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CRISM Protocol 001

Optimizing Patient Centered-Care: A Pragmatic Randomized Control Trial Comparing Models of Care in the Management of Prescription Opioid Misuse (OPTIMA Trial)

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1.0 LIST OF ABBREVIATIONS

This section contains a comprehensive alphabetical list of abbreviations used throughout the protocol document.

AE	Adverse Event
BUP/NX	Buprenorphine/Naloxone
CIHR	Canadian Institutes of Health Research
CNS	Central Nervous System
CRF	Case Report Form
CTN	Clinical Trials Network
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
E-CRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEG	Electroencephalogram
EOS	End of Study
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
MAOI	Monoamine Oxidase Inhibitors
NPI	Nominated Principal Investigator
NRC	National Research Coordinator
OAT	Opioid Agonist Therapy
OUD	Opioid Use Disorder
PI	Principal Investigator
PK	Pharmacokinetic
PO	Prescription Opioid
QA	Quality Assurance
QoL	Quality of Life
RCT	Randomized Control Trial
REB	Research Ethics Board
RPI	Regional Principal Investigator
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TCPS	Tri-Council for the Protection of Human Subjects
UDS	Urine Drug Screen
URCA	URCA Applied Clinical Research Unit

2.0 INTRODUCTION

Global use of prescription opioid (PO) analgesics has increased dramatically in recent years, and accidental deaths, harms and social costs associated with PO misuse and addiction have escalated in parallel, particularly in North America.(1-5)The United States and Canada report the highest PO consumption rates worldwide,(6) and opinion leaders across North America have identified PO misuse as a growing public health crisis. Although the US reports higher overall levels of consumption, PO use has increased at a much faster rate in Canada than in the US over the past 10 years (98% vs. 185%).(6, 7) Based on available data, PO-related harms (e.g. hospitalization, deaths due to overdose) have also increased substantially in Canada, and likely constitute the third-highest burden of disease attributable to substance use after alcohol and tobacco.(1) As a result, the prevention and treatment of opioid use disorder (OUD) in Canada has become an urgent public health priority necessitating an evidence-based response.(8-10)

There are a number of evidence-based options available for the treatment of OUD, but only two opioid agonist medications are currently approved in Canada for opioid agonist therapy (OAT), namely methadone and buprenorphine/naloxone (BUP/NX). Methadone has emerged as the standard of care in Canada, while in other jurisdictions including the United States, buprenorphine/naloxone is the predominant pharmacotherapy of choice for the treatment of OUD.(11, 12) Unfortunately, adherence to long-term maintenance treatment, either with methadone or buprenorphine/naloxone, is associated with a number of challenges that undermine the population impact of these treatments. For instance, because of its low therapeutic index, strict programmatic regulations (e.g. daily witnessed consumption) govern the initiation of methadone administration in most jurisdictions, and, for individuals with OUD, these requirements have consistently been reported to have a negative impact on motivation to participate in methadone maintenance treatment.(4, 13) In contrast, while the improved safety profile of buprenorphine/naloxone with respect to overdose can permit flexible take-home dosing, studies have also demonstrated significant barriers to uptake, also stemming from patient unwillingness to engage with long-term maintenance therapy.(14-16)

While long-term maintenance treatment with opioid agonists is considered the standard of care for the treatment of OUD, patient preference often reflects an inclination to progressively taper off pharmacotherapy.(16) In addition, research indicates that patients with OUD hold distinct attitudes and expectations with regard to methadone and buprenorphine/naloxone therapies, and that these preferences and attitudes can, along with factors such as treatment motivation, influence willingness to initiate OAT, program retention if OAT is started, and other relevant clinical outcomes.(17-19) Moreover, the external validity of previous results on the relative efficacy of buprenorphine/naloxone versus methadone in the treatment of prescription opioid (PO) users (as opposed to other types of opioid use such as heroin) has been shown to be limited (see Section 2.1, Relevant Systematic Reviews and Meta-Analyses).

To the best of our knowledge, no previous randomized trials have examined the relative benefits of buprenorphine/naloxone and methadone for PO use disorder when offered within a realistic model of care that is adapted to the respective safety profile of each medication and that is in line with current clinical practice guidelines and Health Canada-approved product monographs.(20) Therefore, questions remain as to how these medications perform in PO-dependent individuals under realistic treatment scenarios. For example, methadone (i.e., the Canadian standard of care) is initially provided via daily supervised ingestion for 2-4 months, at which point individuals who are considered reliable candidates (e.g. abstinent from illicit drug use or with other positive treatment outcomes consistent with provincial guidelines) can receive take-home doses on a

case-by-case basis at their care provider's discretion. Many provincial prescription standards and guidelines for methadone will also stipulate requirements on the rate of attribution of take-home privileges and on the frequency of urine drug screens (UDS), physician follow-up appointments, and dosing changes (including prescription cancellation after multiple missed doses). By comparison, the Canadian product monograph for buprenorphine/naloxone allows for a more flexible take-home dosing schedule, at the discretion of the treating physician without requirements for complete abstinence as long as there is reasonable stability such as for housing, etc. These less rigid requirements are also outlined in many provincial OAT standards and guidelines.

Pragmatic trials have recently emerged as a strategy to examine the effectiveness of interventions delivered to heterogeneous patient populations in real-life treatment settings. As opposed to double-blind efficacy studies designed to maximize internal validity under ideal service delivery conditions, pragmatic trials incorporate, rather than eliminate or standardize, diversity in presenting patient characteristics (e.g. treatment preferences and attitudes, comorbidities) into the study design. This approach not only acknowledges diversity in program delivery but also attempts to model heterogeneity. All of these features are designed to enhance the external validity of the study results and, in doing so, to provide evidence to inform real-life programs and policies.(21, 22)

2.1 Relevant Systematic Reviews and Meta-Analyses

A Cochrane library systematic review comparing buprenorphine maintenance treatment to placebo and methadone maintenance treatment in individuals with OUD was first published in 2008.(23) In the most recently updated version (2014), Mattick et al.(20) included 31 randomized controlled trials, 22 of which compared buprenorphine or buprenorphine/naloxone to methadone. Primary outcomes were retention in treatment and suppression of illicit opioid use, as determined by urinalysis for opioids and/or self-reported heroin use. The included studies about buprenorphine or buprenorphine/naloxone versus placebo or methadone were stratified into flexible or fixed dosing schedules, with fixed schedules further categorized into low, medium, and high doses. In addition, all 22 studies comparing methadone to buprenorphine maintenance therapy utilized near-identical double-blind designs with rigid dispensing schedules for both treatments (e.g. daily dosing or multiple times per week).(20) This review demonstrated that buprenorphine/naloxone is an effective maintenance treatment, with significantly higher retention rates at all doses above 2 mg, and reduced illicit opioid use at high doses compared to placebo. In comparison to methadone, buprenorphine retains fewer patients at low fixed doses or when doses are flexibly delivered. Importantly, no difference was observed in patient retention in medium to high fixed dose studies. Both treatments were equally effective in suppressing illicit drug use across all fixed and flexible doses studied. Of note, this review was not specifically designed to focus on PO use disorder.

In 2016, Nielsen et al. published another Cochrane review specifically on OAT for individuals with PO use disorders, including only 6 randomized controlled trials (RCTs).(24) Three studies comparing different opioid maintenance treatments (methadone versus buprenorphine) had an average duration of 24 weeks. They found little to no difference between how well methadone and buprenorphine reduced opioid use, worked to retain patients in treatment, or side effects. They also concluded that buprenorphine probably keeps more people in treatment, may reduce the use of opioids, and has fewer side effects compared to detoxification or psychological treatment alone.(24)

While authoritative, some unresolved issues remain beyond the scope of the Cochrane reviews. As noted above, and perhaps most relevant to the modern opioid epidemic, the large majority of

trials focused largely on heroin users rather than prescription opioid users. As such, it is not known how these medications compare in real-life settings in Canadian health services where methadone is initially provided via daily witnessed ingestion vs. buprenorphine/naloxone provided with more flexible take-home dosing.

2.2 Study Rationale

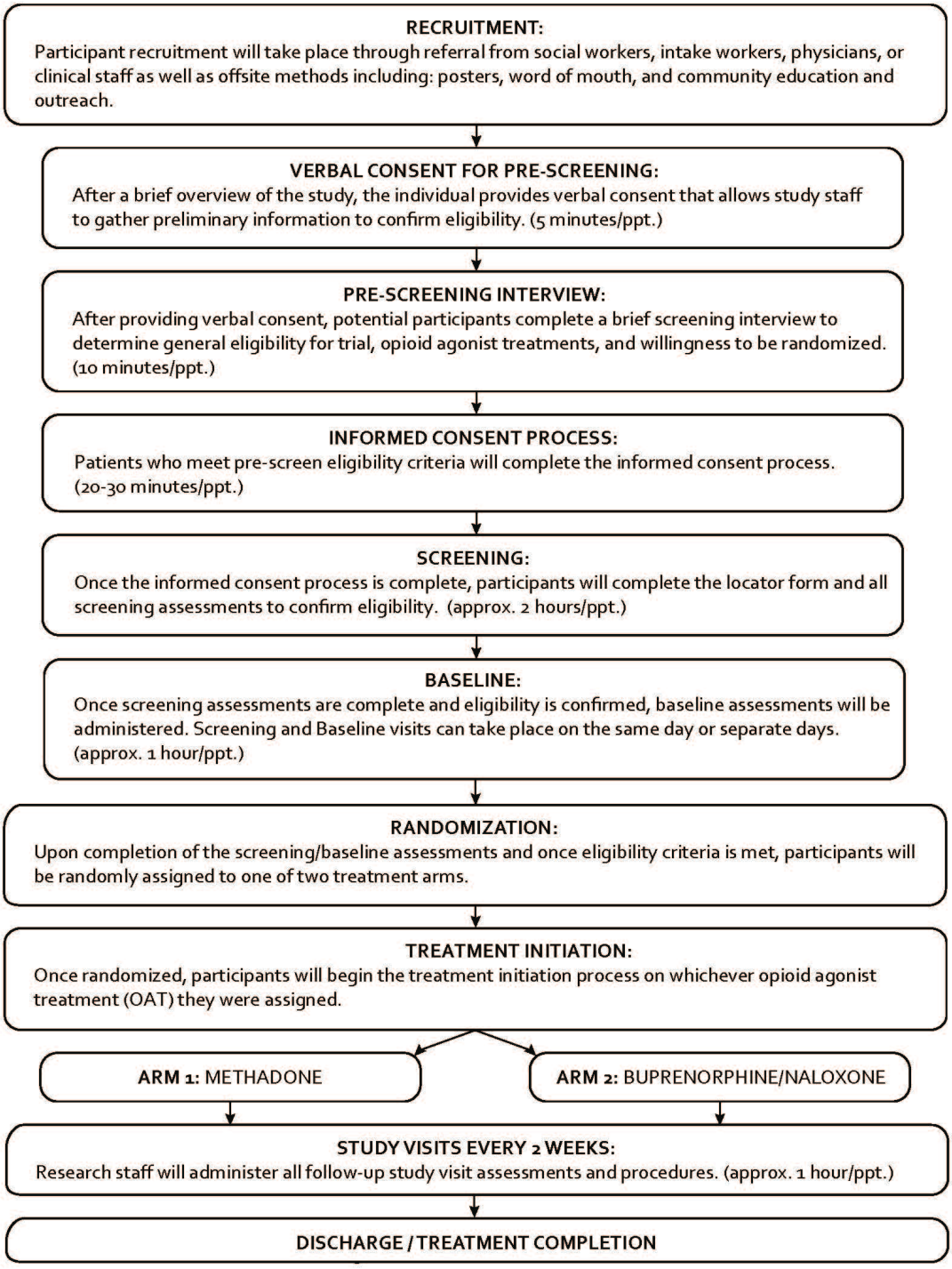
The premise of this study is that optimizing OUD treatment requires a shift in emphasis toward effectiveness studies designed to evaluate the relative benefit of different models of care under conditions that more closely approximate real-life treatment programs. Although methadone has long been the standard of care for treatment of OUD in Canada, there is growing consensus that the superior safety profile of buprenorphine/naloxone, as well as other comparative advantages, supports its use as a first-line OUD therapy. To our knowledge, no previous randomized trials have examined the relative benefits of buprenorphine/naloxone and methadone when offered within a realistic model of care, adapted to the respective safety profiles of these medications and in line with current clinical practice guidelines and product monographs approved by Health Canada.(20) Thus, questions remain as to how these medications perform in individuals with PO use disorder under realistic treatment scenarios, especially in reducing opioid use and retention in treatment, as well as side effects.

We propose an open-label, pragmatic, randomized trial, which will compare the two models of care in the management of PO use disorder.

2.3 Significance to the Field

There is an urgent need for evidence-based treatment solutions to address the rise of prescription opioid misuse and related harms in Canada. This study aims to provide evidence supporting model-of-care optimization for individuals who have become dependent on, and are actively using, prescription opioids. The overarching goal is to evaluate methadone vs. buprenorphine/naloxone treatment options within a Canadian practice-based framework, generating evidence that is directly relevant to a recognized national priority in public health. Evaluating the impact of these two therapies in real-life settings and exploring several outcomes will generate new practice-based evidence that is of direct relevance for front-line service providers.

3.0 STUDY FLOW CHART



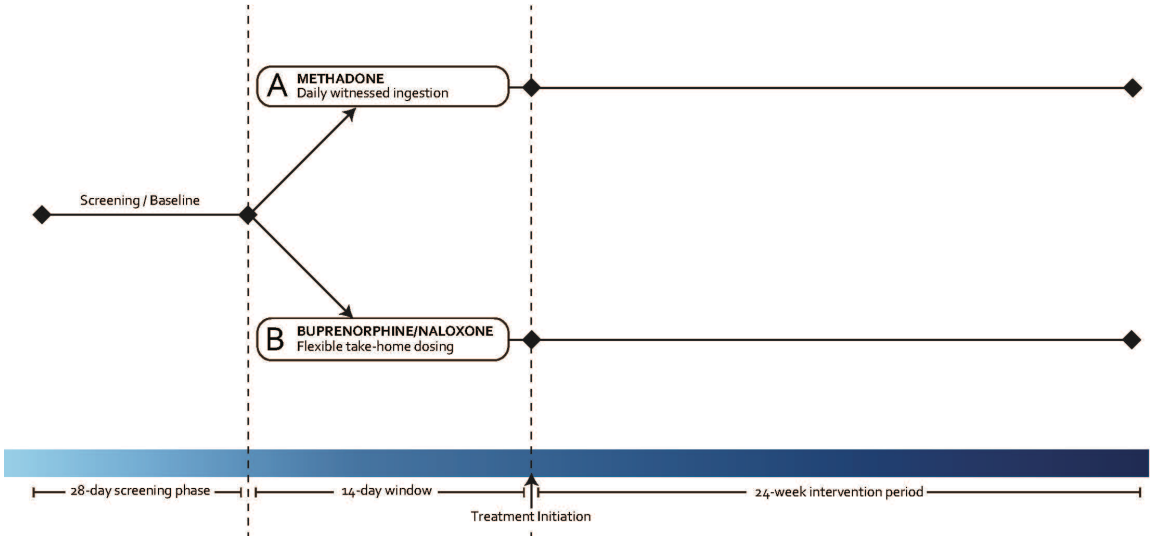
4.0 STUDY DESIGN

This is a multicentre, open-label, 2-arm, randomized trial with a pragmatic design involving 276 individuals with prescription OUD. Participants will be randomized to receive either:

a) Methadone provided via initial daily witnessed ingestion as per local guidelines; or
b) Buprenorphine/naloxone maintenance therapy provided via flexible take-home dose regimens dispensed as per the physician's discretion once clinical stability is achieved.

