A pragmatic, multi-centre, open-label, randomized, 12-month, parallel group, superiority study to compare the effectiveness of subcutaneous buprenorphine depot (Sublocade®) vs daily sublingual buprenorphine with naloxone (Suboxone®) for the treatment of opioid use disorder

STOP-IT

Protocol version: version 4.0 (10-Aug-2022)
Protocol version: version 3.12 (6-June-2022)
Protocol version: version 3.1 (2-May-2022)
Protocol version: version 3.0 (11-APR-2022)
Protocol version: version 2.0 (02-FEB-2022)
Original version: version 1.0 30-NOV-2021
ClinicalTrials.gov:

RAAM
North Simcoe Muskoka
Rapid Access Addiction
Medicine Services

RVH Royal Victoria Regional Health Centre | Research Institute

Table of Contents

1 Trial Registration

1.1 Data set

Data Category	Information
Primary registry and trial identifying number	ClinicalTrials.gov
Date of registration in primary registry	TBD
Secondary identifying numbers	TBD
Source(s) of monetary or material support	N/A
Primary sponsor	Royal Victoria Regional Health Centre Research Institute
Contact for public queries	Philip Wong NP, MN [wongp@rvh.on.ca]
Contact for scientific queries	Giulio DiDiodato MD, PhD [didiodatog@rvh.on.ca] Royal Victoria Regional Health Centre Research Institute, Barrie, Canada
Public title	Monthly versus daily buprenorphine formulations for treatment of opioid use disorder (OUD)
Scientific title	A pragmatic, multi-centre, open-label, randomized, 12-month, parallel group, superiority study to compare the effectiveness of subcutaneous buprenorphine depot (Sublocade®) vs daily sublingual buprenorphine with naloxone (Suboxone®) for the treatment of opioid use disorder (**STOP IT**)
Country of recruitment	Canada
Health condition/problem studied	Agonist treatment, opioid use disorder
Intervention	Experimental: Sublocade® Active Comparator: Suboxone®
Key Inclusion and exclusion criteria	Ages eligible: 18 to 65 years Sexes eligible: Male; Female; Other OUD eligible: Moderate-to-severe OUD as defined by the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-V) Induction/Stabilization therapy: Started and stabilized on Suboxone® (8mg/2mg to 24mg/6mg) for ≥7 days as determined by the following criteria: 1) No allergic reaction to buprenorphine, and

	2) Clinical Opiate Withdrawal Scale score ≤12 (scale:0-48), and 3) Opiate Craving Visual Analog Scale score ≤20 (scale:0-100) Inclusion criteria: 1) Written informed consent prior to enrolment 2) Must have an active Ontario Health Insurance Plan number 3) Contact information (telephone) available 4) Must have drug insurance coverage for either medication for duration of study or demonstrate ability to pay for the drug out-of-pocket Exclusion criteria: 1) Receiving any investigational drug for OUD in previous 4 weeks 2) Congenital long QT syndrome or QT prolongation at baseline
Study type	Interventional Allocation: randomized 1:1 Intervention model: parallel assignment Masking: open-label Primary purpose: comparative effectiveness
Date of first enrollment	November 1, 2022
Target sample size	90
Recruitment status	Not yet started
Primary outcome(s)	1) Difference in proportion of relapse-free weeks (time-frame; 12 months) 2) Difference in incidence rates of opioid-related healthcare utilization (time-frame; 12 months)
Key secondary outcome(s)	1) Difference in Medication Satisfaction Questionnaire scores 2) Difference in World Health Organization Quality of Life – BREF Questionnaire scores 3) Difference in proportion of patients who attend ≥80% of scheduled clinic visits 4) Difference in opioid-related mortality proportions

1.2 Glossary of abbreviations and terms

CADTH	Canadian Agency for Drugs and Technologies in Health
COWS	Clinical Opiate Withdrawal Scale
DSM-V	Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition
ICD-10-CA	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada
OUD	Opioid use disorder
RAAM	Rapid Access Addiction Medicine
RVH	Royal Victoria Regional Health Centre
OAT	Opioid agonist therapy
ODB	Ontario Drug Benefit
SC-BPN-XR	Monthly subcutaneous buprenorphine
SL-BPN/NX	Daily sublingual buprenorphine/naloxone
SOPs	Standard operating procedures
VAS	Visual analog scale
WHOQOL-BREF	World Health Organization Quality of Life – Brief

2 Protocol Version

2021-November-30	Original (version 1.0)
2022-February-02	Revised (version 2.0)
2022-April-11	Revised (version 3.0)
2022-May-02	Revised (version 3.1)
2022-June-06	Revised (version 3.12)
2022-Aug-10	Revised (version 4.0)

3 Funding

All clinical services provided at the study sites (RAAM clinics), including staff salaries, equipment and consumables will be provided by the Royal Victoria Regional Health Centre. While there is no funding currently available for this study, some funding may be provided by the Royal Victoria Regional Health Centre Foundation at some later date to support data abstraction from the Institute for Clinical Evaluative Sciences.

4 Administrative information

4.1 Investigators

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4.11 Contributions

PW conceived of the study.

PW, GD initiated and revised the study design and protocol.
PW, GD approved the protocol.

4.2 Rapid Access Addiction Medical (RAAM) Clinics

4.21 Administrative

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Barrie, Ontario, Canada, L4N 1K4
Telephone: (705)797-3095

RAAM Clinic (Orillia)
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Orillia, Ontario, Canada, L3V 4S8
Telephone: (705)797-3095

RAAM Clinic (Midland)
287 Bayshore Drive, Second floor, Chigamik Community Health Centre
Midland, Ontario, L4R 0B7
Telephone: (705)797-3095

RAAM Clinic (Wasaga Beach)
14 Ramblewood Drive, Unit#202, South Georgian Bay Community Health Centre

Wasaga Beach, Ontario, L9Z 0C4
Telephone: (705)797-3095

4.3 Trial sponsor

4.31 Contact information

Trial sponsor: Royal Victoria Regional Health Centre (RVH) Research institute
Sponsor's Reference: 119129260 RR 0001 (Charitable Registration Number)
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4.32 Roles and responsibilities

4.32a Trial sponsor

The trial sponsor has no role in the design, analyses, interpretation of the data, writing or decision to report the study results. The sponsor will support study coordination and execution, including informed consent, enrollment, randomization, follow-up, administering questionnaires, data collection and storage, and monitoring. The study sponsor is responsible for taking all reasonable steps to ensure proper conduct of the clinical trial protocol, and that the clinical trial is performed in accordance with the International Council for Harmonisation for Good Clinical Practice (https://www.ich.org/page/efficacy-guidelines#6) and all applicable regulatory requirements.

4.32b Trial funders

The funding source (Royal Victoria Regional Health Centre/Royal Victoria Hospital Foundation) has no role in the design, execution, analyses, interpretation of the data, writing or decision to report the study results.

4.4 Committees

4.41 Investigators

4.41a Members

Principal investigator: Philip Wong
Biostatistician: Giulio DiDiodato

4.41a Roles and responsibilities

Design, conduct and analysis of **STOP-IT** study
Preparation of protocol and revisions
Preparation of electronic case report forms
Publication of study reports
Members of the trial and data management committees

4.42 Trial management committee

4.42a Members

Philip Wong [Chair], Dr. Jesse McLean, Christine DiMarco, Kelly Cruise, Dr. James Shaver, Brian Irving

4.42b Roles and responsibilities

Study planning
Serious unexpected suspected adverse events reporting

Responsible for master file
Site visits and monitoring
Data quality and audit

5 Background and Rationale

5.1 Background

5.11 Definition

Opioid use disorder (OUD) is defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) as a "problematic pattern of opioid use leading to clinically significant impairment or distress."[1] At least 2 of 11 pre-specified criteria must be present within a 12-month period to fulfil the DSM-V clinical definition. The DSM-V also uses the number of criteria present to categorize the severity of OUD, with mild OUD defined as having 2-3 criteria present, moderate OUD defined as having 4-5 criteria present, and severe OUD defined as having ≥6 criteria present.

