but are not limited to: headache, nausea, vomiting, constipation, excessive sleeping/insomnia, excessive sweating, pain, swelling, and overdoses.

(2.) In addition, we will collect all Emergency Department (ED) visits, hospitalizations, overdose, and death of any participant who provided written informed consent.

- Non-fatal overdoses since the last visit will be captured via self-report using the Safety Event Response Checklist at the Intake/Baseline and each monthly research visit following consent (or the Early Termination Visit participant discontinues study participation early). Research staff will report overdose events to PI and Site PI (Dr. Morse) to terminate the participant from the study and return the participant to the OTP for medication administration, change in take home regimen, and other appropriate intervention.

- Data on fatal overdoses may be collected via medical chart record review, if medical records data is available, at Visit 4 (or the Early Termination Visit if the participant discontinues study participation early). This will be supplemented with information from contacts 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.

- 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 using state medical examiner records, National Death Index, and/or review of medical records. Deaths will be reported using the Safety Event Response Checklist.

(3.) Urine drug screens (UDS) will be collected by the OTP clinic at Intake/Baseline, at each monthly research visit (1 month, 2 months, and 3 months following study intake), and/or as needed based on clinical decision.

- In this study, UDS results demonstrating ongoing opioid use or other illicit/nonmedical substance use (e.g., cocaine) will be reported to the site PI to determine whether the participant should continue in the study.

- If illicit or non-prescribed opioid use is reported, found on drug testing, or suspected at any time during treatment, the participant will be contacted to perform at least one random UDS (as needed) prior to the next scheduled visit and referred to the study physician for an assessment and to determine whether the participant should continue in the study.

- 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 will result in early termination from the study and return to the OTP for methadone dosing and possible adjustment of the take home schedule.

(4.) Measures of adherence will be monitored and assessed, including: (1) adherence to scheduled pharmacy visits for dose administration and take-home pickup and (2) success in methadone call-back (e.g., failed methadone dose call back as an indicator treatment non-adherence). Failure to attend the random methadone dose call-back visit will be considered as an indicator of non-adherence.

- If the participant fails to return to the pharmacy for the random methadone call back visit during the study or any tampering/diversion is suspected, the participant will be discontinued from the study and returned to the OTP for methadone dosing and adjustment of their take home schedule as determined by the OTP provider.

- If the participant misses two consecutive visits, 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 OTP clinic.

15.3. Plan for reporting unanticipated problems or study deviations.

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 PI and/or site PI according to the Manual of Operating Procedures. 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 Monitor (Paolo Mannelli, MD) will review or provide consultation for each safety event as necessary. The study Medical Monitor, study PI, and site PI 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. 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-intervention outcomes.

- Serious adverse events (SAEs) will be reviewed by study Medical Monitor and discussed with PI, Site PI and other investigators, and reported to the Duke IRB based on the current Duke IRB policy:
  - Immediately (within 24 hours) upon learning of an unanticipated study-related death, study personnel will notify the IRB via phone or email by providing a brief summary of the event. Then within 1 week (5 business days), study personnel will send to the Duke IRB a Safety Event submission.
  - For a reportable serious adverse event, study personnel will notify the IRB within five (5) business days of the investigator becoming aware of the event. Study personnel will send a Safety Event submission to the Duke IRB.
  - For any other problem or event requiring prompt reporting to the Duke IRB, within ten (10) business days of the investigator becoming aware of the event, study personnel will send to the Duke IRB a Safety Event submission.
- For the purposes of this study, any attempts to divert methadone will be recorded as an SAE and reported according to the above guidelines). Study PI (Dr. Wu) is responsible for informing NIDA of any actions taken by the Duke IRB as a result of its regular reviews of the project.
- Study PI will inform the NIDA Program Official immediately of any major change in the protocol or its status, such as suspension or termination of subject recruitment or of the protocol itself; changes in the informed consent or IRB approval status; and other problems or issues that could have a significant impact on participants. All changes to the protocol must be approved by the Duke IRB prior to implementation**.**

15.4. Legal risks such as the risks that would be associated with breach of confidentiality.

There is the potential for breeches in participant confidentiality. Whenever sensitive personal information is handled, there is a small risk of an accidental or intentional breach of confidentiality. To protect the confidentiality of study participants, all information collected as part of this study will be maintained in locked cabinets and/or secured project folders approved by Duke IRB. Research staff with access to this information must have completed IRB required training and study supervision in the protection of research confidentiality. No individually identifiable information will be released without prior and proper written authorization from study participants. All study staff will be trained in the rules and procedures of confidentiality and of the possibility of personal legal liability, should a breach of confidentiality occur.

15.5. Financial risks to the participants.

There are no financial risks to the participants.

16. Benefits

Description of the probable benefits for the participant and for society.

Study participants may enjoy the convenience of receiving methadone dosing at the community pharmacy, a setting which has longer daily hours of operation than the OTP clinic. Data from this study will be used to support further study of using community pharmacies to extend access of methadone treatment services to patients in both urban, and perhaps most important, rural areas.

17. Payment and Remuneration

Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Pilot trial: Each participant will be compensated for their time and transportation for the baseline assessment ($50) and the 3 follow-up research assessments ($50/each). Participants who sign the informed consent but they are found to be a screen failure (i.e., not meeting all inclusion criteria) will be compensated for $10 for their time.

Qualitative interviews following the pilot trial: Follow the completion of the pilot trial, qualitative interview will be conducted with study participants, pharmacists/staff, and OTP providers/staff to better understand barriers and facilitators of pharmacist dispensing methadone for opioid use disorder. Each participant will be compensated $50 for their time for participating in the qualitative interview.

18. Costs

Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

There will be no charge to study participants for receiving their methadone administration and dispensing through the pharmacy during the study. These costs of methadone medication dispensed at the pharmacy for the study will be paid by research funds from the National Institute on Drug Abuse, the National Institutes of Health (NIH).

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