Once randomized to a study medication and the treatment initiation process has begun, study physicians and participants will discuss the treatment plan and procedures going forward. Once the treatment initiation visit has taken place, the participant will attend study visits every 2 weeks (including collection of urine samples) for the 24-week intervention period. For all study sites, standardized guidelines exist for the safe induction of both medications, and these will be adhered to in both arms of the study.

Figure 1 - OPTIMA Design



4.1 Duration of the Study

Each participant will participate in the study for up to 28 weeks, including a 24-week intervention period and up to 28 days between screening and randomization (Figure 1), as follows:

- Informed consent, screening assessments, confirmation of eligibility criteria, baseline assessments and randomization to treatment arm, to be completed within 28 days. Screening assessments, baseline assessments and treatment initiation may take place on the same day.
- The time from randomization to treatment initiation can last a maximum of 14 days. If the allocated treatment is not initiated before the end of this 14-day window the participant will be considered a treatment initiation failure.
- The intervention period is 24 weeks beginning from the day of first ingestion of assigned treatment or other form of OAT (e.g. slow release oral morphine, injectable opioid agonist

treatment), as long this occurs within the 14-day window. If no OAT is started within this window, the intervention period will start on day 15 after randomization.

5.0 STUDY OBJECTIVES & HYPOTHESIS

5.1 Primary Objective

The primary objective of the trial is to compare the effectiveness of methadone versus buprenorphine/naloxone models of care in suppressing illicit opioid use in real-life clinical practice settings in individuals with prescription OUD.

5.2 Primary Hypothesis

Buprenorphine/naloxone flexible take-home dosing is non-inferior to methadone standard model of care in treating prescription OUD, as measured by the mean percentage of opioid-free urine drug screens over the 24-week intervention period.

5.3 Secondary Objectives

The secondary objectives measure differences between study arms in:

1. Retention in treatment
2. Safety
3. Medication adherence
4. Treatment satisfaction
5. Patient engagement

5.4 Exploratory Objectives

The exploratory objectives measure differences between study arms in:

1. Cost-effectiveness
2. Quality of life
3. Pain
4. Proportion of participants who initiate taper

In addition, we will also explore predictors of treatment success, employment, interaction with the criminal justice system, mental health, risk behaviours, self-reported use of other substances and related problems, and other health-related outcomes.

6.0 STUDY POPULATION

6.1 Participant Inclusion Criteria

Participant must meet ALL the following criteria:

1. Be aged between 18 and 64 years of age, inclusively;
2. Be diagnosed with prescription opioid use disorder (as defined by the DSM-5 criteria) which requires opioid agonist therapy as per the discretion of the physician;
3. If female:
    a. Be of non-childbearing potential, defined as (i) postmenopausal (12 months of spontaneous amenorrhea and ≥ 45 years of age); or (ii) documented surgically sterilized (i.e., tubal ligation, hysterectomy, or bilateral oophorectomy); or

   b. Be of childbearing potential, have a negative pregnancy test at screening, and agree to use an acceptable method of birth control throughout the study;
4. Be willing to be randomized to 24 weeks of either methadone or buprenorphine/naloxone adapted model of care, and to be followed for the duration of the trial;
5. Be able to provide written informed consent;
6. Be willing to comply with study procedures;
7. Be able to communicate in English or French.

6.2 Participant Exclusion Criteria

Participants will be excluded if ANY of the following criteria are met:

1. Any disabling medical condition, as assessed by medical history, physical exam, vital signs and/or laboratory assessments that, in the opinion of the study physician, precludes safe participation in the study or the ability to provide fully informed consent;
2. Any disabling, unstable or acute mental condition that in the opinion of the study physician precludes safe participation in the study or ability to provide fully informed consent;
3. Heroin reported as the most frequently used opioid in the past 30 days;
4. Methadone or buprenorphine/naloxone use as maintenance OAT in the four weeks prior to screening;
5. Pain of sufficient severity as to require ongoing pain management with opioids;
6. History of a severe adverse event, hypersensitivity reaction, or allergic reaction to either methadone or buprenorphine/naloxone;
7. Pregnancy, nursing, or planning to become pregnant during the study period;
8. Current or past use of an investigational drug in another study in the last 30 days, confirmed via self-report;
9. Pending legal action or other reasons in the opinion of the study physician that might prevent completion of the study;
10. Presence of a substance use disorder that, in the opinion of the study physician, precludes safe participation in the study (e.g. unstable or severe alcohol use disorder, unstable or severe benzodiazepine use disorder);
11. Current treatment with medications that may interact with either methadone or buprenorphine/naloxone (e.g. clonazepam, benzodiazepines) OR anticipation that the patient may need to initiate pharmacological treatment during the trial that is deemed unsafe by the study physician or could prevent study completion.

6.3 Study Population

The study will be implemented at various sites in four Canadian regions, or Nodes: British Columbia, Alberta, Ontario, and Quebec. Study participants will meet DSM-5 Diagnostic Criteria for Opioid Use Disorder primarily attributed to prescription opioids. Participants will be required to meet all inclusion and exclusion criteria (see Section 6.6, Site Selection). The total number of participants will be 276 (138 participants per arm).

6.4 Participant Recruitment

A total of 276 participants will be randomized. Clinic staff at all sites will be informed of the study and may inform potential participants. Those interested in learning more about the study will be referred to research staff for a pre-screening interview. Prior to administration of the pre-screening questionnaire, verbal consent will be obtained. During the verbal consent process, a brief overview of the study and of opioid agonist therapy will be provided. If full comprehension is verified and verbal consent is obtained, research staff will proceed with the pre-screening

questionnaire to determine general eligibility. The purpose of this pre-screening process is to minimize screening failure rates. If the participant meets all general eligibility criteria, a screening visit will be scheduled, full informed consent will take place and screening assessments will be administered. Study visits may be conducted in person or remotely over the telephone (in the case of incarceration or hospitalization). Specific recruitment methods (e.g. community outreach, engagement of peer recruiter, emergency department referral, and print advertisements) will be employed by sites according to local recruitment needs. Strict ethical guidelines regarding professional conduct and confidentiality will be enforced by all study staff in accordance with local Research Ethics Board (REB) policy and procedures.

6.5 Special Populations to Consider

This study may enroll persons involved in the criminal justice system who are receiving care at any of the clinics where the study will recruit. This study will not recruit persons incarcerated or detained in a correctional facility but will not exclude parolees, probationers, or persons in sentencing diversion. Research staff will make best efforts to follow up with participants for study visits in the case of incarceration. Opioid agonist treatment may be continued as per local regulations. If necessary, and for the safety and with the permission of the participant, correctional facilities will be informed of study participation. Whenever possible, participants will be contacted to complete questionnaires, which would include safety assessments. These visits can occur over the telephone or as an in-person visit according to local regulatory policies. The visit will only occur if confidentiality can be strictly maintained. No biospecimens (urine samples) will be collected from incarcerated participants and all additional study documents administered to the incarcerated participant will be approved by the local REB (e.g. contact letters, appointment reminders). All interactions with the participant will be recorded in the participant's progress notes, specifically mentioning how confidentiality was maintained on the study visit.

6.6 Site Selection

6.6.1 Number of Sites

The study will be implemented in sites spanning the four Canadian Nodes, each led by the CRISM Nominated Principal Investigators (NPIs) and Regional Principal Investigators (RPIs). Each Node will select between 1 and 3 participating study sites. A total of 276 participants will be randomized over a target 18-month enrolment.

6.6.2 Site Characteristics

Sites will be selected on the basis of the following characteristics:

1. Provide opioid agonist therapy;
2. Have physicians who are able and willing to prescribe methadone and buprenorphine/naloxone according to Health Canada-approved product monographs and provincial guidelines, and accept to adhere to study procedures;
3. Have a sufficient population of potential participants to achieve study enrolment targets;
4. Have access to a pharmacy (or to community pharmacies) within their region that provides both buprenorphine/naloxone and daily witnessed ingestion of methadone.

6.6.3 Rationale for Site Selection

Nodes will need to select sites based also on their predicted ability to recruit, enroll and retain study participants. Each site will complete a feasibility questionnaire identifying patient population, resource availability, and experience conducting clinical research. The sites selected for

participation will have an adequate number of participants with prescription OUD who have not been maintained on either methadone or buprenorphine/naloxone in the 4 weeks prior to enrolment in the study, and who do not require pain management with a prescription opioid medication.

7.0 STUDY PROCEDURES

7.1 Recruitment

Individuals are recruited via referral from either the existing patient population at the site or from offsite locations (e.g. withdrawal management facilities, hospital, self-referral, etc.). Interested individuals will approach study staff by contacting sites (in person or telephone) or will be approached by study staff in the clinic setting. Study staff will provide a brief summary of the study and continue with the pre-screening interview process.

7.2 Pre-screening

Once the interested patient makes contact with research staff, verbal consent will be obtained and a pre-screening questionnaire will be administered to determine general eligibility for the trial. If general eligibility is confirmed, a screening visit can be scheduled. The verbal consent and pre-screening questionnaire will take approximately 10-15 minutes to complete. Information gathered in the pre-screening questionnaire will not be entered into REDCap electronic data capture (EDC) forms and will be recorded on paper source only. The primary purpose of the pre-screening questionnaire is to reduce screening failures at each site. A pre-screening log will be maintained by each site coordinator and stored in a secure location accessible only by research staff.

7.2.1 Informed Consent Process

Verbal consent will take place during the pre-screening interview and written informed consent during the screening visit. At the pre-screening interview, research staff will determine general eligibility and gather information on prescription opioid use. Those individuals who meet general eligibility criteria at the pre-screening interview will be invited to schedule a screening visit with a member of the research staff. During the screening visit, the candidate will provide written, informed consent (20-30 min). The research staff will review the consent form with the candidate. The candidate will then complete a consent quiz. The purpose of the consent quiz is to assess comprehension of the voluntary nature of participation, study purpose, study participation requirements, and risks and/or potential benefits of the trial. The research staff will review incorrect answers with the candidate until comprehension is exhibited. Once the participant signs the consent form, they will be offered a copy to keep for their records. Given the multisite nature of the trial, it is possible that ancillary studies will be proposed before or after recruitment begins. For this reason, during the informed consent process, we also will briefly provide a summary of each ancillary study and the participant will have the opportunity to consent to the respective ancillary study. During the consent process, research staff will also seek permission to contact the participant in the future about other research studies. Staff at research sites will follow standard operating procedures (SOPs) for obtaining written informed consent. The entire screening visit, including consent process and administration of screening assessments, may take up to 2 hours.

7.2.2 Locator Form

Participants will complete a Locator Form, which will be used to contact them to remind them of follow up visits and locate participants who cannot be found. When completing this form, participants will be asked to provide their full name, aliases, address, telephone numbers, personal health number (PHN), date of birth and contact information for two other persons. Permission will also be requested to obtain locating information for additional agencies or publically accessible databases as outlined on the form. In addition, participant contact information will be updated at every study visit for the duration of the trial.

7.2.3 Medical Release of Information

Study sites are required to obtain written authorization from participants for using protected health information. Participants will complete the Medical Release form at the screening visit, allowing study staff to review inpatient, outpatient, mental health, and substance use treatment records and/or pharmacy dispensing records. Each site will be responsible for communicating with their REB and obtaining the necessary approvals to ensure regulatory compliance. The purpose of the medical record review is to assess eligibility.

7.3 Screening and Baseline Measures

Once candidates have completed the pre-screening questionnaire, general eligibility is confirmed, and if the individual expresses interest in participating in the study, the screening visit will be scheduled. The pre-screening and screening visits can take place either on the same day or on different days (based on staff and potential participant availability). Candidates will be seen by both the research staff and the study physician during the screening visit. During the screening visit, research staff will obtain full written informed consent from the candidate (see Section 7.3.3). After consent is obtained, screening assessments will be completed to assess eligibility (see Table 1, Table of Assessments). The screening visit could take up to 2 hours to complete. Once screening assessments are administered and eligibility is confirmed, candidates will complete baseline assessments. Baseline assessments could take up to 1 hour to complete. Screening and baseline assessments can take place on the same day or separate days. If the participant is receiving care from a physician for either primary care or addiction treatment, the study physician will make all efforts to contact him/her directly, as part of the screening process, and discuss the trial and the patient's interest in participating.

Participants will complete the following assessments as part of screening visit:

- Informed Consent Process
- Medical Release of Information
- Locator Form
- Demographic Questionnaire
- For females: Pregnancy Test and Birth Control Assessment
- Urine Drug Screen
- DSM-5 Opioid Use Disorder Diagnostic Checklist
- Medical & Psychiatric History
- Concomitant Medications
- Physical Exam & Vital Signs
- Addiction Severity Index – Self-Report Form
- Non-Fatal Overdose Questionnaire
- Adverse Events

If all eligibility criteria are met, participants will complete the following baseline assessments:

- HIV History
- Brief Pain Inventory (BPI)
- Beck Depression Inventory (BDI)
- Beck Anxiety Inventory (BAI)
- Kessler Psychological Distress Scale (K10)
- EuroQol 5D-5L (EQ 5D-5L)
- EuroQol 5D-3L (EQ 5D-3L)
- Health Utilities Index (HUI)
- Health Service Utilization Questionnaire (HSU)
- Risk Behavior Survey (RBS)
- Brief Substance Craving Scale (BSCS)
- Timeline Follow Back (TLFB)
- Treatment Entry Questionnaire (TEQ)
- Control Preference Scale (CPS)
- Collaborate Questionnaire
- Adverse Events
- Blood work and ECG *(as per local standard of care)*

7.3.1 Demographic Questionnaire

A demographic questionnaire will be administered at the screening visit to collect basic demographic information (e.g. age, ethnicity, gender, education, housing). Demographic information that is sensitive to change over time will also be collected at each follow up study visit.