5.12 Epidemiology

Opioid use disorder and opioid-related deaths are increasing in Ontario and Canada.[2,3] Compared to 2016, the age-adjusted opioid-related mortality rates in 2020 have increased by 161% in Ontario to 16.5 per 100 000 population and 114% in Canada to 16.7 per 100 000 population. Over 90% of these deaths were non-intentional, with 87% of all deaths involving fentanyl or fentanyl analogues. The majority of deaths occurred in males (75%) between the ages of 20 to 59 (88%). In the North Simcoe Muskoka Local Health Integration Network, the study region, there were 128 opioid-related deaths in 2020, an increase of 191% from 2016.

Like deaths, opioid-related healthcare utilization as measured by hospitalization and emergency department visits have also been increasing over the same time period.[3,4] Compared to 2016, the age-adjusted opioid-related hospitalization rates in 2020 have increased by 19.8% in Ontario to 16.3 per 100 000 population and 5.9% in Canada to 17.8 per 100 000 population. Emergency room visits have increased by 166% during the same time period in Ontario to 84.5 per 100 000 population. In the North Simcoe Muskoka Local Health Integration Network, there were 622 emergency room visits and 128 hospitalizations that were opioid-related in 2020. The majority of hospitalizations and emergency room visits occurred in males (60%) between the ages of 20 to 59 (73%). The median length of hospitalization from 2016 to 2020 has remained unchanged at 3 days (Range 1 to 207 days), with an average cost per hospitalization of $9 626 (CDN) (Range $26 to $296 831) (Source: The Ontario Case Costing Initiative; N=889 cases; Reporting period 2017 to 2018; ICD-10-CA codes F11.0 to F11.9 & T40.2; Accessed November 8, 2021).

5.13 Treatment

Opiate substitution treatment with either full (methadone) or partial (buprenorphine) opioid agonist therapy (OAT) has been shown to reduce self-reported opioid use or opiate positive urine drug tests compared to detoxification or psychological treatments.[5,6] Opiate substitution treatment is also associated with a reduced risk of death.[7,8] Relative adherence to OAT is highest when delivered as part of a comprehensive treatment program.[6,9] Rapid access addiction medicine (RAAM) clinics have been established in Ontario to facilitate access to opiate substitution treatment as part of a comprehensive substance use disorder program.[10]

There are 2 main opioid agonists used to treat OUD, methadone and buprenorphine.[11] Buprenorphine has been approved by Health Canada for use in OUD, and is available in immediate (Suboxone®) and extended-release (Sublocade®) formulations. Monthly subcutaneous buprenorphine (SC-BPN-XR) has been shown to be non-inferior to daily sublingual buprenorphine/naloxone (SL-BPN/NX) for medication adherence and treatment retention.[12] Other extended-release buprenorphine formulations have also demonstrated similar results (Table 1).[13,14] The rationale for extended-release buprenorphine is to minimize the risk of suboptimal medication adherence, diversion, intravenous misuse and unintended exposures associated with buprenorphine/naloxone films and tablets.[6]

Table 1: Summary of comparative effectiveness of extended-release versus immediate release buprenorphine

Author (Country/year)	Buprenorphine		Time Period (weeks)	Primary Outcome	Effect size (extended vs immediate) (mean difference (95% CI))
	Extended (N)	Immediate (N)			
Rosenthal *et al.* (USA/2013)	Implants (4 x 80mg) (N=114)	SL-BPN/NX (12-16 mg/d) (N=119)	24	Mean % negative uds[1] + self-report opioid use (weeks 1 to 24)	31% vs 33.1% (-2.1 (-10.7, 6.2))
Rosenthal *et al.* (USA/2016)	Implants (4 x 80mg) (N=84)	SL-BPN/NX (≤8 mg/d) (N=89)	26	Responder proportion[2]	96.4% vs 87.6% (8.8% (0.009, ∞))
Lofwall *et al.* (USA/2018)	SC-BPN (8-32 mg/week) (weeks 1-11) SC-BPN (64-160 mg/month) (weeks 12-24) (N=215)	SL-BPN/NX (4-24 mg/d) (weeks 1-11) SL-BPN/NX (8-32 mg/d) (weeks 12-24) (N=213)	24	Mean % negative uds + self-report opioid use Responder proportion[3]	35.1% vs 28.4% (6.7% (-0.1, 13.6)) 37.0% vs 31.0% (3.0% (-4.0, 9.9))

[1] uds=urine drug screen; missing uds imputed as positive; denominator was 72 uds (3 per week x 24 weeks)
[2] responder proportion defined as participant with ≥4 of 6 months with negative uds + negative self-report (uds + self-report scheduled every month plus 4 random uds; total 10 uds + self-reports); all patients had been on SL-BPN/NX ≥ 12 months prior to enrollment; missing uds imputed as positive or negative with a 20% penalty for positive in extended-release group

[3] responder proportion defined as participant with ≥ 2 weeks uds/self-report negative of weeks 9-11 + uds/self-report negative at week 12, plus ≥ 5 weeks uds/self-report negative of weeks 12-24 + uds/self-report negative from weeks 21-24; missing uds imputed as positive

In Ontario, OAT prescriptions and prescribers have been increasing.[15] Compared to 2016, buprenorphine prescription rates have increased by 61% to 1.91 patients per 1 000 population. While methadone still represents the most commonly prescribed OAT in Ontario, with a prescription rate of 2.88 patients per 1 000 population, its use has declined by 9% since 2016. The number of OAT prescribers in Ontario in 2020 was 4887, an increase of 112% from 2016. In 2020, 87.8% of OAT prescribers prescribed only buprenorphine (71.4%) or both buprenorphine and methadone (16.4%), while the remainder (12.2%) prescribed only methadone. In the North Simcoe Muskoka Local Health Integration Network, buprenorphine and methadone prescription rates are higher than the provincial average at 2.08 and 4.13 patients per 1 000 population, respectively. The number of buprenorphine only (N=259), buprenorphine and methadone (N=140) and methadone only (N=143) prescribers has also increased in the study region, with the largest increase in the buprenorphine only group (+123% from 2016 to 2020).

5.14 Costs

The Canadian pharmaceutical costs of Sublocade® and Suboxone® differ substantially (Table 2).[16]

Table 2: Canadian costs of buprenorphine-based OAT

Drug	Health Canada Approval Date	Dose	Monthly Costs ($CDN)
Sublocade®	November 21, 2018	100 mg/0.5 ml 300 mg/0.5 ml	550 550
Suboxone®	August 25, 2015	2 mg/0.5 mg 8 mg/2 mg	72 77

The costs of both drugs are covered through the Ontario Drug Benefit (ODB) program. However, Sublocade® is limited for use in patients with moderate- to severe-OUD who have been stabilized on 8 to 24 mg/day of transmucosal buprenorphine/naloxone for at least 7 days and who are also receiving counselling and psychosocial supports by experienced healthcare providers in the diagnosis and management of OUD. Eligibility criteria for the ODB program are limited to patients aged 25 years and under or 65 years and older; or are enrolled in the Ontario Works, Ontario Disability Support Program or Trillium Drug Program; or are receiving professional home and community services; or are living in a long-term home or a home for special care. As a result, the majority of patients meeting criteria for Sublocade® use must pay for the drug out-of-pocket resulting in significant restriction to access for this population that has a high burden of chronic homelessness and poverty.