7.3.2 Non-Fatal Overdose & Opioid Agonist Treatment History

Information will be collected at screening on history of non-fatal overdose, lifetime use of opioid agonist therapy and take-home naloxone interventions. This questionnaire will also be used to verify eligibility criteria on opioid agonist treatments taken as maintenance in the past 30 days.

7.3.3 Collection of Biological Specimens

Blood work to assess safety will be ordered on an individual basis for each participant based on local standard of care guidelines for treatment initiation on opioid agonist treatment. Clinical blood samples will be collected, handled, processed, and analyzed at site local laboratories as per local practice. These laboratory findings may also be abstracted from the participant's medical record. Results for HIV and Hepatitis B and C serology may be abstracted from the medical records if testing was completed in the 6 months prior to the screening visit. If there is no record of HIV and viral hepatitis serology results in the past 6 months, participants will be offered testing during the screening period alongside pre- and post-screening counselling in accordance with local guidelines. Participants may refuse these tests without comprising their eligibility for the study. Urine specimens for drug screening will be collected at the screening visit and every 2 weeks for the 24-week intervention period. Results will be recorded on the appropriate case report form. Results from urine drug screens that take place as part of regular clinical care cannot be abstracted from the medical charts to use for research purposes.

7.3.4 Pregnancy Tests and Birth Control Assessment

A pregnancy test and birth control assessment will be conducted during the screening visit, and every 4 weeks for the 24-week intervention period. As part of regular clinical care, the study physician may also request an additional pregnancy test at any time during the study. Participants with a positive pregnancy test result at screening will not be eligible to participate in the study. Participants who test positive for pregnancy after inclusion in the trial will be withdrawn from the study. The investigators will ensure that referrals to addiction care in the community are made, so the participant can continue on OAT as appropriate. All actions will be in accordance with applicable federal and/or provincial regulations and guidelines.

7.3.5 DSM-5 OUD Checklist

The DSM-5 Opioid Use Disorder Diagnostic Criteria is a semi-structured, interviewer-administered instrument. This diagnostic tool will be administered during the screening visit to diagnose prescription OUD and determine eligibility; i.e. the participant must meet DSM-5 criteria for moderate to severe OUD.

7.3.6 Physical Examination for Medical Exclusion

As part of regular clinical care and physician assessment, consenting participants will undergo a physician screening, which will include:

a) Complete medical and psychiatric history;
b) Basic health indicators/vital signs (e.g. temperature, blood pressure, heart rate, respiratory rate, body height and weight);

Physicians may order an electrocardiogram (ECG) and/or other clinical labs to assess safety for treatment initiation on an opioid agonist therapy and as needed over the course of the study, in accordance with local standard of care guidelines. Information on vital signs will be collected both at the screening visit and 24 weeks (end of study) and recorded in a case report form.

7.4 Randomization

Once eligibility is confirmed, and baseline assessments are completed, participants will be randomized in a 1:1 ratio to receive methadone or buprenorphine/naloxone, using a stratified permuted block design, with blocks of varying sizes. Stratification will be made both at a site level and presence of lifetime heroin use. This will ensure relative balance across the 2 treatment arms and relative balance of treatments across study sites, while decreasing the likelihood of predictability of treatment assignment. The date, assigned treatment arm and participant identifier will be generated and registered in the EDC system. A Master Enrolment Log will be maintained containing participant's name, identifier, and assigned treatment arm and will be securely stored at the research site.

7.5 Treatment Initiation

Following randomization, participant's initiation of his/her assigned opioid agonist therapy will take place in accordance with local standard of care guidelines and Health Canada approved product monographs. For participants in the buprenorphine/naloxone arm, the participant can receive take-home doses once clinical stability is achieved as per the discretion of the study physician, and a safe place to store the medication is established and documented. The date and initial

dose[1] of methadone or buprenorphine/ naloxone given to the participant at treatment initiation will be documented in a case report form and later entered into the EDC system. Participants may initiate the treatment up to 14 days' post- randomization. If the participant does not initiate their assigned treatment within this 14-day window, this will be considered a treatment initiation failure, and clinical care will be provided as usual, irrespective of the assigned treatment arm. In such a situation, participants will not be withdrawn from the study and will be offered to continue to attend study visits, as appropriate.

7.5.1 Ancillary Treatments

Participants who experience symptoms of withdrawal prior to or during the early initiation phase of the assigned OAT may be treated with ancillary medications as per standard of care or at physician's discretion.

7.5.2 Adjunct Services

Referral to community agencies or other local treatment services may be offered to the participant for additional medical, psychiatric, and substance use services as needed (e.g. hepatology consultation for chronic viral hepatitis, HIV, primary care, psychiatric care). Information on healthcare service utilization will be collected at each study visit through participant self-report and recorded in the participants' progress notes and a case report form. Attendance to these referrals will not affect participation in the trial. All referrals and attendance to adjunct services (including addiction care) will be documented.

7.5.3 Diagnostic Procedures

Research staff will gather information on any medical procedures that have taken place during the 24-week intervention period (e.g. ECG, x-ray, blood work). If the participant reports a diagnostic procedure taking place since the last study visit, research staff will record this in a case report form and follow up and discuss with the participant any adverse events that may have taken place.

7.5.4 Physician Clinic Visits

All participants will receive medical management through the study physician as per regular standard practice. Clinic visits and research visits may take place on separate days or on the same day. Study physicians are expected to routinely review recent drug and alcohol use, co-prescribed medications, review medication side effects, encourage adherence to opioid agonist

[1] The initial dose(s) for buprenorphine/naloxone may be provided in one full dose or multiple doses depending on site-specific usual care practice. Participants may receive additional dose(s) of medication on day of initiation. In that case, the full first day dose of buprenorphine/naloxone will be considered the start dose.

treatment, and to support abstinence, if applicable. Participants will continue to receive any required health care services as per local standard of care, regardless of ongoing study participation.

7.6 Study Discharge Considerations for Continued Treatment

Close to the end of the 24-week intervention period (study completion), the research team will arrange continuation of treatment, as needed and as locally appropriate. All sites will have the responsibility of ensuring that participants receive appropriate care for their prescription opioid use disorder upon trial completion in order to avoid treatment disruption. Prior to study completion research staff will connect participants with physicians and care teams in the community as appropriate or within the programs at the site where the study is conducted. Each site will adhere to the standard operating procedures for participant continued care after the treatment phase.

7.7 Loss to Follow-up

The trial seeks to limit loss to follow-up through site-specific standard operating procedures outlining strategies for retention of participants. Research staff has extensive experience in retaining substance-using groups and have developed innovative ways of locating participants, which will minimize loss to follow-up rates. Participants considered 'loss to follow-up' (3 consecutive missed visits), the investigator will perform "due diligence" by documenting all steps taken to contact the participant (e.g. dates of telephone calls).

7.8 Premature Withdrawal from the Study

The Investigator or study physician can discontinue study treatment for any participant or withdraw the participant from the study if, he/she deems clinically appropriate or, due to either of the following reasons, including but not limited to:

1. Significant side effects that are likely to have been caused by the study medication;
2. Serious or unexpected AEs which would make further study medication dosing not in the participant's best interest;
3. Inability or lack of willingness of the participant to comply with the study protocol;
4. Serious concomitant illness.
5. Pregnancy

Participation is entirely voluntary and participants may withdraw from the study or end the study medication at any time. If the participant stops his/her medication, he/she will be invited to remain in the study and continue to attend study visits for the purpose of the intention-to-treat analysis. All participants who discontinue from the study prematurely, regardless of the reason, will be asked to complete the end of study assessments. Participants who are prematurely withdrawn from the study will not be replaced with an equal number of newly enrolled participants. Attempts will be made by research staff to follow up participants for the duration of the study unless he/she withdraws consent.

7.9 Study Halting Rules

The decision to stop the trial can be made by the Data Safety Monitoring Board (DSMB), Research Ethics Board, or the Investigator. Criteria for study stoppage may include occurrence of unanticipated adverse effects, in cases when continuing the trial would not sufficiently provide useful information to warrant continuation or due to statistical or ethical considerations.

7.10 Blinding

This trial is an open-label, un-blinded study. Given the pragmatic nature of the trial and the different methods of administration of each medication (i.e., methadone daily witness ingestion versus BUP/NX take-home dosing), participants, providers and research staff will not be blinded.

7.11 Participant Compensation

Participants will receive compensation for completing each study visit. Participants may receive a maximum of $560 in compensation for their participation on the study. Compensation will be provided in the amount of $40 for completion of the screening assessments, $40 for the completion of baseline assessments, and $40 at each study visit for the 24-week intervention period. Method of compensation may vary in adherence to site-specific REB guidelines.

8.0 MEDICATION MANAGEMENT DURING VISITS

8.1 Study Medication Management & Records

Each Node is required to observe provincial and federal regulations in regards to medication records. Medications will be dispensed through onsite or community pharmacies. Each pharmacy will maintain an adequate supply of unexpired study medications onsite (usual care/marketed products). Given the pragmatic nature of the trial and also that both study medications are post-market, approved medications, there will be no medication management procedures in this trial.

8.2 Concomitant Medications

Information on concomitant medications use will be collected during the screening visit through both self-report and chart abstraction to assess eligibility. Any information on new medications prescribed since the last study visit will be also be collected at treatment initiation and study visits every 2 weeks for the 24-week intervention period.

8.2.1 Medication Interactions to Be Considered During the Trial

Physicians need to be aware of common drug interactions for each study medication. Many of these interactions involve the cytochrome P450 (CYP450) enzymes. For more prescribing information, please refer the Health Canada approved product monographs for methadone and buprenorphine/naloxone.

Methadone should be used cautiously when co-administered with:

- Benzodiazepines: This combination may result in death due to respiratory depression of central origin. Preference should be given to benzodiazepines which are absorbed more slowly and have longer half-lives, such as diazepam (Valium®), clonazepam (Rivotril®), prazepam (Demetrin®), clobazam (Urbanyl®).
- Opioid analgesics: The potential for overdose should be considered with any concomitant prescribed or illicit opioids
- Other central nervous system (CNS) depressants (e.g. alcohol).
- Other sedating medications (e.g. dimenhydrinate, clonidine).
- Medications causing similar effects (e.g. constipation or urinary retention by anticholinergics).
- Medications, which may increase the corrected QT interval (QTc), i.e. QT interval prolongation (e.g. tricyclic antidepressants, cocaine).

- Naltrexone: is an opioid antagonist that blocks the pharmacological effects of opioids and may precipitate a sudden onset of prolonged and intense opioid withdrawal
- HAART (highly active antiretroviral therapy): Nevirapin (Viramune®) and ritonavir (Norvir®) may cause a marked reduction in the methadone serum levels, and in both cases a dose adjustment of up to 45% may be necessary.
- Antidepressants: Tricyclic antidepressants, in particular, may trigger cardiac conduction disorders, reduce the seizure threshold or cause changes in the thyroid hormone levels. In case of doubt, ECG/EEG examination and monitoring of thyroid parameters are advised. Some selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine (Fluctine®) and fluvoxamine (Floxyfral®), are not contraindicated but should be administered with caution because they may increase methadone and naltrexone levels.

Buprenorphine/Naloxone should be used cautiously when co-administered with:

- Benzodiazepines: This combination may result in death due to respiratory depression of central origin.
- Opioid analgesics: The potential for overdose should be considered with higher than usual doses of opioids, such as methadone or analgesics, especially when attempting to overcome the buprenorphine partial agonist effects, or when the buprenorphine plasma levels are declining.
- Naltrexone: Naltrexone is an opioid antagonist that blocks the pharmacological effects of opioids and may precipitate a sudden onset of prolonged and intense opioid withdrawal.
- CYP3A4 inhibitors: Example of CYP3A4 inhibitors include protease inhibitors, macrolide antibiotics, and azole antifungals.
- CYP3A4 inducers: Example of CYP3A4 inducers include phenobarbital, carbamazepine, phenytoin, rifampicin.
- Monoamine oxidase inhibitors (MAOI): The concomitant use of MAOIs may exaggerate the effects of opioids.
- Other central nervous system depressants: such as other opioids (e.g. methadone, analgesics, antitussives), certain antidepressants, sedative H1-receptor antagonists, barbiturates, anxiolytics, neuroleptics, clonidine and related substances.
- Buprenorphine/naloxone should not be taken with alcohol.

9.0 OUTCOME ASSESSMENT MEASURES

9.1 Primary Outcome Assessment

9.1.1 Opioid use

Opioid use will be measured by the overall proportion of opioid-free urine drug screens during the 24 weeks of the trial (excluding the assigned metabolites of opioid agonist treatments, as appropriate), with missing values defined as positive UDS (binary, laboratory assay). Urine samples for drug screens will be collected at screening, and every 2 weeks for the 24-week intervention period. All urine specimens will be collected and analyzed using Health Canada-approved, Rapid Response™ Multi-Drug One Step Screen Test Panel and single test strips for both Hydromorphone and 6MAM (primary metabolite in heroin), and will follow all of the manufacturer's recommended procedures, to test for the presence of the following drugs or respective metabolites: morphine, oxycodone, fentanyl, benzodiazepines, cocaine, amphetamine, methamphetamine, THC, buprenorphine, methadone, methadone metabolite, and tramadol. A further validity check will be performed using a commercially available adulterant test strip. If urine specimen tampering is suspected, either based on the observation, temperature or

the adulterant tests, the study staff should request a second urine sample and may observe the urine collection process according to the clinic's standard operating procedures.

9.2 Secondary Outcome Assessment

9.2.1 Retention in treatment

Retention in treatment is defined as the proportion of participants on assigned OAT at the end of the study, defined as both a) having an active prescription for the assigned OAT at week 24, and b) a positive UDS result for the assigned OAT at week 24.

9.2.2 Medication Adherence

Opioid agonist medication adherence is defined as the proportion of assigned treatment doses received over the 24-week trial period assessed by self-report including questions on the number of doses taken, dosage amounts since the last visit, and diversion of medication. Research staff will collect information on adherence to assigned OAT using both pharmacy abstraction (through either prescription drug monitoring system or medication records provided by the pharmacist depending on regional differences) and participant self-report records collected at treatment initiation and every 2 weeks. Once collected, this information will then be entered into REDCap EDC. Pill counts will also be conducted by research staff to assess possible diversion.

9.2.3 Safety

Safety in the trial will be evaluated by monitoring adverse events (AEs) and serious adverse events (SAEs) from screening up to 30 days after the 24-week intervention period. Adverse events (AEs) and serious adverse events (SAEs) will be defined and documented according to the adverse reporting procedures (see Appendix C). All AEs will be documented by research staff first using case report form then in the electronic data capture (EDC) system. Research staff will then document in an AE Log recording date and time of onset, the end date and time (i.e., when the AE was resolved or stabilized), the severity of the event, any action taken with respect to the study medication (e.g. no treatment or dose adjustment), and the relationship with study protocol or study medication. Research staff will also record if the event was reportable to REB and further if the AE is classified as an SAE. All AEs/SAEs will be monitored by the study physician and overseen by the Node Medical Monitor until resolved or stabilized. The Lead Medical Monitor for the trial will oversee all SAE's across clinical sites to ensure proper documentation, follow up to resolution and reporting.

9.2.4 Participant Satisfaction

Information on participant satisfaction will be collected through participant self-report using the Client Satisfaction Questionnaire-8 (CSQ-8).(25) This information will either be completed by the participant on paper source or entered by the participant directly into the EDC system. This collects information on the participant's satisfaction as it relates to the assigned medication and the clinical care received at the site. Participant satisfaction will be assessed at 4, 12, and 24 weeks (end of study). Participants who discontinue participation in the study (withdraws participation or is withdrawn by the Investigator) will be invited to complete the CSQ-8 upon discontinuation.

9.2.5 Patient Engagement

Patient engagement occurs when patients meaningfully and actively collaborate in the governance, priority setting, and conduct of research, as well as in summarizing, distributing,

sharing, and applying its resulting knowledge (26). Patient engagement will be assessed at various time points using a battery of brief questionnaires which include the Treatment Entry Questionnaire (27), Health Care Climate Questionnaire-modified version (28), the Control Preference Scale(29) and the CollaboRATE questionnaire(30). The Treatment Entry Questionnaire and the Control Preference Scale will be administered at baseline, while the CollaboRATE questionnaire will be administered at baseline and each bi-weekly study visit as a measure of ongoing patient engagement. The Health Care Climate Questionnaire will be administered at week 4, 12 and 24 (end of study). This information will either be collected on paper source or entered by the participant directly into the EDC system.

9.3 Exploratory Outcome Assessment Measure(s)

9.3.1 Cost-effectiveness and Quality of Life Measures

Along with measuring quality of life as an outcome of the OPTIMA trial, this trial also provides the opportunity for rigorous assessment of the incremental cost-effectiveness of buprenorphine/naloxone versus methadone for the treatment of prescription opioid use disorders in a real-world setting. Health-related quality of life (HRQoL) data will be collected during the trial using three different HRQoL instruments (EuroQol-5D-3L(31), EuroQol-5D-5L(32), Health Utilities Index III (33). This information will either be collected on paper source or entered by the participant directly into the EDC system. Additionally, information on health service utilization will be collected at baseline and every 4 weeks for the 24-week intervention period. Data required to perform economic analyses will be collected using standardized self-reporting instruments that have been validated and used in previous studies. Quality-adjusted life year (QUALY) estimates and analysis will be conducted using data from the instrument that is determined to provide the best quality of life measure for our study population, via the independent validation sub-study (see section 11.8 for detailed analysis).

9.3.2 Pain

The Brief Pain Inventory-Short Form (BPI-SF) is a 9-item assessment of intensity of pain and interference with functioning and is widely used to assess both acute and chronic pain.(34) It will be administered at baseline, week 6, 12, 18 and 24 (end of study). This information will be collected by the research staff on a paper CRF then entered into the EDC system.

9.3.3 Proportion of Participants Who Initiate Taper

Dosage information will be collected through pharmacy abstraction and documented on a case report form and self-report medication adherence at bi-weekly study visits for the 24-week intervention period.

9.3.4 Clinical Opiate Withdrawal Scale (COWS)

The Clinical Opiate Withdrawal Scale (COWS) is an 11-item interviewer-administered scale to assess common signs and symptoms of opioid withdrawal.(35) This scale will be administered at treatment initiation to assess sign and symptoms of withdrawal prior to the participant initiating the assigned OAT. This information will be collected by the research staff on a paper CRF then entered into the EDC system. This scale will also be administered every 2 weeks up to week 6 to assess withdrawal symptoms during the early dose adjustment phase.

9.3.5 Brief Substance Craving Scale (BSCS)

The Brief Substance Craving Scale (BSCS) is a 16-item, self-report instrument which assesses cravings for substances (specifically prescription opioids) over a 24-hour period.(36) Intensity and frequency of cravings are recorded on a five-point Likert scale. This information will be collected by the research staff on a paper CRF then entered into the EDC system. It will be completed at baseline, week 2, and every 4 weeks for the remaining 24-week intervention period.

9.3.6 Timeline Follow-Back (TLFB)

The Timeline Follow-Back is a self-report measure of drug use and will be administered at baseline and bi-weekly study visits to evaluate frequency and patterns of use of opioids and other substances, including alcohol. (37) This information will be collected by the research staff on a paper CRF then entered into the EDC system.

9.3.7 Addiction Severity Index- Self Report

The ASI Self-Report will be completed by the participant to assess eligibility criteria and identify primary prescription opioid use at the screening visit. The ASI Self-Report assesses problem use in the past 30 days in seven areas commonly affected by substance use, including medical, employment/support, alcohol, drug, legal, family/social, and psychiatric drug and alcohol sections. (38)This questionnaire will be administered at screening and 24 weeks (end of study).

9.3.8 Psychological Functioning

Psychological functioning will be assessed using a battery of brief self-report questionnaires which include the Beck Depression Inventory-Second Edition (BDI-II)(39), which is a 21-item self-reporting instrument for measuring the severity of depression, the Beck Anxiety Inventory (BAI) which is a 21-item self-report scale that measures the severity of anxiety in adults. (40) Both instruments will be administered at baseline, week 12 and week 24 (end of study). The Kessler Psychological Distress Scale (K10) is a 10-item questionnaire measuring global distress and will be administered at baseline and every 4 weeks for the 24 week intervention period.(41) This information will either be collected on paper source or entered by the participant directly into the EDC system.

9.3.9 Risk Behaviours

The Risk Behaviours Survey (RBS) is an interviewer-administered tool of engagement in activities that increase the likelihood of contracting HIV and other blood-borne and sexually-transmitted pathogens.(42) It specifically looks at drug use practices and sexual behaviors associated with increased risk of transmission. This information will be collected by the research staff on a paper CRF then entered into the EDC system. The RBS will be administered at baseline, week 12 and week 24 (end of study).

9.4 Table 1: Research Time Points and Planned Data Collection

					24 Week Intervention Period											
	PreSCR	SCR	BSL/RAND[(a)]	Treatment initiation												End of Study
Visit	N/A	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Week	N/A			0	2	4	6	8	10	12	14	16	18	20	22	24
Day	N/A	- 28		0	14	28	42	56	70	84	98	112	126	140	154	168
Verbal Consent and Pre-screening Questionnaire	x															
Informed Consent Form		x														
Demographic Questionnaire		x														
Medical Release Form		x														
Locator Form		x		x	x	x	x	x	x	x	x	x	x	x	x	x
Urine Drug Screen (UDS)		x			x	x	x	x	x	x	x	x	x	x	x	x
DSM-5 Opioid Use Disorder Diagnostic Criteria		x														
Medical and Psychiatric History		x														
Non-Fatal Overdose Questionnaire		x														
Physical Exam & Vital Signs		x														
Clinical Opiate Withdrawal Scale (COWS)				x	x	x	x									
Pregnancy Test and Birth Control Assessment		x				x		x		x		x		x		x
Addiction Severity Index-Self Report Form		x														x
Beck Depression Inventory (BDI)			x							x						x
Health Service Utilization Questionnaire			x			x		x		x		x		x		x
Beck Anxiety Inventory (BAI)			x							x						x
Kessler Psychological Distress Scale (K10)			x			x		x		x		x		x		x
Brief Pain Inventory-SF (BPI-SF)			x				x			x			x			x
EuroQol-5D-5L (EQ 5D 5L)			x			x		x		x		x		x		x
EuroQol-5D-3L (EQ 5D 3L)			x			x		x		x		x		x		x
Health Utilities Index (HUI-III)			x			x		x		x		x		x		x
Risk Behaviour Survey (RBS)			x							x						x
Brief Substance Craving Scale (BSCS)			x		x		x		x		x		x		x	
Timeline Follow Back (TLFB)			x		x	x	x	x	x	x	x	x	x	x	x	x
Client Satisfaction Questionnaire-8 (CSQ-8)						x				x						x
OAT Assigned Treatment- Pharmacy Abstraction					x	x	x	x	x	x	x	x	x	x	x	x
OAT Assigned Treatment Self- Report					x	x	x	x	x	x	x	x	x	x	x	x
Treatment Entry Questionnaire (TEQ)			x													
Health Care Climate Questionnaire (HCCQ)						x				x						x

					24 Week Intervention Period											
	PreSCR	SCR	BSL/RAND[(a)]	Treatment initiation												End of Study
Visit	N/A	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Week	N/A			0	2	4	6	8	10	12	14	16	18	20	22	24
Day	N/A	- 28		0	14	28	42	56	70	84	98	112	126	140	154	168
Control Preference Scale (CPS)			x													
Collaborate Questionnaire (COL)			x		x	x	x	x	x	x	x	x	x	x	x	x
Adverse Events (AE)		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

(a) Treatment initiation refers to the day on which the participant takes his/her first dose of assigned study medication (Day-0/week-0). Information on first dose prescribed will be recorded in a case report form Screening visit, baseline visit, randomization and treatment initiation visit may take place on the same day (provided all screening assessments take place, eligibility is confirmed and baseline assessments are complete). Treatment Initiation must take place within 14 days of randomization or participant will be considered a treatment initiation failure. . If a participant does not start their assigned treatment (i.e., treatment initiation failure) or any other form of OAT (e.g. slow release oral morphine, injectable opioid agonist treatment) within the 14-day treatment initiation window, the date of the first day following the 14th day of that window will be used as Day-0/week-0. If a participant initiates another OAT than the assigned treatment during that 14-day window, the day on which the participant takes the first dose of that treatment will be used as Day-0/week-0.

10.0 TRAINING REQUIREMENTS

The study staff will be trained to full competency on all assessments and procedures as per protocol and will be documented in the Training Log. Required training will include Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS-2) and Good Clinical Practice (GCP) (with renewal every 3 years), as well as protocol-specific training as needed (e.g. assessments, study interventions, safety procedures, data management and collection). All study staff will be required to complete all training requirements prior to recruitment, enrolment and randomization of participants. Training is an ongoing activity that occurs at all phases of a study, including before the beginning of the study, during implementation, and in preparation for study close out.

Training in study-specific assessments will be provided through a comprehensive training plan that will be developed by the National Research Coordinator in collaboration with Principal Investigators and the Data Management Centre. All training on the REDCap EDC system is expected to be delivered via interactive face to face format, conference call, webinar, and self-study. The majority of study specific training will occur via in-person training sessions which will take place onsite.

11.0 STATISTICAL DESIGN AND ANALYSES

11.1 Overview and Summary of Design

This is a multi-site, two-arm, randomized, open label, non-inferiority, pragmatic trial. A total of approximately 276 participants will be randomly assigned in a 1:1 ratio to 2 treatment arms:

- Methadone provided via daily witnessed ingestion as per local guidelines
- Buprenorphine/naloxone provided via flexible take-home dosing dispensed as per physician discretion

The main objective of the trial is to assess the non-inferiority of buprenorphine/naloxone flexible take-home dosing to methadone standard model of care in supressing illicit opioid use.

11.2 Study Endpoints

11.2.1 Primary Endpoint

Opioid use will be measured by the overall proportion of opioid-free urine drug screens during the 24 weeks of the trial (excluding the assigned metabolites of opioid agonist treatment, as appropriate), with missing values defined as positive UDS (binary, laboratory assay).

11.2.2 Secondary Endpoints

Secondary endpoints include retention in treatment, safety, medication adherence, treatment satisfaction, and patient engagement. Secondary endpoints will be measured using a combination of pharmacy records, charts abstractions, and self-report measures.

11.3 Sample Size and Power Calculations

The sample size calculation for the primary outcome is based on assumptions, from previous research on opioid use disorder with the similar outcome measures, (20) and consultations with experts in addiction medicine.

Primary analysis will involve the comparison of two group means. For each arm of the trial, a mean of the primary endpoint will be computed. A proportion is computed for each participant; however, the mean of these proportions will be used for the comparison. The methadone arm will have an expected mean of 0.75 for opioid-free urine drug screen test results during the 24-week intervention period. Given the pragmatic design and varying methods of administration of the two medications, adherence to take-home buprenorphine/naloxone may be lower than methadone provided via daily witnessed ingestion. Thus, we expect that participants on the buprenorphine/naloxone arm may have a lower mean of opioid-free urine drug screen test results during the 24-week intervention period. We have assumed that the absolute magnitude of this difference to be 0.075 (i.e. a mean of 0.675 in the BUP/NX arm). Based on the literature, the standard deviation is expected to be 0.25, meaning approximately two thirds of the participants will have mean proportions between 0.50 and 1.00.

Given the non-inferiority design of the trial, one of the critical parameters for determining the sample size is the non-inferiority margin. Following consultation with addiction medicine experts, the margin was set at 0.15. This margin also reflects our willingness to accept a potential small decrease in effectiveness in supressing opioid use, but increased safety and treatment satisfaction with buprenorphine/naloxone compared to methadone.

Given the above assumptions and using a one-sided α-level of 0.05, power of 80%, and 1:1 allocation ratio, a total of 276 participants (138 per arm) will be required. The sample size calculation was performed using the R software, version 3.3.1 (TrialSize 1.3 package). Note that this sample size estimate is sensitive to both the standard deviation estimate and the expected difference between the methadone and BUP/NX. Assuming a 45% screening failure rate, we estimate that we will need to screen approximately 500 participants to achieve our target sample size.

11.4 Data Analysis

All proposed analyses will be conducted under the intention-to-treat (ITT) principle.

A “switch equals failure” approach will be used, where participants who discontinue their assigned medication for any reason (including switches to the other arm) are classified as failures. (43, 44) Although data collection may continue, for the purposes of the analyses, urine drug screens

collected from the time they discontinue their assigned OAT, will be considered positive for opioids.

A 'per-protocol' analysis, where non-adherent and/or non-compliant participants are excluded from the analysis, will also be conducted to explore the sensitivity of the conclusions obtained with the analyses under the ITT principle. The exclusions associated with the per-protocol analysis will be provided in the statistical analysis plan prior to the final analysis.

The following methods will be used for descriptive analysis: frequency distributions for categorical variables; and mean, median, standard deviation, quartiles and range (minimum, maximum) for continuous variables. Within-arm assessment of the change from baseline to follow-up measurement will be analyzed using McNemar's test (for categorical response variables) or the paired t-test or Wilcoxon signed-ranks test (for continuous variables). To assess differences between arms: for binomial response variables, chi-square tests and logistic regression will be used; for continuous variables, t-tests and linear regression, or nonparametric methods if data are non-normal. Baseline characteristics such as demographic information, will be used to assess the adequacy of the randomization.