A recent pharmacoeconomic report by the Canadian Agency for Drugs and Technologies in Health (CADTH) concluded that the current evidence base for supporting cost-effectiveness of Sublocade® over buprenorphine/naloxone is limited by the absence of studies directly comparing the effectiveness of the two treatments on clinically important outcomes such as healthcare utilization.[16] Additionally, the comparative effectiveness studies reviewed in Section 5.13 were all conducted in the United States, making inferences about Canadian settings such as the RAAM clinics and their clientele uncertain. With limited evidence and significant uncertainty, the CADTH analysis suggested that a price reduction of at least 73% would be required for Sublocade® to be a cost-effective alternative to buprenorphine/naloxone.

5.2 Rationale

An extended-release OAT formulation that can be safely delivered in RAAM clinics across Canada might prevent costly healthcare and poor outcomes in hundreds, if not, thousands of patients. A real-world (pragmatic) randomised study is therefore needed to compare the treatment effectiveness of Sublocade® versus Suboxone® in Canadian patients attending RAAM clinics for OAT for moderate- to severe-OUD. This study is needed to demonstrate the superior benefits of Sublocade® on important clinical outcomes such as reduced opioid and healthcare utilization in order to demonstrate its cost-effectiveness and justify expanded access to Sublocade® for this at-risk population.

5.3 Choice of Comparator

According to the Canadian and Ontario guidelines for OAT, transmucosal buprenorphine/naloxone is the first-line treatment for moderate- to severe-OUD.[6,17] Suboxone® will be the active comparator in this study. The medically active ingredients in Suboxone® are buprenorphine, a partial μ-opioid receptor agonist, and naloxone, a μ-opioid receptor antagonist. Suboxone® (buprenorphine/naloxone) formulations approved for use in Canada come in sublingual tablets (SL) and soluble films (SF) in doses ranging from 2 mg/0.5 mg (SL/SF), 4 mg/1 mg (SF), 8 mg/2 mg (SL/SF), 12 mg/3 mg (SL/SF) and 16 mg/4 mg (SL). Both formulations can be administered sublingually, but the SF can also be administered buccally. The usual treatment course requires induction, stabilization, and maintenance phases, with the ultimate goal being weaning to abstinence if possible. For those patients attending any one of the study RAAM clinics who have been started on treatment with Suboxone® for moderate- to severe-OUD after discussion with their healthcare provider, those who have been stabilized on 8 mg to 24 mg/day of buprenorphine for at least 7 days will be eligible to be enrolled in the study. For those who are enrolled in the study and are randomly allocated to continue receiving Suboxone® for the remainder of the study period, their ongoing Suboxone® maintenance dosing will be determined by themselves and their healthcare provider through the usual processes of clinical care. In general, treatment with Suboxone® is directly observed by the pharmacist in a community pharmacy experienced with OAT during the induction and stabilization phases. Once stabilized, the patient and provider can negotiate unsupervised Suboxone® administration through varying amounts of take-home doses during the

maintenance phase. Initially, the unsupervised intervals are short, typically one to several days, and depending on patient compliance with treatment that includes counselling and RAAM clinic visits every one to two weeks, abstinence from other non-prescription opioid and non-opioid substances as determined through self-report and urine drug screens, and evidence of absence of withdrawal symptoms, the take-home intervals may be extended. Breakthrough doses of Suboxone® may also be prescribed during the maintenance phase if the patient is experiencing withdrawal symptoms. It is not expected that any patient in the maintenance phase of OAT with either Suboxone® or Sublocade® during the 12-month study period will be ready for an attempted wean to abstinence.

6 Hypotheses

In patients with moderate- to severe-OUD between the ages of 18 to 65 years old who seek care or are referred to one of the four RAAM clinics in the North Simcoe Muskoka Local Health Integrated Network for opioid-substitution therapy and are stabilized on Suboxone®, subsequent maintenance therapy with Sublocade® (intervention) versus Suboxone® (control) for a period of 12-months will be superior for reducing opioid positivity (as determined by proportion of negative urine drug screens and self-reports) and healthcare utilization (as determined by the total number of ER visits and hospital days per patient days exposure)

7 Objectives

7.1 Primary

1) To compare the effect of Sublocade® versus Suboxone® on reducing non-prescription opioid utilization in patients with moderate- to severe-OUD

2) To compare the effect of Sublocade® versus Suboxone® on reducing healthcare utilization in patients with moderate- to severe-OUD

7.2 Secondary

1) To compare the effect of Sublocade® versus Suboxone® on improving patient satisfaction

2) To compare the effect of Sublocade® versus Suboxone® on improving patient quality of life

3) To compare the effect of Sublocade® versus Suboxone® on clinic retention

4) To compare the effect of Sublocade® versus Suboxone® on patient mortality

8 Design

The **STOP-IT** trial is designed as a pragmatic, multi-centre, randomised, controlled, open-label, superiority study with two parallel groups and primary endpoints of opioid positivity and healthcare utilization at 12 months after enrollment. Randomization will be performed with a 1:1 allocation ratio using a stratified, permuted-block group schema according to the following strata (no fixed ratio):
1) RAAM clinic site (Barrie, Orillia, Midland, Wasaga Beach)
2) Severity of OUD according to DSM-V criteria (moderate vs severe)

9 Study Setting

The four RAAM clinics in the North Simcoe Muskoka Local Health Integrated Network will recruit patients for the study. The North Simcoe Muskoka Local Health Integrated Network is a provincial regional health authority mandated to plan, integrate and fund local health services across the District of Muskoka, Simcoe County and Grey County. This region serves a population of 479 471 (2015), representing 3.5% of the province of Ontario's population. The Network distributes over $880 million (CDN) in funding to 61 unique health service provider organizations that include 7 hospitals, 21 long-term care homes, 3 community centres, 23 community support services and 7 community health centres. In partnership with the Simcoe Muskoka District Health Unit, the Network developed the Simcoe Muskoka Opioid Strategy in 2017 in response to the higher-than-average provincial rates of opioid-related morbidity and mortality being experienced in the region.[18] Increased access to OAT through the RAAM clinics is an essential component of that strategy (p.38).

The four RAAM clinics are located in the cities of Barrie, Orillia, Midland and Wasaga Beach. These clinics are part of a provincial strategy to remove barriers to access for addiction services and provide a more patient-centred model of addiction services.[18] There are currently 54 RAAM clinics located across Ontario, with the plan to continue to open new RAAM clinics across the province. All the RAAM clinics are based on a similar service model.[10] The four study clinics are owned and managed by the Royal Victoria Regional Health Centre, a 388-bed acute care community hospital in Barrie. Patients can self-refer or be referred for addiction services from any healthcare provider. The clinics provide voluntary outpatient services that include medical and psychosocial treatments for substance use disorders. The clinics are staffed by an interdisciplinary team of physicians, nurse practitioners, registered nurses, registered practical nurses, social workers, addiction counsellors who work together to create a unique treatment plan for each patient. Pharmacotherapy for alcohol and opioid use disorders is available. The clinics do not provide treatment for acute or decompensated mental health illness, treatment for chronic pain disorders or serve as safe injection sites. Since April 1, 2021, there have been 801 consultations, of which 346 involved prescription and non-prescription opioid use.

10 Eligibility

Patients must provide written, informed consent before any study procedures occur.