11.5 Primary Endpoint Analysis

As a general guide, we will follow the recommendations and guidelines stated in the Extension of the CONSORT 2010 Statement for the reporting of non-inferiority and equivalence randomized trials. (45) Modified hypothesis testing methods exist; however, a more informative confidence interval approach is preferred in the design, analysis, and reporting of non-inferiority trials. Since a non-inferiority trial reflects a one-sided situation, only the 100(1 - α)% lower confidence limit will be of interest where α level of 5% will be used. The mean difference between the BUP/NX and methadone arms (means of BUP/NX minus methadone) along with its lower confidence limit will be calculated. If this limit lies within (-0.15, +∞), then the null hypothesis of inferiority is rejected in favor of the alternative hypothesis of non-inferiority at the 5% significance level.

11.6 Secondary Endpoint Analyses

All the analyses for the secondary endpoints (refer to secondary outcomes, Section 9.2) except for the safety endpoint will use 'superiority' hypotheses (as used in superiority trials). To assess differences between arms: for binomial response variables, chi-square tests and logistic regression will be used; for continuous variables, t-tests and linear regression, or nonparametric methods if data are non-normal. Two-sided tests will be performed with an α level of 5%. ITT analyses will be performed followed by secondary sensitivity analyses using a per-protocol analysis.

11.7 Safety Analysis

Adverse events will be analyzed using MedDRA preferred terms. The number and percentage of participants experiencing each specific AE will be tabulated by severity and by relationship to the assigned OAT. Each adverse event will be counted once under the maximum severity or the strongest recorded causal relationship to study product. For each arm, all AEs will be grouped by body system and a p-value and confidence interval for the relative risk (comparing both arms) of each AE, as well as the difference in rates and confidence interval between arms will be calculated. To safeguard against too many "false positive" safety findings, the statistical significance of the p-values will be assessed after a multiplicity adjustment.(46) Safety and toxicity data will be compared between arms using Andersen Gill Proportional Hazards Models stratified by site and robust variance estimates adjusting for the correlation of events within participants. (47) For this analysis, a safety and toxicity endpoint is defined as the occurrence in a participant

of any safety endpoint during follow-up. In addition, the above analysis will be supplemented by performing an analysis that allows recurring events in individual participants.

11.8 Health Economics Analysis

A cost effectiveness analysis will be conducted on health-related quality of life (HRQoL). This data will be collected during the trial using three quality of life measures (see Section 9.3.1). Data required to perform economic analyses will be collected using standardized self-report instruments. Quality-adjusted life-year (QUALY) estimates and analysis will be conducted using data from the instrument that is determined to provide the best measure for our study population, via independent validation study. The cost-effectiveness of BUP/NX vs. methadone will be evaluated by trial-based, as well as model-based analysis. Trial-based analysis will be conducted using a net-benefit regression approach, which will allow for subgroup assessment of cost-effectiveness, controlling for individual demographics, drug-use characteristics, baseline indicators of health and criminality, as well as city of residence, within a hierarchical structure. Model-based evaluation will be conducted using a semi-Markov cohort model, to project all relevant costs and benefits from both a societal and third-party-payer perspective over a range of longer time-horizons (5-year, 10-year and lifetime). We will report incremental cost-effectiveness ratios (ICERs) with 95% credible intervals, along with a range of predicted health outcomes, including mortality rates, the costs of medical care and crime over the lifetime of representative people with PO use disorders.

Durations spent in each state of our semi-Markov model will be estimated using time-to-event analysis, adjusted for competing risks. Sensitivity analysis for trial-based analysis will be conducted via multiple-imputation methods, while uncertainty in ICER estimates will be quantified by non-parametric bootstrapping methods. Sensitivity analysis for our model-based approach will be conducted both deterministically, evaluating the effects of varying key individual parameters, and probabilistically, where all parameters are simultaneously varied over multiple simulations, to account for the full range of uncertainty in our ICER estimates. Our analysis will adhere to best-practice guidelines for economic evaluations alongside randomized control trials, and a societal perspective will be adopted for all cost analysis that incorporates the direct and indirect costs of treatment, including costs of criminal activity and lost productivity, along with medication and inpatient/outpatient care.

12.0 REGULATORY COMPLIANCE AND SAFETY

12.1 Statement of Regulatory 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. A Manual of Operations (MOP) will be provided to all Node research staff as a reference guide and study quality assurance tool. Participating sites must obtain written approval of the study protocol, consent form, other supporting documents, and any advertising for participant recruitment from their local Research Ethics Board (REB) in order to participate in the study. Any amendments to the protocol or consent materials must be approved by the REB prior to implementation. Annual progress reports and local Adverse Event (AE) and Serious Adverse Event (SAE) reports will be submitted to each REB, in accordance with local guidelines and procedures.

12.2 Research Ethics Board Approval

Prior to initiating the study, site investigators will obtain written local approval to conduct the study at their respective site. All protocol amendments will be submitted in writing by the investigators for approval prior to implementation. In addition, REBs will approve all consent forms, recruitment materials, and any other study related materials given to the participant. Annual reports and progress reports will be submitted to the REBs annually or at a frequency requested by each so that continuous study approval is maintained without lapse. The Site Principal Investigator is responsible for maintaining, in the Trial Master File, copies of all performance site(s) current approval notice(s), REB-approved consent document(s), including approval for all protocol modifications. These materials must be received by the Principal Investigator prior to the initiation of research activities at a given site and must be available at any time for audit.

12.3 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. Each study site must have the study informed consent approved by their REB(s). A copy of the REB-approved consent, along with the study approval, must be sent to the National Research Coordinator prior to the site initiation visit and with each subsequent consent revision. Every study participant is required to sign a valid, REB-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 their and institutional policies and that is accessible to the study monitors. A copy of the signed consent form will be given to every participant.

Prior to obtaining informed consent, the 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 have. The participant will consent by signing and dating the consent document. The person obtaining consent and a witness, if required by the local (s), 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 staff signature log and must be approved by the REB. All persons obtaining consent must have completed appropriate training and follow standard operating procedures for the informed consent process.

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. 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.

12.4 Quality Assurance and Safety Monitoring

A total of 3 or more monitoring visits are planned in each site during the course of the trial (1 to 3 sites per Node, up to 12 sites). The monitor will prepare each visit using site-specific data to review the content of documents to be prepared for special situations or site-specific requirements. The monitor will prepare for the visit by compiling monitoring report forms from

previous visits, correspondence, deficiency lists from previous visits, reports on serious adverse events requiring follow-up, and will evaluate the documents' status (case report forms, queries) by consulting the data management lists. During the visit, the monitor will meet with the personnel and local investigators, will verify files such as documentation of participant status, CRFs (review and status), protocol compliance, staff changes, documentation of adverse events and serious adverse events (and ensure their proper reporting), documentation of source data, concomitant medications. The monitor will also verify the documentation of protocol deviations and the informed consent forms for all participants. At the end of the visit, the monitor will prepare a visit report.

The first monitoring visit will occur after approximately 2 to 4 patients have been enrolled, and other visits will be scheduled over the course of the study and once at the end (i.e., the close-out visit). If issues exist either with the quality of the data or operationally, the monitor will ensure the implementation of corrective measures and will follow a detailed monitoring plan.

12.5 Confidentiality

Confidentiality will be maintained in accordance with all applicable federal regulations and/or provincial laws and regulations. By signing the signature page of the protocol, the Investigator affirms that the information provided to the Investigator will be maintained confidential and that such information will only be divulged to the REB, the affiliated institution, and the employees that are bound under an appropriate understanding of confidentiality.

12.6 Clinical Monitoring

Clinical monitoring for the trial will examine whether study procedures are conducted appropriately and that study data are generated, documented, and reported in compliance with the protocol, GCP, and any provincial and federal regulations. At mutually agreed upon times, clinical monitors will audit the 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.

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 REB. Monitors will pay particular attention to the participant's informed consent forms, protocol adherence, reported safety events and corresponding assessments, and Investigator oversight and involvement in the trial. Reports will be prepared following the visit and forwarded to both the principal investigators and the clinical monitor.

12.7 Regulatory Files Requirements

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

12.8 Records Retention Requirements

All sites for this trial will use a centralized data management system provided by the URCA Applied Clinical Research Unit of the CHU Sainte-Justine Research Centre. The REDCap web-based distributed data entry system will be implemented. REDCap offers an application containing the required technical requirements of a compliant system in clinical trials. All regulatory files, study documentation, and records should be archived by each site for a minimum period of 5 years following completion of the study, after which they will be destroyed in keeping

with privacy and confidentiality regulations and guidelines. Upon completion of the trial and data cleaning activities, the URCA Statistical and Data Management Centre will "lock" the study database from further modification. The dataset used in the final analysis will be transferred to the Principal Investigator or designee.

12.9 Audits

Principal Investigators have an obligation to ensure that the trial is conducted according to GCP guidelines and may perform quality assurance audits for protocol compliance. The Research Ethics Board or a provincial or federal regulatory agency may inspect research records for verification of data, compliance with federal, provincial and /or local guidelines on human participant research, and to assess participant safety.

12.10 Study Documentation

Study documentation includes all case report forms, research files, and source documents, monitoring logs and appointment schedules, signed protocol and amendments, REB-correspondence, REB-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.

12.11 Protocol Deviations

Any departure from the procedures and requirements outlined in the protocol will be classified as a protocol deviation. All protocol deviations will be assessed on the seriousness of the event and the corrective action required. Protocol deviations may not affect the scientific soundness of the investigation or seriously affect the safety, rights, or welfare of a study participant or may indeed 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-occurring. The National Research Coordinator and site Coordinators will be responsible for developing corrective action plans for protocol deviations as appropriate. Those corrective action plans may be reviewed/approved by the PIs with overall approval through the site's REB as required. 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. Additionally, each site is responsible for reviewing their local REB's definition of a protocol deviation or violation and understanding which events need to be reported. Sites must recognize that the definition of a reportable event may differ and act accordingly in following all reporting requirements for different entities. For the purposes of this trial, missed visits will not be considered protocol deviations.

Each site will keep a 'Protocol Deviation Log' and all protocol deviations will first be recorded on a paper case report form then entered in the Electronic Data Capture (EDC) system. Both URCA and the Site Principal Investigator must be contacted immediately if a participant who does not meet eligibility is randomized into the trial.

13.0 SAFETY MONITORING

13.1 Data and Safety Monitoring Board (DSMB)

An independent DSMB will examine accumulating data to assure protection of participants' safety while the study's scientific goals are being met. The DSMB is responsible for conducting periodic reviews of accumulating safety and efficacy data. It will determine whether there is ground for continuation of the trial, or evidence that study procedures should be changed, or if the trial should be halted for either participant safety or studied treatment efficacy issues or inadequate trial performance (e.g. poor recruitment, non-compliance with study protocol) reasons.

The DSMB review of safety data will be conducted approximately every 6 months. There is no formal efficacy data interim review planned for this trial. A no-data DSMB meeting will be scheduled prior or close to study initiation where the protocol and the complete interim monitoring plan will be presented to the DSMB members. At subsequent DSMB reviews, besides safety data presentations, tables will be prepared for these reviews to assess the study conduct operational characteristics (mainly accrual, adherence, and retention). That information will be compared to the protocol assumptions, and alterations will be made to the study design (e.g. increase or decrease in accrual and/or number of sites, sample size) if recommended by the DSMB.

The study may be terminated or modified for poor accrual/recruitment, adherence/product use, retention, and/or other issues. In addition, the DSMB may recommend early termination of the study or modification when there is clear evidence of benefit, futility, or harm, or may recommend continuation of the study if the balance between potential benefit and harm remains adequate. Therefore, the DSMB may recommend stopping or modifying the study early in the following situations:

Clear evidence of serious safety problems including:

- Excess in frequency of any AEs (judged by the DSMB to be harmful to the participants) in one of the arms.
- Excess in frequency of any SAEs (Grade 4 and higher) in one of the arms.
- An excess in frequency safety endpoints as defined in Section 11.7 in one of the arms.

The DSMB may request additional analyses of the safety, toxicity, and/or effectiveness data from this study. The statistical analysis plan for this study will provide further details on the interim monitoring strategy including the specifics of the above guidelines and other relevant details.

13.2 Adverse Events (AEs)

The Regional Principal Investigator(s) have appointed Node Medical Monitors for this study, who will review or provide consultation for each Serious Adverse Event (SAE) that take place at their assigned clinical sites (see Appendix C for definitions of AE's and SAE's). This will include an assessment of the possible relatedness of the event to the study intervention or other study procedures. The Medical Monitors may also provide advice for decisions to exclude, refer, or withdraw participants as required. Each site will be responsible for tracking and reporting AEs and SAEs and for providing reports accordingly to the URCA and the National Research Coordinator through the EDC. URCA will be responsible for coding all events using MedDRA and for providing appropriate reports as needed by the DSMB. All AEs are reviewed on a weekly basis to observe trends or unusual events. The National Research Coordinator will be responsible for the coordination of reporting to both the market authorization holder of each study medication and the DSMB and ensure that sites have submitted to local ethic boards as required. This will include

events that are serious, related and unexpected. Training will be provided to all study staff on reporting and monitoring procedures of Adverse Events and Serious Adverse Events. Each of the sites will establish practices for managing medical and psychiatric adverse events in through local SOP's. Treatment providers at each site will be responsible for monitoring participants for possible clinical deterioration or other problems, and for implementing appropriate courses of action.

14.0 DATA MANAGEMENT

14.1 Design and Development

The URCA Statistical and Data Management Centre will be responsible for developing the electronic case report forms (eCRFs), developing and validating the clinical study database, ensuring data integrity, and training sites and participating Node staff on applicable data management procedures. The REDCap web-based distributed data entry system will be implemented. This system will be developed to ensure that guidelines and regulations surrounding the use of computerized systems in clinical trials are upheld. The remainder of this section provides an overview of the data management plan associated with this protocol.

14.2 Site Responsibilities

The data management responsibilities of each individual site will be specified by the URCA Statistical and Data Management Centre and outlined in the REDCap User's Guide and OPTIMA EDC Training Manual.

14.3 URCA Statistical and Data Management Centre – Responsibilities

The responsibilities of the URCA Statistical and Data Management Centre include: 1) development of a data management plan and to conduct these activities in accordance with that plan; 2) develop eCRFs for the collection of all data required by the study; 3) assist in the development of data dictionaries for each eCRF that will comprehensively define each data element; 4) conduct ongoing data monitoring activities on study data from all participating sites; 5) monitor any preliminary analysis data cleaning activities as needed; and 6) rigorously monitor final study data cleaning.

14.4 Data Collection, Training and Quality Assurance

Data will be collected at the study sites on source documents and entered by the site into eCRFs in the REDCap system. A data entry assistant should be appointed by the site coordinator to enter the trial data in REDCap. Data entry into REDCap should be completed according to the instructions provided in the OPTIMA EDC Training Manual. The investigators are responsible for maintaining accurate, complete and up-to-date records, and for ensuring the completion of the eCRFs for each research participant. If incomplete or inaccurate data are found, a query will be generated to the sites for a response. Sites will resolve data inconsistencies and errors and enter all corrections and changes into REDCap. Data monitoring will take place during regularly scheduled clinical monitoring visits and provided by the URCA Statistical and Data Management Centre.

14.5 Data Transfer/Lock

Once the final data has been entered in the EDC system, final data quality assurance checks will be conducted and the study database will be locked prohibiting further modification. The dataset used in the final analysis will be returned to the CHUM Research Centre located in Québec-Maritimes CRISM Node for storing and archiving. Data lock can take place up to 2 months after trial completion.

15.0 SIGNATURES

ACKNOWLEDGEMENT BY INVESTIGATOR:

- I am in possession of version 6.0 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 when an alteration is required and necessary to protect the safety, rights, or welfare of a participant, but after the REB have been notified.

- I will ensure that the requirements relating to obtaining informed consent and research ethics board (REB) review and approval Health Canada Division 5 regulations 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 for implementing this version of the protocol and that they are qualified to meet the responsibilities that they have been assigned.

- I agree to comply with all the applicable federal, provincial, and local regulations regarding the obligations of clinical investigators as required by the Division 5 regulations, the province, and the research ethics board.

CLINICAL SITE PRINCIPAL INVESTIGATOR

Printed Name	**Signature**	**Date**

Clinical Site Name _____

Node Affiliation _____

16.0 APPENDIX A: METHADONE OVERVIEW

Pharmacokinetics

Absorption: Methadone is a lipid soluble opioid and is well absorbed by the gastrointestinal tract. Following oral administration, the bioavailability of methadone ranges between 36%-100% and peak plasma concentrations are achieved between 1 and 7.5 hours. Dose proportionality of methadone pharmacokinetics is not known. However, after administration of daily oral doses ranging from 10 to 225 mg, the steady-state plasma concentrations ranged between 65 to 630 ng/mL and the peak concentrations ranged between 124 to 1255 ng/mL. Effect of food on the bioavailability of methadone has not been evaluated.

Distribution: Methadone undergoes fairly extensive first pass metabolism. It is bound to albumin and other plasma proteins and to tissue proteins, the concentrations in lung, liver and kidneys is much higher than plasma concentration. Methadone is unusual in the opioid class, in that there is extensive binding to tissue proteins and fairly slow transfer between some parts of this tissue reservoir and the plasma. Methadone is a lipophilic drug and the steady-state volume of distribution ranges between 1.0 to 8.0 L/kg. In plasma, methadone is predominantly bound to a1-acid glycoprotein (85% to 90%). Marked variations in plasma levels occur in dependent persons on a stable dose of oral methadone, without any relation to symptoms. Methadone is secreted in saliva, sweat, breast milk, amniotic fluid and umbilical cord plasma. The concentration in cord blood is about half the maternal levels.

Metabolism: Methadone is primarily metabolized by N-demethylation to an inactive metabolite, 2-ethylidene- 1,5-dimethyl-3,3-diphenylpyrrolidene (EDDP). Cytochrome P450 enzymes, primarily CYP3A4, CYP2B6, CYP2C19, and to a lesser extent CYP2C9 and CYP2D6, are responsible for conversion of methadone to EDDP and other inactive metabolites, which are excreted mainly in the urine.

Excretion: The elimination of methadone is mediated by extensive biotransformation, followed by renal and fecal excretion. Published reports indicate that after multiple dose administration the apparent plasma clearance of methadone ranged between 1.4 and 126 L/h, and the terminal half-life (T½) was highly variable and ranged between 8 and 59 hours in different studies. Since methadone is lipophilic, it has been known to persist in the liver and other tissues. The slow release from the liver and other tissues may prolong the duration of methadone action despite low plasma concentrations.

Table 2: Methadone Product Information

Name	Methadose ™*
Route	Oral
Form	Liquid
Strength	10 mg/ml
Drug Class	Opioid
Non-medicinal ingredients	Methadose™ Oral Concentrate contains: Artificial cherry flavor, citric acid anhydrous, FD&C Red No. 40, D&C Red No. 33, methylparaben, poloxamer 407, propylene glycol, propylparaben, purified water, sodium citrate dihydrate, sucrose. Methadose™ Sugar-Free Oral Concentrate contains: citric acid anhydrous, purified water, sodium benzoate.
Induction dose	The initial Methadose™ dose should be carefully titrated to the individual. Too rapid titration for the patient's sensitivity is more likely to produce adverse effects. The initial Methadose™ dose should be administered, under supervision, when there are no signs of sedation or intoxication, and the patient shows symptoms of withdrawal. The dosage schedules indicated below are recommended but could be varied in accordance with clinical judgment. Initially, a single dose of 20 to 30 mg of Methadose™ will often be sufficient to suppress withdrawal symptoms. The initial dose should not exceed 30 mg. If same-day dosing adjustments are to be made, the patient should be asked to wait 2 to 4 hours for further evaluation, when peak levels have been reached. An additional 5 to 10 mg of Methadose™ may be provided if withdrawal symptoms have not been suppressed or if symptoms reappear. The total daily dose of Methadose™ on the first day of treatment should not ordinarily exceed 40 mg. Initial doses should be lower for patients whose tolerance is expected to be low at treatment entry. Loss of tolerance should be considered in any patient who has not taken opioids for more than 5 days. Initial doses should not be determined by previous treatment episodes or dollars spent per day on illicit drug use. Over the first week of treatment, dose adjustments should be made based on control of withdrawal symptoms at the time of expected peak analgesic activity (e.g. 2 to 4 hours after dosing). Prescribers are reminded that methadone's peak respiratory depressant effects typically occur later, and persist longer, than its peak analgesic effects. Dose adjustment should be cautious; deaths have occurred in early treatment due to the cumulative effects of the first several days' dosing. Patients should be reminded that the dose will "hold" for a longer period of time as tissue stores of methadone accumulate.
Stabilization and maintenance dose	During prolonged administration of Methadose™, as in a methadone maintenance treatment program, there is usually a gradual, yet progressive, disappearance of side effects over a period of several weeks. However, constipation and sweating often persist. Methadone may be used in a maintenance treatment program of varying duration, or in a shortterm detoxification protocol of gradually decreasing

	doses to the point of abstinence. Patients may remain in methadone maintenance treatment indefinitely, or may be ready for a medically supervised taper at some point. Regardless of maintenance or detoxification treatment, increased risk of relapse following withdrawal of methadone treatment should be considered. Prescribers are referred to clinical practice treatment standards and guidelines in their area.
Contraindications	-patients with a known hypersensitivity to methadone hydrochloride or any other ingredient in Methadose™. -in any situation where opioids are contraindicated, such as patients with respiratory depression (in the absence of resuscitative equipment or in unmonitored settings), obstructive airway disease, and in patients with acute bronchial asthma or hypercarbia. -in any patient who has or is suspected of having a paralytic ileus. -patients taking monoamine oxidase inhibitors (MAOIs) or within 14 days of such therapy. -patients with diarrhea associated with pseudomembranous colitis or caused by poisoning, until toxic material has been eliminated from the gastrointestinal tract.

* This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Mallinckrodt Canada ULC at: 1-866-885-5988. Mallinckrodt, the “M” brand mark, the Mallinckrodt Pharmaceuticals logo, and other brands are trademarks of a Mallinckrodt company. © 2015 Mallinckrodt. This leaflet was prepared by Mallinckrodt Canada ULC. Mallinckrodt Canada ULC Saint-Laurent, QC, H4R 2N1 CANADA Revised: 26 October 2016.

**Find the full product monograph that is prepared for healthcare professionals and includes this patient medication information by visiting the Health Canada website; the manufacturer’s website http://www.paladinlabs.com, or by calling 1-888-867-7426. This leaflet was prepared by Paladin Labs Inc. Last Revised: 26 October 2016.

17.0 APPENDIX B: BUPRENORPHINE/NALOXONE OVERVIEW

Pharmacokinetics- Buprenorphine

Absorption: When taken orally, buprenorphine undergoes first-pass hepatic metabolism with N-dealkylation and glucuroconjugation in the small intestine. The use of this medication by the oral route is therefore ineffective. When taken sublingually, there is wide inter-patient variability in the absorption of buprenorphine but within participant variability was low. Plasma levels of buprenorphine increased with dose in the range of 4 mg to 16 mg, although the increase was not directly dose proportional. Mean Cmax for buprenorphine 4 mg was 2.00 ng/mL and increased to 2.65 ng/mL at 8 mg and 4.42 ng/mL at 16 mg. Mean AUC0-inf for sublingual tablet doses of 4 mg, 8 mg and 16 mg were, respectively, 13.90, 27.83 and 44.16 (h*ng/mL).

Distribution: Buprenorphine is highly lipophilic, which leads to rapid penetration of the blood brain barrier. Buprenorphine is approximately 96% protein-bound, primarily to alpha and beta globulin.

Metabolism: Buprenorphine is primarily metabolized through N-dealkylation by liver microsomal CYP3A4. The parent molecule and the primary dealkylated metabolite, norbuprenorphine, undergo subsequent glucuronidation. Norbuprenorphine binds to opioid receptors in vitro; however, it is not known whether norbuprenorphine contributes to the overall effect of buprenorphine.

Excretion: Buprenorphine is essentially eliminated in the feces by biliary excretion of the glucuroconjugated metabolites (approximately 70%), the rest being eliminated in the urine. In feces, almost all of the buprenorphine and norbuprenorphine were free (buprenorphine, 33% free and 5% conjugated; norbuprenorphine, 21% free and 2% conjugated). In urine, most of buprenorphine and norbuprenorphine were conjugated (buprenorphine, 1% free and 9.4% conjugated; norbuprenorphine, 2.7% free and 11% conjugated). The overall mean elimination half-life of buprenorphine in plasma is 37 hours, although the levels are very low 10 hours after dosing (majority of AUC of buprenorphine is captured within 10 hours), indicating that the effective half-life may be shorter.

Pharmacokinetics- Naloxone

Absorption: Naloxone mean peak plasma concentrations were achieved at approximately 1hr post-dose, and were measurable up to 8 hours' post-dose. Across the doses of 1 mg to 4 mg, a trend towards increasing naloxone plasma exposure with an increase in dose was observed. Naloxone has not been found to affect the pharmacokinetics of buprenorphine and both buprenorphine alone and buprenorphine/naloxone sublingual tablets deliver similar plasma concentrations of buprenorphine.

Distribution: Following oral administration, naloxone is barely detectable in plasma; following sublingual administration of buprenorphine/naloxone, plasma naloxone concentrations are low and decline rapidly. Naloxone is approximately 32-45% protein bound, primarily to albumin.

Metabolism: The drug is metabolized in the liver, primarily by glucuronide conjugation. Naloxone undergoes direct glucuronidation to naloxone 3-glucuronide, as well as N-dealkylation, and reduction of the 6-oxo group.

Excretion: The drug is excreted in the urine. Naloxone has a mean elimination half-life from plasma of 1.3 hours.

Table 3: Buprenorphine/Naloxone Product Information

Name	Suboxone® *	N-Teva-buprenorphine/naloxone**	N-Mylan-buprenorphine/naloxone***
Route	Sublingual	Sublingual	Sublingual
Form	Tablets	Tablets	Tablets
Strength	2 mg buprenorphine/0.5 mg naloxone OR 8 mg/2 mg	2 mg buprenorphine/0.5 mg naloxone OR 8 mg/2 mg	2 mg buprenorphine/0.5 mg naloxone OR 8 mg/2 mg
Drug Class	Opioid	Opioid	Opioid
Non-medicinal ingredients	Acesulfame potassium, citric acid anhydrous, lactose monohydrate, magnesium stearate, maize starch, mannitol, natural lemon & lime flavour, povidone K30, and sodium citrate	Acesulfame potassium, citric acid anhydrous, corn starch, lactose monohydrate, mannitol, lemon & lime flavour, povidone K30, sodium citrate, and sodium stearyl fumarate.	Aspartame, citric acid anhydrous, colloidal silicon dioxide, crospovidone, lactose monohydrate, lemon lime flavour, magnesium stearate, mannitol and sodium citrate.
Induction dose	The recommended starting dose is 4 8 mg SUBOXONE® on Day 1, initiating with 4 mg and then an additional 4 mg dose may be administered depending on the individual patient's requirement. The suggested total dose target for treatment on Day 1 is within the range of 8 and 12 mg. During the initiation of treatment, closer dosing supervision is recommended to ensure proper sublingual placement of the dose and to observe patient response to treatment as a guide to effective dose titration according to clinical effect.	When initiating treatment with TEVA-BUPRENORPHINE/NALOXONE, the physician should be aware of the partial agonist profile of buprenorphine to the mu-opioid receptors, which may precipitate a withdrawal syndrome in opioid-dependent patients. The recommended starting dose is 4 mg TEVA-BUPRENORPHINE/NALOXONE on Day 1. An additional 4 mg dose may be administered depending on the individual patient's requirement.	When initiating treatment with Mylan-Buprenorphine/Naloxone, the physician should be aware of the partial agonist profile of buprenorphine to the mu-opioid receptors, which may precipitate a withdrawal syndrome in opioid-dependent patients. The recommended starting dose is 4 mg Mylan-Buprenorphine/Naloxone on Day 1. An additional 4 mg dose may be administered depending on the individual patient's requirement
Stabilization and maintenance dose	Following treatment induction, the patient should be rapidly stabilised on an adequate maintenance dose by	The dose of TEVA-BUPRENORPHINE/NALOXONE should be increased progressively according to	The dose of Mylan-Buprenorphine/Naloxone should be increased progressively according to