10.1 Inclusion criteria

Patients eligible for the trial must comply with all of the following at randomization:

1. Ages 18 to 65 years old
2. OAT indicated for moderate- to severe-OUD[1]
3. Attend a RAAM clinic in the North Simcoe Muskoka Local Health Integrated Network for opiate substitution treatment
4. Successfully completed induction and stabilization OAT with Suboxone® tablet or film defined as receiving 8mg/2mg to 24mg/6mg of Suboxone® for ≥7 days with no evidence of allergic reaction to Suboxone®, Clinical Opiate Withdrawal Scale[19] (COWS) score ≤12 (scale:0-48) for ≥24 hours, and Opiate Craving Visual Analog Scale[20] (VAS) score ≤20 (scale:0-100)) for ≥24 hours
5. Must have an active Ontario Health Insurance Plan number
6. Must have a telephone that can receive calls, text messages or emails
7. Must have drug insurance coverage for either medication for duration of study or demonstrate ability to pay for the drug out-of-pocket

10.2 Exclusion criteria

1. Receiving any investigational drug for OUD in previous 4 weeks
2. Congenital long QT_c syndrome or QT_c prolongation at baseline by electrocardiogram (QT_c ≥450 milliseconds in men and QT_c ≥470 milliseconds in women)
3. Pregnant or lactating women
4. Women of childbearing potential who are not using an effective and reliable method of contraception

11 Interventions

11.1 Medications

Eligible patients will be randomly allocated in a 1:1 ratio between Suboxone® and Sublocade®. Both study drugs will be provided to participants in their commercially available forms. For those patients who are not eligible for drug coverage under the Ontario Drug Benefit Plan or other insurance plan, eligible patients must demonstrate the ability to pay for either medication out-of-pocket. The commercially available drugs will be provided by the RAAM clinics (Sublocade®) or pharmacies (Suboxone®) as per the usual process of care. This is an open-label study so no changes in labelling or packaging will take place, and both drugs will be stored, handled, administered and disposed of in accordance with the manufacturer's recommendations and the RAAM clinics' and pharmacies' standard operating procedures (SOPs). This is a pragmatic, comparative effectiveness study so the management of the participants and their medications in the RAAM clinics will be left up to the discretion of the RAAM healthcare personnel who have all received training and are experienced in the diagnosis, management and treatment of OUD.

For eligible patients randomly allocated to Sublocade®, the first dose will be administered at the time of randomization (Day 0). Sublocade® comes in two formulations, 100 mg and 300 mg buprenorphine doses in a pre-filled syringe. Sublocade® administration is by subcutaneous injection in the abdomen. Sublocade® is administered at intervals ≥26 days. For patients randomly allocated to Sublocade®, they will receive the 300 mg dose for the first 2 months, followed by the 100 mg dose every month until the end of the 12-month period. All Sublocade® doses will be administered in the RAAM clinics by trained personnel according to SOPs. All patients receiving Sublocade® will have their vital signs monitored every 5 minutes for 15 minutes after the injection before leaving the clinic.

For eligible patients randomly allocated to Suboxone®, the first study dose will be administered at the time of randomization (Day 0) and will match the Suboxone® type (tablet versus film), route (sublingual versus buccal) and dose used for stabilization prior to study enrollment. For the first 2 weeks of the study period, all Suboxone® administration will be directly observed at community pharmacies by trained personnel according to the usual standard of care. Subsequent to this period, healthcare providers and participants will develop a care plan for ongoing directly observed therapy vs unsupervised take-home dosing according to usual standard of care.

11.2 Counselling

For eligible patients enrolled in the study, each will receive individual patient counselling for addictions, mental health and trauma by trained RAAM clinic personnel at each clinic visit according to the usual standard of care. In addition, each participant will be provided with links to community social support services. For those participants who need it, connection to a primary care provider will be provided.

11.3 Screening

For eligible patients enrolled in the study, each will receive pregnancy screening at regular intervals. Female patients of child-bearing age will also be questioned about contraceptive use, and counselled about the potential risks of OUD treatment in pregnancy. Screening for illicit drug use will be done using a combination of a validated self-reporting tool[21] and urine drug testing at each clinic visit. Screening for opioid withdrawal[19] and craving[20] will be done at each clinic visit. Weight, vital signs and mental status[22] will be screened at each clinic visit.

11.4 Modifications

For eligible patients randomly allocated to Sublocade®, missed doses can be administered up to 42 days after the last dose. For those with longer intervals between Sublocade® doses, it will be up to the discretion of the RAAM clinic healthcare providers whether repeated induction and stabilization with Suboxone® is required, and if Sublocade® treatment should be re-

initiated. At the discretion of the RAAM clinic healthcare providers, some participants may receive breakthrough doses of Suboxone® and/or an increased maintenance dose of Sublocade® of 300 mg per month instead of 100 mg per month as clinically indicated to prevent opioid cravings (VAS ≥ 21) or withdrawal (COWS ≥ 5) symptoms. In some cases, Sublocade® doses may need to be reduced or discontinued due to adverse effects.

For eligible patients randomly allocated to Suboxone®, at the discretion of the RAAM clinic healthcare providers, some participants may receive breakthrough doses of Suboxone® and/or increased maintenance doses of Suboxone® as clinically indicated to prevent opioid cravings (VAS ≥ 21) or withdrawal (COWS ≥ 5) symptoms. Daily dose of Suboxone® should not exceed 24 mg buprenorphine. In some cases, Suboxone® doses may need to be reduced or discontinued due to adverse effects.

For eligible patients with abnormal vital signs (a change from baseline measurements and any of the following: systolic blood pressure ≤ 90 mm Hg OR mean arterial blood pressure ≤ 55 mm Hg OR heart rate ≥ 130 beats per minute OR temperature ≥ 38.1^{o}C OR ≤ 36^{o}C OR respiratory rate ≤ 8 breaths per minute OR ≥ 30 breaths per minute or mental status (Glasgow coma scale ≤14), RAAM healthcare personnel will investigate the causes for these abnormalities prior to consideration of buprenorphine dosing, and make all necessary arrangements for medical management of the patient.

For eligible patients who have either a positive urine drug screen, illicit drug use by self-report, or refuse to submit to these screens, individualized patient counselling with an addictions counsellor will attempt to understand the underlying reasons for relapse or refusal to screen as per usual standard of care. RAAM healthcare personnel will take into consideration opioid positivity (either positive urine drug screen or self-report) or refusal to screen prior to the administration of study medications.

For eligible patients with a positive pregnancy test after a negative pre-enrollment test, RAAM healthcare personnel will counsel the patient about the potential negative effects (teratogenicity, neonatal opioid withdrawal syndrome) of ongoing study medication treatment, and the options for alternative management of OUD as per usual standard of care.

11.5 Retention and adherence

For eligible patients enrolled in the study, retention and adherence interventions will include:

1) Phone call 2 days before each scheduled clinic visit to determine if there will be any barriers to attending the scheduled visit, and working on solutions to remove these barriers to maximize compliance with scheduled visits
2) Assistance to complete scheduled questionnaires (quality of life and medication satisfaction) either in clinic or remotely
3) Provide in-home laboratory and electrocardiographic services as needed if a patient cannot travel to the lab site

4) Instructions about taking study tablets/films including dose timing, route, storage, and what to do in the event of a missed dose
5) All participants will be provided with the RAAM clinic's nurse practitioner's contact number with instructions to call if experiencing problems possibly related to study treatment such as symptoms or lost pills.

12 Outcomes

12.1 Primary outcome measures

12.11 Opioid positivity

Difference in proportions of relapse-free weeks (RFWs) at 12-months from the date of randomization, where ***relapse-free weeks are defined by the cumulative number of weeks alive during the study period in which there was a negative urine drug screen and negative self-report for non-prescribed opioids***. The potential number of RFWs for each patient is the cumulative number of weeks that the patient is alive during the 12-month study period, with a maximum of 48 weeks. A week is defined as a consecutive 7-day period starting on the day of the week that randomization occurred. A patient is considered to have 'completed' a week as long as they are alive for ≥ 1 day of that week. For example, if a patient is randomized on a Tuesday, and subsequently dies on a Thursday of the 32nd week, the patient will have been considered to have been alive for 32 weeks. The denominator used in estimating the proportion of RFWs will be the total number of weeks that the patient was alive during the study period. Vital statistics for all participants (date and year of death) will be available through linkage with the Office of the Registrar General of Ontario database.[23] The cumulative number of RFWs alive will be used as the numerator in estimating the proportion of RFWs. Scheduled urine drug testing and self-reports will occur every 2 weeks during the study period starting in week 2 from randomization. Imputation of missing data will occur for those weeks in which a urine drug screen/self-report was not scheduled according to the results of the subsequent week's urine drug screen/self-report. For example, if a urine drug screen/self-report was not scheduled for week 11, but a scheduled urine drug screen/self-report was done on week 12 and week 12 met the criteria for a RFW, then week 11 would be imputed as a RFW (Figure 1). Similarly, for weeks with scheduled urine drug screen/self-reports that are missed, that week and the preceding week in which there was no scheduled urine drug screen/self-report will not be counted as RFWs (for example, see Figure 1, week 17 and 18). In the hypothetical patient represented in Figure 1, 20 urine drug screens/self-reports were completed, with 5 positive and 15 negative urine drug screens/self-reports, resulting in 30 cumulative RFWs over the 48-week study period, or a proportion of RFWs of 0.625.