	titrating to clinical effect. Dose titration in increments or decrements of 2 - 8 mg buprenorphine to a level that holds the patient in treatment and suppresses opioid withdrawal effects is guided by reassessment of the clinical and psychological status of the patient. A maintenance dose of 12 mg to 16 mg of SUBOXONE® used once daily is clinically effective for most patients. Doses should not exceed a maximum single daily dose of 24 mg. During maintenance therapy, it may be necessary to periodically re-stabilise the patient to a new maintenance dose in response to changing patient needs.	individual patient need and should not exceed a maximum single daily dose of 24 mg. The dosage is titrated according to reassessment of the clinical and psychological status of the patient. During the initiation of treatment, daily dispensing of TEVA-BUPRENORPHINE/NALOXONE is required for a minimum of two months. After clinical stabilisation, has been achieved, a graduated schedule of take-home doses may be granted.	individual patient need and should not exceed a maximum single daily dose of 24 mg. The dosage is titrated according to reassessment of the clinical and psychological status of the patient. During the initiation of treatment, daily dispensing of Mylan-Buprenorphine/Naloxone is required for a minimum of two months. After clinical stabilisation has been achieved, a graduated schedule of take-home doses may be granted.
Less than daily dose	Following successful induction and after the patient is receiving a stable dose, the frequency of SUBOXONE® dosing may be decreased to dosing every other day at twice the individually titrated daily dose. For example, a patient who receives a stable daily dose of 8 mg may be given 16 mg on alternate days, with no medication on the intervening days. However, the dose given on any one day should not exceed 24 mg. In some patients, following successful induction and after the patient is receiving a stable dose, the frequency of SUBOXONE® dosing may be decreased to 3 times a week (for example on Monday, Wednesday and Friday). The dose on Monday and Wednesday should be twice the individually titrated daily dose, and the dose on Friday should be three times the individually titrated daily dose, with no medication on the intervening days.	Following successful induction and after the patient is receiving a stable dose, the frequency of TEVA-BUPRENORPHINE/NALOXONE dosing may be decreased to dosing every other day at twice the individually titrated daily dose. For example, a patient who receives a stable daily dose of 8 mg may be given 16 mg on alternate days, with no medication on the intervening days. However, the dose given on any one day should not exceed 24 mg. In some patients, following successful induction and after the patient is receiving a stable dose, the frequency of TEVA-BUPRENORPHINE/NALOXONE dosing may be decreased to 3 times Page 20 of 37 a week (for example on Monday, Wednesday and Friday). The dose on Monday and Wednesday should be twice the individually titrated daily dose, and the dose on Friday should be three times the individually titrated daily dose, with no	Following successful induction and after the patient is receiving a stable dose, the frequency of Mylan-Buprenorphine/Naloxone dosing may be decreased to dosing every other day at twice the individually titrated daily dose. For example, a patient who receives a stable daily dose of 8 mg may be given 16 mg on alternate days, with no medication on the intervening days. However, the dose given on any one day should not exceed 24 mg. In some patients, following successful induction and after the patient is receiving a stable dose, the frequency of Mylan-Buprenorphine/Naloxone dosing may be decreased to 3 times a week (for example on Monday, Wednesday and Friday). The dose on Monday and Wednesday should be twice the individually titrated daily dose, and the dose on Friday should be three times the individually titrated daily dose, with no medication on the

	However, the dose given on any SUBOXONE® (buprenorphine and naloxone) Product Monograph Page 22 of 40 one day should not exceed 24 mg. Patients requiring a titrated daily dose > 8 mg/day may not find this regimen adequate.	medication on the intervening days. However, the dose given on any one day should not exceed 24 mg. Patients requiring a titrated daily dose > 8 mg/day may not find this regimen adequate.	intervening days. However, the dose given on any one day should not exceed 24 mg. Patients requiring a titrated daily dose > 8 mg/day may not find this regimen adequate.
Reducing and terminating dose	The decision to discontinue therapy with SUBOXONE® should be made as part of a comprehensive treatment plan. To avoid withdrawal symptoms and potential relapse to illicit drug use, the SUBOXONE® dose may be progressively decreased over time in favourable cases until treatment can be discontinued. The decision to taper should be made by the prescriber, patient, and counsellor/support staff. The risk of relapse following withdrawal of treatment should be considered.	The decision to discontinue therapy with TEVA-BUPRENORPHINE/NALOXONE should be made as part of a comprehensive treatment plan. Both gradual and abrupt discontinuation have been used but controlled trials to determine the best method of dose taper have not been done. Gradual discontinuation is recommended with careful monitoring of the patient's progress. The risk of relapse following withdrawal of treatment should be considered.	The decision to discontinue therapy with Mylan-Buprenorphine/Naloxone should be made as part of a comprehensive treatment plan. Both gradual and abrupt discontinuation have been used but controlled trials to determine the best method of dose taper have not been done. Gradual discontinuation is recommended with careful monitoring of the patient's progress. The risk of relapse following withdrawal of treatment should be considered.
Contraindications	-patients with known hypersensitivity to buprenorphine, naloxone, or any other components of the drug product -opioid naïve patients. patients who have severe respiratory or severe hepatic insufficiency. -patients with acute alcoholism or delirium tremens.	-patients with known hypersensitivity to buprenorphine, naloxone, or any other components of the drug product. -opioid naïve patients. -should not be administered to women who are breast-feeding, -patients who have severe respiratory insufficiency, severe hepatic insufficiency, acute alcoholism, or delirium tremens.	-patients with known hypersensitivity to buprenorphine, naloxone, or any other components of the drug product. -opioid naïve patients. -should not be administered to women who are breastfeeding, -patients who have severe respiratory insufficiency, severe hepatic insufficiency, acute alcoholism, or delirium tremens.

Name	Pharmascience****	ACT buprenorphine/naloxone*****
Route	Sublingual	Sublingual
Form	Tablets	Tablets
Strength	2 mg buprenorphine/0.5 mg naloxone OR 8 mg/2 mg	2 mg buprenorphine/0.5 mg naloxone OR 8 mg/2 mg
Drug Class	Opioid	Opioid
Non-medicinal ingredients	Acesulfame potassium, citric acid anhydrous, corn starch, lactose monohydrate, mannitol, lemon & lime flavour, povidone K30, sodium citrate, and sodium stearyl fumarate.	Citric acid, crospovidone, lactose monohydrate, magnesium stearate, mannitol, natural & artificial lemon flavor, povidone, pregelatinized starch, sodium citrate and sucralose
Induction dose	When initiating treatment with Pharmascience BUPRENORPHINE/NALOXONE, the physician should be aware of the partial agonist profile of buprenorphine to the mu-opioid receptors, which may precipitate a withdrawal syndrome in opioid-dependent patients. The recommended starting dose is 4 mg BUPRENORPHINE/NALOXONE on Day 1. An additional 4 mg dose may be administered depending on the individual patient's requirement.	When initiating treatment with ACT The recommended starting dose is 8 mg ACT BUPRENORPHINE/NALOXONE on Day 1, initiating with 4 mg and then an additional 4 mg dose may be administered depending on the individual patient's requirement. The suggested total dose target for treatment on Day 1 is within the range of 8 and 12 mg. During initiation of treatment, closer dosing supervision is recommended to ensure proper sublingual placement of the dose and to observe patient response to treatment as a guide to effective dose titration according to clinical effect.
Stabilization and maintenance dose	The dose should be increased progressively according to individual patient need and should not exceed a maximum single daily dose of 24 mg. The dosage is titrated according to reassessment of the clinical and psychological status of the patient. During the initiation of treatment, daily dispensing of BUPRENORPHINE/NALOXONE is required for a minimum of two months. After clinical stabilisation, has been achieved, a graduated schedule of take-home doses may be granted.	Following treatment induction, the patient should be rapidly stabilised on an adequate maintenance dose by titrating to clinical effect. Dose titration in increments or decrements of 2 - 8 mg buprenorphine to a level that holds the patient in treatment and suppresses opioid withdrawal effects is guided by reassessment of the clinical and psychological status of the patient. A maintenance dose of 12 mg to 16 mg of ACT BUPRENORPHINE/NALOXONE used once daily is clinically effective for most patients. Doses should not exceed a maximum single daily dose of 24 mg.

		During maintenance therapy, it may be necessary to periodically re-stabilise the patient to a new maintenance dose in response to changing patient needs.
Less than daily dose	Following successful induction and after the patient is receiving a stable dose, the frequency of BUPRENORPHINE/NALOXONE dosing may be decreased to dosing every other day at twice the individually titrated daily dose. For example, a patient who receives a stable daily dose of 8 mg may be given 16 mg on alternate days, with no medication on the intervening days. However, the dose given on any one day should not exceed 24 mg. In some patients, following successful induction and after the patient is receiving a stable dose, the frequency of BUPRENORPHINE/NALOXONE dosing may be decreased to 3 times Page 20 of 37 a week (for example on Monday, Wednesday and Friday). The dose on Monday and Wednesday should be twice the individually titrated daily dose, and the dose on Friday should be three times the individually titrated daily dose, with no medication on the intervening days. However, the dose given on any one day should not exceed 24 mg. Patients requiring a titrated daily dose > 8 mg/day may not find this regimen adequate.	Following successful induction and after the patient is receiving a stable dose, the frequency of ACT BUPRENORPHINE/NALOXONE dosing may be decreased to dosing every other day at twice the individually titrated daily dose. For example, a patient who receives a stable daily dose of 8 mg may be given 16 mg on alternate days, with no medication on the intervening days. However, the dose given on any one day should not exceed 24 mg. In some patients, following successful induction and after the patient is receiving a stable dose, the frequency of ACT BUPRENORPHINE/NALOXONE dosing may be decreased to 3 times a week (for example on Monday, Wednesday and Friday). The dose on Monday and Wednesday should be twice the individually titrated daily dose, and the dose on Friday should be three times the individually titrated daily dose, with no medication on the intervening days. However, the dose given on any one day should not exceed 24 mg. Patients requiring a titrated daily dose > 8 mg/day may not find this regimen adequate.
Reducing and terminating dose	The decision to discontinue therapy with BUPRENORPHINE/NALOXONE should be made as part of a comprehensive treatment plan. Both gradual and abrupt discontinuation have been used but controlled trials to determine the best method of dose taper have not been done. Gradual discontinuation is recommended with careful monitoring of the patient's progress. The risk of relapse following withdrawal of treatment should be considered.	The decision to discontinue therapy with ACT BUPRENORPHINE/NALOXONE should be made as part of a comprehensive treatment plan. To avoid withdrawal symptoms and potential relapse to illicit drug use, the ACT BUPRENORPHINE/ NALOXONE dose may be progressively decreased over time in favourable cases until treatment can be discontinued. The decision to taper should be ACT made by the prescriber, patient, and counsellor/support staff. The risk of relapse following withdrawal of treatment should be considered
Contraindications	-patients with known hypersensitivity to buprenorphine, naloxone, or any other components of the drug product. -opioid naïve patients.	-Patients who are hypersensitive to buprenorphine, naloxone, or to any ingredient in the formulation. -Opioid naive patients.

	-should not be administered to women who are breast-feeding, -patients who have severe respiratory insufficiency, severe hepatic insufficiency, acute alcoholism, or delirium tremens.	-Patients with severe respiratory insufficiency: e.g., acute or severe bronchial asthma, chronic obstructive airway, status asthmaticus, acute respiratory depression and/or cor pulmonale. -Patients with severe hepatic impairment. -Patients with acute alcoholism, delirium tremens and convulsive disorders. Patients with known or suspected mechanical gastrointestinal obstruction (e.g., bowel obstruction or strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type). -Patients with suspected surgical abdomen (e.g., acute appendicitis or pancreatitis). Patients with severe CNS depression, increased cerebrospinal or intracranial pressure, and head injury. - Patients taking monoamine oxidase (MAO) inhibitors (or within 14 days of such therapy).

*Find the full product monograph that is prepared for healthcare professionals and includes this consumer medication information by visiting the Health Canada website; the manufacturer's website, www.indivior.com, or by calling 1-877-782-6966. This leaflet was prepared by Indivior Canada, Limited. Last revised: December 20, 2016.

**The full product monograph, prepared for health professionals can be obtained by contacting the manufacturer, Teva Canada Limited at: 1-800-268-4127 ext. 1255005 (English); 1-877-777-9117 (French) or druginfo@tevacanada.com This leaflet was prepared by: Teva Canada Limited 30 Novopharm Court Toronto, Ontario M1B 2K9 Canada Last prepared: June 2, 2017.

*** The full product monograph prepared for health professionals can be obtained by contacting the manufacturer, Mylan Pharmaceuticals ULC at: 1-800-575-1379 This leaflet was prepared by Mylan Pharmaceuticals ULC Etobicoke, Ontario M8Z 2S6 Revised on: March 30, 2017. Mylan Pharmaceuticals ULC Etobicoke, ON M8Z 2S6 1-800-575-1379 www.mylan.ca

**** Find the full product monograph that is prepared for healthcare professionals by visiting the Health Canada website (http://www.hc-sc.gc.ca/); or by calling 1-888-550-6060. This leaflet was prepared by Pharmascience Inc. Montréal, Canada H4P 2T4 www.pharmascience.com. Last revised: August 24, 2017

****** Find the full product monograph that is prepared for healthcare professionals and includes this consumer medication information by visiting the Health Canada website; the manufacturer's website, www.indivior.com, or by calling 1-877-782-6966. This document plus the full product monograph,

prepared for health professionals can also be obtained by contacting the sponsor, Actavis Pharma Company, at: 1-866-254-6111. This leaflet was prepared by Actavis Pharma Company. Date Revised: March 7, 2017.

18.0 APPENDIX C: ADVERSE EVENT REPORTING AND PROCEDURES

Each participating site's Principal Investigator is responsible for study oversight, including ensuring human research participant protection by designating appropriately qualified and trained study personnel to assess, report, and monitor adverse events.

Definition of Adverse Events and Serious Adverse Events

An **adverse event** (AE) is any untoward medical occurrence in humans, whether or not considered study medication/intervention related which occurs during the conduct of a clinical trial. Any change from baseline in clinical status, ECGs, lab results, x-rays, physical examinations, etc., that is considered clinically significant by the study physician are considered AEs. For the purpose of this study, the symptoms associated with opioid withdrawal are not defined as AEs. However, symptoms of precipitated withdrawal will be documented as AE's.

Suspected adverse reaction is any adverse event for which there is a reasonable possibility that the study medication/intervention caused the adverse event. A reasonable possibility implies that there is evidence that the study medication/intervention caused the event.

Adverse reaction is any adverse event related to the study medication/intervention.

An **adverse event, suspected adverse reaction,** or **adverse reaction** is considered "**serious**" (i.e., a serious adverse event, serious suspected adverse reaction or serious adverse reaction) if, in the view of either the study physician it:

- Results in death: A death occurring during the study or which comes to the attention of the study staff during the protocol-defined follow-up period, whether or not considered caused by the study medication/intervention, must be reported.
- Is life-threatening: Life-threatening means that the study participant was, in the opinion of the study physician at immediate risk of death from the reaction as it occurred and required immediate intervention.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Is a congenital abnormality or birth defect
- Important medical event that may not result in one of the above outcomes but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event.

Definition of Expectedness

Any adverse event is considered "unexpected" if it is not listed in the Product Monograph or the package insert or is not listed at the specificity or severity that has been observed. If neither is available, then the protocol and consent are used to determine an unexpected adverse event.

Medical and Psychiatric History

A thorough medical and psychiatric history during the screening visit and should record any chronic, acute, or intermittent pre-existing or current illnesses, diseases, symptoms, or laboratory signs of the participant, to avoid reporting pre-existing conditions as new AEs and to assist in the assessment of worsening in intensity or severity of these conditions that would indicate an AE.

Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and do not worsen are not considered AEs.

Site's Role in Eliciting and Reporting Adverse Events

Appropriately qualified and trained personnel will elicit participant reporting of AEs and SAEs at each study visit designated to collect AEs. Adverse events (medical and/or psychiatric) assessment will initiate with participant consent and follow-up will continue through 30 days post last study visit. Study staff will obtain as much information as possible about the reported AE/SAE to complete the AE/SAE forms and will consult as warranted.

Standard reporting, within 7 days of the site becoming aware of the event, is required for reportable AEs. Expedited reporting (within 24 hours of their occurrence and/or site's knowledge of the event) is required for reportable SAEs (including death and life-threatening events). Local sites are responsible for reporting SAEs to their REB, per their REB's guidelines.

Sites are also required to enter reportable AEs and SAEs in the REDCap system. The AE form is used to capture reportable AEs (as defined in the protocol). Additional information may need to be gathered to evaluate SAEs and to complete the appropriate CRFs and the summary. This process may include obtaining hospital discharge reports, medical records, autopsy records or any other type records or information necessary to provide a complete and clear picture of the serious event and events preceding and following the event. If the SAE is not resolved or stable at the time of the initial report or if new information becomes available after the initial report, follow-up information must be submitted as soon as possible.

Reportable adverse events will be followed until resolution, stabilization or study end. Any serious adverse reactions will be followed until resolution or stabilization even beyond the end of the study.

Site's Role in Assessing Severity and Causality of Adverse Events

Appropriately qualified and trained study staff will conduct an initial assessment of seriousness, severity, and causality when eliciting participant reporting of adverse events. A study physician will review reportable AEs for seriousness, severity, and causality on at least a weekly basis.

Guidelines for Assessing Severity

The severity of an adverse event refers to the intensity of the event:

Grade 1	**Mild** Transient or mild discomfort (typically < 48 hours), no or minimal medical intervention/therapy required, hospitalization not necessary (non-prescription or single-use prescription therapy may be employed to relieve symptoms, e.g. aspirin for simple headache, acetaminophen for post-surgical pain)
Grade 2	**Moderate** Mild to moderate limitation in activity some assistance may be needed; no or minimal intervention/therapy required, hospitalization possible.

Grade 3	**Severe** Marked limitation in activity, some assistance usually required; medical intervention/ therapy required hospitalization possible.
Grade 4	**Life-threatening** Extreme limitation in activity, significant assistance required; significant medical/ therapy intervention required, hospitalization or hospice care probable.
Grade 5	**Death** related to AE

Guidelines for Determining Causality

The study physician will use the following question when assessing causality of an adverse event to study medication/intervention where an affirmative answer designates the event as a suspected adverse reaction:

Is there a reasonable possibility that the study medication/intervention caused the event?

Safety Management Procedures of AEs/SAEs

The assigned Medical Monitor is responsible for reviewing all serious adverse event reports. Sites will report all SAE's to the Node Medical Monitor, Lead Medical Monitor, site PI and National Research Coordinator. All SAEs will be reviewed by the Lead Medical Monitor in REDCap and, if needed, additional information will be requested. SAEs will be reported to the DSMB who will also receive summary reports of all adverse events annually, at a minimum. The DSMB or REB may also request additional and updated information. Details regarding specific adverse events, their treatment and resolution, will be summarized by the Medical Monitor in writing for review by the DSMB. The REB or relevant local regulatory authorities may also suspend further trial treatment at a site, or the entire study as applicable.

Regulatory Reporting for a Non-IND Study

If an SAE meets the expedited reporting criteria (serious and unexpected suspected adverse reactions) the Lead Medical Monitor and National Research Coordinator will report to the Market Authorization Holder for the respective study medication. Expedited reporting of reactions which are serious but expected is not required. Expedited reporting is not required for serious events from clinical investigations that are considered unrelated to the study product, whether or not the event is expected.

Each ADR which is subject to expedited reporting should be reported individually in accordance with the Health Canada / ICH Guidance Document E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

Ongoing safety information respecting a drug should be conveyed to Investigator(s) and their Research Ethics Board(s). For further information refer to ICH Guidance Documents E6: Guideline for Good Clinical Practice and E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

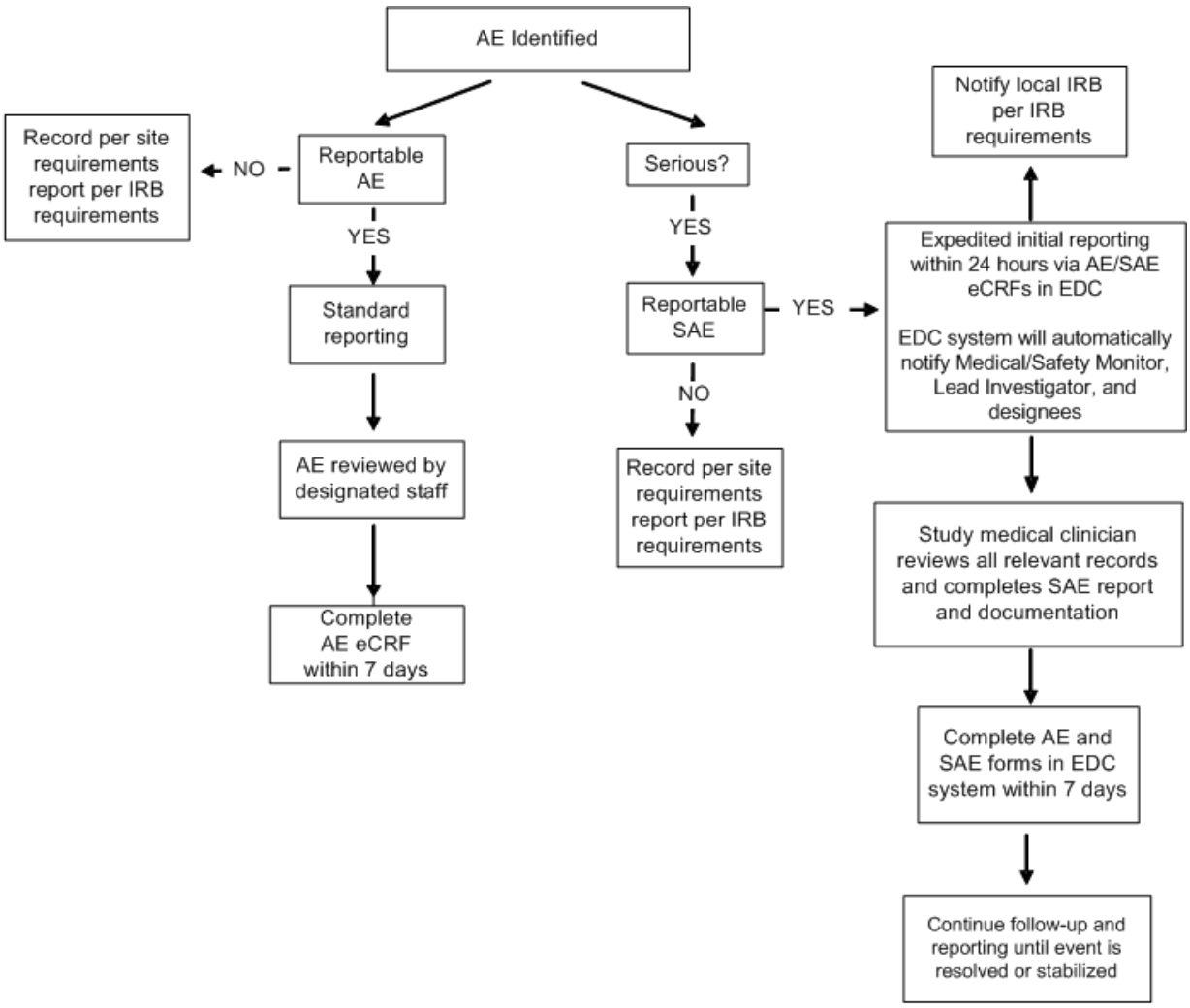
Reporting to the Data and Safety Monitoring Board

The DSMB will receive a list of AEs and summary reports of all SAEs at a frequency requested by the DSMB, but at least annually and will be informed of expedited reports of SAEs.

Participant Withdrawal

The study physician must apply his/her clinical judgment to determine whether or not an adverse event is of sufficient severity to require that the participant will be withdrawn from further study medication administration/study intervention. The study physician should consult with the site Principal Investigator, the co-investigator and/or Medical Monitor as needed. If necessary, a study physician may suspend any trial treatments and institute the necessary medical therapy to protect a participant from any immediate danger. A participant may also voluntarily withdraw from treatment due to what he/she perceives as an intolerable adverse event or for any other reason. If voluntary withdrawal is requested, the participant will be asked to complete an end-of-medication form to assure safety and to document end-of-medication outcomes and will be given recommendations for medical care and/or referrals to treatment, as necessary.

Adverse Event Reporting (Chart)



19.0 APPENDIX D: PHARMACOGENOMICS ANCILLARY STUDY

GENETICS ANALYSIS AND DNA BIOBANKING FOR FUTURE RESEARCH STUDIES

1.0 General Information

Principal Investigators:

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2.0 Background and Rationale

Genetic variation in metabolizing enzymes and receptor targets substantially alters individual response to drugs of abuse as well as their treatments. We propose to examine the influence of this genetic variation on prescription opioid (PO) misuse and response to treatment with methadone or buprenorphine/naloxone. Our studies will provide greater mechanistic understanding of pharmacogenetic variation in PO treatment response, which will in turn improve harm reduction efforts, as well as identify strategies for treatment optimization.

3.0 Study Goals and Objectives

The main objective of this study is to determine if genetic variants in the following enzymes and receptor targets are associated with treatment outcomes: 1) Opioid Receptor Mu 1 (OPRM1), 2) Cytochrome P450 2B6 (CYP2B6), 3) Opioid Receptor Delta 1 (OPRD1), 4) Cytochrome P450 2C19 (CYP2C19), 5) Cytochrome P450 3A4 (CYP3A4), and 6) UDP-Glucuronosyltransferase-2B7 (UGT2B7). These CYP and UGT enzymes have been selected *a priori* due to their demonstrated effects in the metabolism pathways of the treatment drugs, while the opiate receptors have been selected *a priori* because they serve as the drug targets of POs and the treatment drugs (methadone and buprenorphine/naloxone). As a secondary objective, we will also examine whether genetic variation in these enzymes and receptors is associated with severity of PO use disorder and other markers related to the pattern of PO use disorder during the screening period.

4.0 Study Design

Individuals will be invited to participant in this study at the screening visit for the main trial and once the informed consent for the main trial is signed. A separate consent process will take place for those who wish to participate in this ancillary study. This study would involve the collection of a small amount of blood (approximately 20 mL). Individuals can take part in the study during the screening period or at any time during the 24-week intervention period. This sample would then be stored, shipped and analyzed in the Department of Pharmacology & Toxicology at the University of Toronto (PI: Rachel Tyndale). DNA extraction and subsequent genotyping will be performed in batches as samples are sent from different sites over a period of 24 months. The involvement of the OPTIMA research staff will remain minimal requiring only appropriate initial acquisition and freezing of blood samples, and storage, before shipping to the University of

Toronto for DNA extraction and genotyping experiments. Each site will designate research staff with specialized training for manipulation and organization/shipping of the samples as described above.

5.0 Methodology

DNA extraction. DNA will be extracted from a blood sample drawn during the initial screening visit, or at any time over the course of the 24-week intervention period, from participants that provided written informed consent for ancillary blood draw for genetic testing. Genetic variants in *OPRM1*, *CYP2B6*, *OPRD1*, *CYP2C19*, *CYP3A4* and *UGT2B7* will be assessed by standard genotyping methods.

Blood samples and genotyping. Blood samples will be collected in commercially available lavender top vacutainer tubes containing 10 ml EDTA (BD, cat#: 366643). The lavender top EDTA tubes will be labeled before the participant leaves the blood draw chair; labels will include SAMPLE ID (which is a combination of Study ID + Visit) and Collection Date. No centrifugation is required. As quickly as possible after collection, tubes will be transferred into 15 ml centrifuge tubes (Sarstedt, cat#: 62.554.205) that can be safely stored at temperatures down to -80^{o}C. Samples will be stored at 4^{o}C (e.g. if storage < 2 weeks), -20^{o}C (if storage < 2 months) or -70^{o}C (for extended storage; ≥ 2 months). Blood samples in centrifuge vials will be shipped on dry ice to Dr. Rachel Tyndale at the University of Toronto; Dr. Tyndale will be conducting genetic analyses using standard genotyping and statistical analysis methods in conjunction with Dr. Bernard Le Foll at CAMH. Initial analyses will focus on the influence of polymorphisms in the μ opioid receptor (OPRM1) gene and genes involved in the metabolism of opiate treatment drugs on collected clinical phenotypes (e.g., PO use, withdrawal, craving, medication adherence, etc.).

6.0 Data Management and Statistical Analysis

Interim analyses could include associations between genetic variants and main clinical outcomes, which could be performed as the outcomes data become available for analyses. We will evaluate the influence of genetic variants on the main outcome of this study (i.e., proportion of opioid-free urine drug screens during the 24 weeks of the trial) by using a mixed design ANOVA with two factors (genotype and treatment). We will also compare each genotype separately using Chi-square tests and regression models. The influence of genetic variation on treatment outcomes is innovative as it has not studied before; likewise, our secondary aim will examine genetic risk for having a prescription opioid use disorder. Characterizing genetic variation in the level of prescription opioid (PO) use at baseline in the screened population of PO users will complement our assessments of genetic influences on treatment outcomes.

7.0 Quality Assurance and Monitoring

Monitoring and quality assurance for this study will be conducted by the monitor for the OPTIMA trial. During the visit, the monitor will meet with the personnel and local investigators, will verify files such as documentation of participant status, CRFs (review and status), protocol compliance, staff changes, documentation of adverse events and serious adverse events (and ensure their proper reporting), as well as documentation of source data and concomitant medications (see protocol section 12.4). To minimize safety concerns regarding blood sampling, manipulation, and transportation, research staff will complete specific training (i.e., Blood Borne Pathogens and Transportation of Dangerous Goods Training) at their respective sites. Each site will designate specific research staff for manipulation (i.e. completed Blood Borne Pathogens training) and organization/shipping of the samples (i.e. completed Transportation of Dangerous Goods training). Required items necessary for sample collection/shipment to the different sites will be provided to research staff. Each site will be required to create and properly maintain a log recording each sample collected with date and sample ID as specified in the guidelines for this study. Additional logs specifying the samples shipped in each batch will be also required.

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