Figure 1: Schematic for a hypothetical participant and measurement of RFWs

Variable	Weeks																								
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	**48**
UDS/Self-report[1]		-	+	-	-	+	-	-	+	na	-	-	+	-	na	-	-	+	-	na	-	na	-	-	-
RFWs		2	2	4	6	6	8	10	10	10	12	14	14	16	16	18	20	20	22	22	24	24	26	28	**30**

[1] - = negative urine drug screen (uds) and self-report , + = positive urine drug screen and/or self-report, na=not available/missing

12.11a Urine drug testing

The RAAM clinics perform on-site presumptive[24] urine drug testing using Health Canada-approved, lateral flow immunoassay-based point-of-care tests (Rapid Response™ Multi Drug Test Panel, BNTX Inc., Product code: D-1P-07). This qualitative urine assay uses established cut-off values for addictive substances or their metabolites to identify their presence (positive) or absence (negative). The urine assay can detect the following addictive substances/metabolites: benzodiazepines, buprenorphine, cocaine, ethyl glucuronide, fentanyl, morphine, oxycodone, EDDP, hydromorphone, and methamphetamine. In addition, the assay also measures urine pH and urine creatinine to screen for specimen integrity. All results are available in 5 minutes. All RAAM clinic healthcare providers must receive training and certification before use of this assay, and biennial re-certification is required. Internal and procedural controls are included in the assay to indicate proper volume of specimen added and that wicking has occurred. In addition, the Royal Victoria Regional Health Centre Laboratory Services is responsible for quality control checks with each new lot number prior to release to the RAAM clinics for use. Definitive[24] urine drug testing will not be used to validate the results of any urine drug test, but at the discretion of the RAAM clinic healthcare providers, may be used to investigate discrepancies between presumptive urine drug test results and self-reports, or detect unexpected addictive substances not available through presumptive testing. While urine sample collection is not directly observed by RAAM clinic healthcare providers, all urine samples must be collected during the clinic visit. To reduce the risk of urine tampering, each urine sample is inspected for temperature, colour, smell and appearance in addition to measuring urine pH and urine creatinine. Any urine sample that is considered substituted or invalid is discarded, and the patient will be imputed to have a positive urine drug test for that scheduled clinic visit. Urine drug screens and self-reports will only occur on day of the scheduled clinic visit, and there will be no opportunity to provide a urine sample either before or after the scheduled clinic visit.

12.11b Opioid use self-reports

Opioid use self-reporting will accompany each scheduled urine drug test.[24] Opioid use self-reporting will be measured using the Timeline Followback questionnaire.[25] This questionnaire will be administered by RAAM clinic healthcare personnel. The questionnaire consists of asking patients to recall and document their use of any addictive substances in the questionnaire on

any or all of the 7 days preceding the clinic visit. A positive self-report will be defined as any report of the use of non-prescribed opioids in the preceding 7 days.

12.12 Healthcare utilization

Difference in incidence rates of healthcare days at 12-months from the date of randomization, where ***healthcare days represent the number of days alive and registered for an emergency room visit or admitted to an acute care or mental health facility for opioid-related harms or poisonings***. For each group, the incidence rate is calculated by dividing the total number of healthcare days by the total person days exposure over the study period. The potential number of healthcare days for each patient is the number of days alive during the 12-month study period, with the maximum being 365 days. Any day in which a patient is documented to have had an emergency room visit or is admitted to an acute care or mental health facility for any opioid-related harm or poisoning will be counted as a healthcare day. To estimate the number of opioid-related harms and poisonings resulting in healthcare utilization, the Discharge Abstract Database, Ontario Mental Health Reporting System database, National Ambulatory Care Reporting database, Registered Persons Database, and Office of the Registrar General of Ontario database will be linked to each patient's Ontario Health Insurance Plan number and the following opioid-related harms and poisonings International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada (ICD-10-CA) codes will be used to estimate the number of healthcare days utilized during the study period: Y45, F11.0-F11.9, T40.0-T40.4, T40.6.[23] All opioid-related harms and poisonings resulting in the utilization of a healthcare day regardless of intent (ICD-10-CA X42 (accidental), ICD-10-CA X62 (intentional), and ICD-10-CA Y12 (undetermined)) will be included in the final analysis. Only those healthcare days in which opioid use was considered to be influential to the ER visit or hospitalization will be included and are identified by the following ICD-10-CA codes: M (most responsible diagnosis), 1 (pre-admit comorbidity), 2 (post-admit comorbidity), W or X or Y (Service transfer diagnosis). In addition, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition codes 304.00 and 305.50 will be used to capture healthcare days for opioid-related harms and poisonings.

12.13 Rationale for primary outcome measures

While the measurement of opioid positivity during opioid substitution therapy is a consistent primary outcome measure used across most trials, there is no gold standard measure of treatment effectiveness.[26] Even in the 3 trials reviewed in Table 1, each had a different measurement outcome for opioid positivity despite 2 of those trials being conducted by the same research group. In a systematic review of outcome measures used in opioid substitution treatment that included 60 trials, opioid positivity was the second most commonly reported outcome.[26] In those trials measuring opioid positivity, there were 17 different definitions, including a further 8 variations in measurement. In those studies that measured opioid positivity using urine drug screening, it was common practice to impute opioid positivity for missing data, often times as a requirement for regulatory agencies for evidence of efficacy and

other times as a practical matter of OAT management in the clinics. The imputation methods differed across studies, with few studies ever explaining the rationale for their technique. Urine drug testing was almost always accompanied by self-reports of opioid use,[26] and is recommended as a standard of practice in opiate substitution therapy.[6,24] The most commonly used tool to measure self-reports of opiate use was the Timeline Followback method.[21] In those studies utilizing both urine drug testing and self-report to measure opioid positivity, opioid positivity was defined as any positive result in either one or both tests. This trial will utilize this measure of opioid positivity because it is consistent with previous approaches (valid), objective, reproducible, relevant to both healthcare providers and patients with OUD, and has been previously demonstrated to be responsive to treatment with both drugs used in this trial.

The choice of healthcare days as a primary outcome reflects the desire to choose a measure that is patient-centered, readily measured and analyzed, and reflects a patient's holistic state rather than a specific symptom or arbitrary measure of effectiveness of opioid substitution therapy on illicit opioid use. Healthcare days have many attractive properties: they are continuous, enhancing power; they can be analyzed reliably and flexibly, to account for different values patients may place on avoiding hospitalization; and in nearly all cases, they are unidirectional, in the sense that nearly all patients prefer longer lives to shorter ones, and to have more of those days spent outside a hospital than within. In addition, healthcare days as a measure of healthcare utilization facilitate the economic valuation of the differences in the two treatment regimens in the trial, an important issue considering the differences in costs and the non-inferior outcomes previously reported for measures of illicit opioid use. The approach used to measure healthcare utilization in this trial has been validated and is currently used by the Canadian Institute of Health Information to measure and report opioid-related harms, poisonings and deaths.[3] This trial will utilize a measure of opioid-related harms and poisonings that is valid, objective, reproducible, relevant to both healthcare providers and patients with OUD, and should be responsive to treatment with both drugs used in this trial.

12.2 Secondary outcome measures

12.21 Medication satisfaction

Difference in the Medication Satisfaction Questionnaire[27] scores. The questionnaire is a single-item, global, patient-completed instrument that has been validated to measure treatment satisfaction, initially in patients receiving antipsychotic treatment for schizophrenia, but subsequently used in trials measuring satisfaction with opiate substitution treatment. The question will be read aloud by the RAAM clinic healthcare providers or study personnel to the patient. The question asks, "Overall, how satisfied are you with your current Suboxone®/Sublocade® medication?". The responses are on a 7-point Likert scale, ranging from 1=extremely dissatisfied to 7=extremely satisfied. This questionnaire is valid, reproducible, relevant to both healthcare providers and patients with OUD, and has been shown to be responsive to opiate substitution treatment in previous studies.[26,28]

12.22 Quality of life

Difference in the World Health Organization Quality of Life – BREF[29] scores (WHOQOL-BREF). The 26-item questionnaire is a validated, self-report instrument that assesses 4 domains of quality of life: physical health (7 items), psychological health (6 items), social relationships (3 items) and environment (8 items). There are also 2 items that measure overall quality of life and general health. The questionnaire takes 15-20 minutes to complete. The questionnaire prefaces each item, "Think about your life in the last two weeks..". The responses are on a 5-point Likert scale, ranging from 1=not at all/very dissatisfied/never/very poor to 5=very good/very satisfied/an extreme amount/extremely/completely/always, depending on the item. The questionnaire is valid, reproducible, relevant to both healthcare providers and patients with OUD, and has been shown to be responsive to changes in quality of life across cultures, geography and etiology.[29]

12.23 Clinic retention

Difference in proportion of patients who attend ≥80% of scheduled clinic visits, where a ***clinic visit is defined as a scheduled visit with a RAAM clinic healthcare provider for any reason, including urine drug testing, medication administration, or counselling***. Clinic retention is the most commonly reported outcome measure in opioid substitution trials, with 46% reporting it as an outcome.[26] However, there is no "gold standard" definition of retention, with over 16 different methodologies used to measure retention in 28 trials of opiate substitution therapy.[26] The number of clinic visits any patient will be assigned will include those scheduled as part of the trial and any other visits scheduled at the discretion of the RAAM clinic healthcare providers. The measure of clinic retention used in this trial is valid, objective, reproducible, relevant to both healthcare providers and patients with OUD, and has been shown to be responsive to opiate substitution therapies in previous studies.[26]

12.24 Mortality

Difference in mortality proportions, where ***mortality is defined as any death attributable to opioid use regardless of the intent.*** Opioid-related deaths continue to increase year after year and have emerged as a public health crisis.[4] Only 2 previous opiate substitution treatment studies measured mortality as an outcome, the latest published in 1980.[26] The method used by the Canadian Institute for Health Information will be used to measure mortality in this study given its validity, reproducibility, importance to both healthcare providers and patients with OUD, and its responsiveness to opiate substitution therapies.[3]

13 Participant timeline

			Study Period (Weeks)																									
			-1	0	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18	T19	T20	T21	T22	T23	T24
Activity	CRF	MRP	W-1	W0	W2	W4	W6	W8	W10	W12	W14	W16	W18	W20	W22	W24	W26	W28	W30	W32	W34	W36	W38	W40	W42	W44	W46	W48
Enrollment																												
Expressed Consent	N	HCP	X																									
Eligibility Screen	Y	HCP SC	X																									
Informed Consent	N	HCP SC	X																									
Randomization	Y	SC		X																								
Demographics	Y	HCP		X																								
Pregnancy test	Y	HCP	X																									
EKG	Y	HCP	X																									
Bloodwork	Y	HCP	X																									
Interventions																												
Suboxone®	Y	HCP		X→																								
Sublocade®	Y	HCP		X		X		X		X		X		X		X		X		X		X		X		X		X
Counselling	Y	HCP		X	X	X	X	X		X		X		X		X		X		X		X		X		X		X
RAAM clinic visit	Y	HCP		X	X	X	X	X		X		X		X		X		X		X		X		X		X		X
Pre-clinic visit phone call	Y	HCP SC		X	X	X	X	X		X		X		X		X		X		X		X		X		X		X
Assessments																												
General exam	Y	HCP		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine drug test	Y	HCP	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Timeline Followback	Y	HCP	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MSQ	Y	HCP SC					X			X			X			X			X			X			X			X
WHOQOL-BREF	Y	HCP SC		X						X						X						X						X
Pregnancy test	Y	HCP				X		X		X		X		X		X		X		X		X		X		X		X
SAE	Y	HCP		X→																								→
EKG	Y	HCP		Discretion of HCP →																								
Bloodwork	Y	HCP		Discretion of HCP →																								

CRF=case report form; MRP=most responsible person; N=No; Y=Yes; HCP=healthcare provider; SC=study coordinator; EKG=electrocardiogram; MSQ=medication satisfaction questionnaire; WHOQOL-BREF=Quality of life questionnaire; SAE=severe adverse event

14 Sample size

14.1 Rationale

The sample size was calculated on the basis of the primary hypotheses. In the three previous comparative effectiveness studies between Suboxone® and Sublocade® (Table 1), the primary outcomes were non-inferiority with an upper margin of difference in opioid positivity of < 15%. None of these trials involved Canadian patients attending RAAM clinics. As previously reviewed, given the significant differences in costs of Sublocade® compared to Suboxone® and the absence of evidence of cost-effectiveness of Sublocade® compared to Suboxone® in the Canadian healthcare system, it would be important to demonstrate to healthcare providers who advise patients that must pay out-of-pocket for their medications that the increased cost of Sublocade® provides clinically significant benefits to important patient-centered outcomes over those of less expensive OAT. In addition, it would be important to demonstrate the same benefits to policy makers and insurers of the superiority of Sublocade® compared to Suboxone® not only in reducing rates of opioid positivity but also healthcare utilization that might offset the cost differential of the two drugs and provide the rationale to promote Sublocade® as an insured first line agent for OUD. As such, a clinically important difference in opioid positivity has been selected as ≥ 15% difference for Sublocade® compared to Suboxone® given that previous studies had used this threshold as the upper margin for non-inferiority. As for healthcare utilization, CADTH estimated that a 73% reduction in cost of Sublocade® would be needed to make it cost-effective for the Canadian healthcare system (see Section 5.14). Given the current cost for a 12-month treatment of Sublocade® in Canada is $6600, a 73% reduction would translate into an annual cost of $1782, a cost reduction of $4818. The average cost of healthcare utilization in Ontario for an opioid-related harm or poisoning was $9626 (Section 5.12). To recoup the drug costs from a reduction in healthcare utilization costs would require at least a 50% reduction in healthcare utilization over a 12-month period. As such, a clinically important difference in healthcare utilization has been selected as ≥ 50% difference for Sublocade® compared to Suboxone®. All sample size estimations were conducted using nQuery version 8.7.2.0 (nQuery | Platform for optimizing trial design (statsols.com); accessed November 17, 2021).

14.2 Opioid positivity

Previous studies have used a simple data generating model for opioid positivity in which the difference in proportions of opioid positivity, regardless of how opioid positivity was defined, never accounted for the clustering of repeated measures of opioid positivity by individual and site. This dramatically reduces the power to detect differences in proportions of opioid positivity between treatment groups. For example, for our trial to detect a difference in proportion of RFWs of ≥ 0.15 with a power of 80% using a Z-test (unpooled variance) significance level at the 2-sided $\propto$ level of 0.05 would require 160 patients per group if the comparator group's RFWs proportion is 0.3 (estimated from Lofwall *et al.*[12]). Contrast this to a

data generating model that more appropriately accounts for clustering of opioid positivity observations. In this study, a mixed model using a 3-level hierarchical design will be used to describe the relationship between repeated measures of opioid positivity (Level 1) obtained from individual patients (Level 2) recruited from 4 different RAAM clinic sites (Level 3), where Level 2 patients will be randomized to either Sublocade® or Suboxone®. In addition to the assumption of a comparator group RFWs proportion of 0.3, if we also assume a Level 1 unit correlation of 0.8, a Level 2 correlation of 0.025, and an average of 5 repeated measures of opioid positivity per Level 2 patient over the study period, then we would need only 34 patients per treatment group to detect a difference in RFWs proportion of ≥ 0.15 with a power of 80% and a mixed model test significance level at the 2-sided ∝ level of 0.05. Sensitivity analysis using different values for the variables used in the hierarchical model assumptions (Table 3) demonstrates that the upper range of sample sizes is consistently less than 70 per group.

Table 3: Sensitivity analysis for sample size estimations needed to detect ≥ 15% difference between RFWs proportions between treatment groups for a mixed model test in a 3-level hierarchical design (Level 2 randomization)

	Scenario[2]									
Variable[1]	1	2	3	4	5	6	7	8	9	10
Power	80	80	80	80	80	80	80	80	90	90
Comparator group RFW proportion	0.3	0.3	0.3	0.3	0.1	0.6	0.3	0.3	0.3	0.3
Level 1 unit correlation	0.8	0.5	0.99	0.99	0.99	0.99	0.8	0.8	0.99	0.99
Level 2 unit correlation	0.025	0.025	0.1	0.001	0.001	0.001	0.025	0.025	0.001	0.001
Level 3 units	4	4	4	4	4	4	3	2	4	3
Average number of Level 1 units per Level 2 units	5	5	5	5	5	5	5	5	5	5
Sample size per group	34	24	37	41	42	38	45	68	41	54

[1] Assumptions: 2-sided ∝ level of 0.05; Difference in RFWs proportion ≥0.15; Treatment group allocation = 1:1
[2] Highlighted cells (Yellow) represent changes from preceding scenario

14.3 Healthcare utilization

In the only recent study that compared non-protocol-driven healthcare utilization using the incidence rates of healthcare days as an outcome measure among patients with OUD receiving opiate substitution therapy with either Sublocade® or placebo, the data demonstrated a combined emergency room visit or hospital day incidence rate of 2.01 healthcare days per 1 000 patient days in the Sublocade® group versus 6.97 healthcare days per 1 000 patient days in the placebo group.[28] These rates likely underrepresent the current rates of healthcare utilization in Canada as the study was conducted in 2015 and the patients included in the trial were residents of the United States and 60% had no medical insurance likely creating barriers to healthcare access and lowered rates of utilization that would not exist for Canadian patients who have universal and free access to acute healthcare services. There have been no direct comparisons between Sublocade® and Suboxone® treatments. As a result, a sensitivity analysis

using different inputs has been conducted given that the maximum person days exposure for each patient is 365 days. We also assume a worse-case scenario of loss-to-follow-up (for any reason) of 50% over the study period, a rate of loss-to-follow-up much higher than the 20% rate reported by Ling *et al.*[28]

Table 4: Sensitivity analysis for attainable power to detect a range of differences in the incidence rates of healthcare days between treatment groups with different sample sizes

	Scenarios	
Variable[1]	1	2
Comparator group incidence	2.0	2.4
Group difference in incidence rates	1.0	1.2
Sample size per group (patient days)[2]	3650	3650
Power	99	99

[1] Incidence = total number (hospital days + emergency room visits)/1 000 patient days; Assumptions: 2-sided ∝ level of 0.05; 50% loss-to-follow-up

[2] Sample size per group derived from a sample of 20 patients * 365 days exposure/patient * 0.5 (=50% rate of loss-to-follow-up)

14.4 Final sample size

In a hierarchical 3-level mixed effects model with 45 and 45 level 2 units (RAAM clinic patients) randomized to Suboxone® and Sublocade® in a 1:1 ratio, 4 level 3 units (RAAM clinics) in total and an average of 5 level 1 units (RFWs) per level 2 unit, 90.0% power is achieved to detect a difference in RFWs proportions of at least 0.15, where the Suboxone® and Sublocade® RFWs proportions are 0.3 and 0.45, respectively, assuming that the correlation between level 1 units in a level 2 unit is 0.8 and the correlation between level 2 units in a level 3 unit is 0.025, and the 2-sided test is performed at the 5% significance level. Using even a much smaller sample size (N=20 patients per group with 50% loss-to-follow-up over 12-month study period), a 2-sided comparison of two incidence rates (number of healthcare days per 1000 patient days exposure) with a sample size of 3650 patient days exposure per group would achieve 99% power at the 0.05 significance level to detect a difference in incidence rates of at least 1 if the Suboxone ®group incidence rate was 2.

15 Recruitment

The 4 RAAM clinics serve the entire North Simcoe Muskoka Local Health Integrated Network region, are owned and operated by the Royal Victoria Regional Health Centre and are administered by the same manager and medical lead (see Section 9 for details).

Each RAAM clinic will screen 100% of patients who successfully complete induction and stabilization with Suboxone® as this is the point at which patients might be eligible for enrollment and randomization. Screening will continue until the target population is achieved. There will be no fixed number of patients that must be recruited from any site, only that each

site will have a 1:1 allocation ratio between the treatment groups. The expectation is that 1 to 2 patients will be enrolled per week.

The RAAM clinic healthcare providers will be responsible for expressed consent in eligible patients. For those patients who provide expressed consent, the RAAM clinic healthcare providers will contact the study team and provide them with the patient's name and contact number and inform the patient that they will be contacted by the study team to further discuss the study. A study team member will contact the patient and arrange a meeting, either in person, telephone or videoconference, to determine eligibility and review the study and secure informed consent.

For patients who cannot travel to a laboratory to complete their screening bloodwork or electrocardiogram, arrangements will be made to have the screen completed at their home address at no charge to the patient.

Patients who are enrolled in the study at the Midland, Orillia, and Wasaga Beach RAAM clinic sites will now be able to receive their Sublocade® doses on-site. Previous to this study, those patients would have had to travel to the Barrie RAAM clinic site to receive Sublocade®. A taxi ride for this travel would be required as there is no bus or train that connects these sites, with the cost for a round trip in excess of $150 (CDN) (personal communication, Philip Wong).

16 Allocation

16.1 Sequence generation

Participants will be randomly assigned to either Suboxone® or Sublocade® with a 1:1 allocation schema as per a computer-generated randomisation schedule stratified by RAAM clinic site and severity of OUD (moderate versus severe by DSM-V criteria) using permuted blocks of size 6 in each strata. A single block size was chosen since the next block size of 18 might be too large to allocate patients in a 1:1 ratio in the smaller RAAM clinics. The block size will not be disclosed to ensure concealment. Sufficient numbers of blocks will be prepared *a priori* to ensure sufficient coverage for all strata in the event that they have different sample sizes as there will be no *a priori* fixed ratio for enrollment in the different strata.

16.2 Concealment mechanism

The random allocation sequence will be generated using the *ralloc* function in STATA 17/MP for Mac by an independent statistician not associated with the trial. This allocation sequence will be uploaded into and accessed from REDCap®, which is an on-line, password-protected, web-based research electronic database system stored on the PHIPA-protected servers at the Royal Victoria Regional Health Centre. Allocation concealment will be ensured as the study coordinator will not release the randomisation code until the patient has been recruited into the trial, which will only take place after all baseline screening measurements have been

completed. The randomisation schedule will only be accessible by independent study coordinators not associated with this study to ensure that randomisation will be conducted without any influence of the principal investigators, RAAM healthcare providers, or other study personnel.

16.3 Implementation

Expressed consent for the study will be obtained by the RAAM clinic healthcare providers. Informed consent will be obtained by the study team. All patients who give consent for participation and who fulfil the inclusion criteria will be randomized. Randomization will be requested by the study team member who secured informed consent from an independent study coordinator who is not associated with the study by calling a centralized study telephone number. The study coordinator will access the random allocation sequence through REDCap®, and then inform the study team member who secured informed consent of the treatment allocation for this patient. The study team member will subsequently inform the RAAM clinic healthcare provider who would then provide the information about treatment allocation to the patient. All RAAM clinic healthcare providers will be made aware of the treatment allocation as this is an open-label study.

17 Masking

This is an open-label, pragmatic, comparative effectiveness study so neither participants nor RAAM healthcare providers nor study personnel, including data analysts, will be masked to the allocation.

18 Data collection

18.1 Methods

All data will be collected by centrally trained RAAM clinic healthcare providers and study personnel. All ***routinely collected data*** will be collected by the RAAM clinic healthcare providers and stored in MEDITECH Expanse, the electronic health record system used across all the study RAAM clinics and the Royal Victoria Regional Health Centre. This routinely collected data will be extracted by study personnel and stored in electronic case report forms created in REDCap®.[30,31] All study-specific data will be collected by study personnel and stored in electronic case report forms created in REDCap®.

18.11 Routinely collected data

18.11a Prior to induction

For all RAAM clinic patients with OUD who are eligible to receive any opiate substitution therapy, the following demographic and baseline clinical and laboratory data are collected ***prior to induction*** with any treatment (Table):

Data	Description	Data type
Demographics		
Date of birth	Month/day/year	Mm/dd/yyyy
Sex at birth	Male: Female	Categorical
Pregnant	Yes: No	Categorical
Ontario health insurance plan number	Unique provincial insurance number assigned to every resident	xxxx-xxx-xxx-version code
Ontario drug plan status	Insured versus non-insured	Categorical
Residency	Homeless; transient (< 6 months at same address, couch surfing or shelter); stable (≥ 6 months at same address)	Categorical
Children in home	Yes: No	Categorical
Children ages	Years	Continuous
Telephone contact	Yes: No	Categorical
Number		(xxx)-xxx-xxxx
Employment status[1]	Full-time (≥ 40 hours per week for ≥ 90 days per year); Part-time (≤ 40 hours per week or ≥ 90 days per year); Casual (≤ 90 days per year); unemployed	Categorical
Incarceration[1]	Incarceration in ≤ 12 months (Yes: No)	Categorical
Race[1]	White: Non-white, non-indigenous: Indigenous	Categorical
Clinical		
OUD diagnostic screen	≥ 2 of 11 DSM-V criteria must be present ≤ 12 months for diagnosis of OUD	Categorical: range 0 to 11:
OUD severity	DSM-V criteria of mild, moderate or severe OUD	Categorical: mild (2-3 criteria); moderate (4-5 criteria); severe (≥6 criteria)
Medical history	Comorbid illness screen, including mental health and substance use	Categorical
Medications	Prescribed	Categorical

Alcohol use	Yes: No	Categorical
Opioid use	Type: Route	Categorical
Other substance use	Type: Route	
Recent substance/opioid use	Timeline Followback questionnaire (assesses use and frequency of use of substances over the previous 7 days)	Categorical
Hospitalization	Substance-related ≤ 12 months (includes emergency room visit, admission to hospital, mental health or detoxification facility) (Yes: No)	Categorical
General physical exam	Vital signs; height; weight	Continuous
Opioid withdrawal screen	≥ 3 of the following: dysphoria; nausea or vomiting; muscle aches; lacrimation or rhinorrhea; pupillary dilation or piloerection or sweating; diarrhea; fever; insomnia; yawning	Categorical; range 0-9
Jaundice	Yes: No	Categorical
Mental status	Glasgow coma scale	Categorical (range 3-15)
Opiate Craving Visual Analog Scale	Score ≥ 21 suggests clinically significant craving	Continuous (range 0-100)
Clinical Opiate Withdrawal Scale	Score ≥ 13 suggests clinically significant withdrawal	Continuous (range 0-48)
Laboratory[2]		
Pregnancy	b-hCG assay (Yes: No)	Categorical
Liver	AST, ALT	Continuous
	Hepatitis virus serology	Categorical
Urine toxicology	Section 12.11a for description	Categorical
Renal	Creatinine	Continuous

[1] Employment status, incarceration and race are routinely collected in treatment studies for OUD as they have been identified as risk factors for outcome differences.

[2] All laboratory and electrocardiogram measurements and interpretations done at *LifeLabs™*

18.11b During treatment

Data	Description	Data type

Urine toxicology	Section 12.11a for description	Nominal
Recent substance/opioid use	Timeline Followback questionnaire (assesses use and frequency of use of substances over the previous 7 days)	Categorical
Counselling	Individual patient counselling for OUD, mental health and trauma	Narrative
General exam	Vital signs: Glasgow coma scale:	Continuous
Pregnancy	b-hCG assay (Yes: No)	Categorical
Bloodwork (optional)	Electrolytes: Liver: Renal	Continuous
Buprenorphine breakthrough dosing	Extra buprenorphine dosed for breakthrough	Continuous
Compliance	Missed appointments or doses (Yes: No)	Categorical
Hospitalization[1]	Any Royal Victoria Regional Health Centre emergency room visits, admissions to hospital or mental health or detoxification centre since previous clinic visit (Yes: No)	Categorical
Reason for visit/admission	Opioid-related (Yes: No)	Categorical
Serious adverse events[1]	Hospitalization (for any reason)	Categorical
Reason	Opioid-related (Yes: No)	Categorical

[1] Only hospitalization events associated with the Royal Victoria Regional Health Centre are accessible to the RAAM clinic healthcare providers as the clinics share the same electronic health record system as previously described. All other hospitalizations would have to be self-reported by the participants and consent for access to the health records would then need to be secured by the RAAM clinic healthcare providers.

18.12 Study-specific data

Data	Description	Data type
Medication Satisfaction Questionnaire	"How satisfied are you with your medication?"	Categorical: Range 1-7
WHOQOL-BREF	26-item questionnaire measuring quality of life in 4 domains: physical health;	Continuous: Each domain score standardized to scores 0 (wore) to 100 (best)

	psychological health; social; environment	
Hospitalization[1]	Any Royal Victoria Regional Health Centre emergency room visits, admissions to hospital or mental health or detoxification centre since previous clinic visit (Yes: No)	Categorical
Reason for visit/admission	Opioid-related (Yes: No)	Categorical
Serious adverse events[1]	Hospitalization (for any reason)	Categorical
Reason	Opioid-related (Yes: No)	Categorical

[1] Only hospitalization events associated with the Royal Victoria Regional Health Centre are accessible to the RAAM clinic healthcare providers as they clinics share the same electronic health record system as previously described. All other hospitalizations would have to be self-reported by the participants and consent for access to the health records would then need to be secured by the RAAM clinic healthcare providers.

18.13 Healthcare utilization

This data (see Section 12.12) is available from the Registered Persons Database, Ontario Mental Health Reporting System, Discharge Abstract Database, and National Ambulatory Care Reporting System through the Institute for Clinical Evaluative Sciences using a data linkage with each patient's unique Ontario Health Insurance Plan number.

As a prescribed entity under the Personal Health Information Protection Act,[32] the Institute for Clinical Evaluative Sciences is authorized to collect personal health information from health organizations without consent for the purposes of evaluation and monitoring of Ontario's health system. The Institute for Clinical Evaluative Sciences is prohibited, under its agreements with data providers, from contacting individuals whose information has been entrusted to the Institute for Clinical Evaluative Sciences. This contractual obligation restricts any opportunity to seek individuals' consent for use of their information for research.

The Institute for Clinical Evaluative Sciences will make available a research-ready, linked and risk-reduced coded dataset to the study investigators. Although highly de-sensitized, the research data is presented at an individual level. Study investigators will access the Research Data remotely on a secure, encrypted VMware virtual desktop called the Institute for Clinical Evaluative Sciences Data & Analytic Virtual Environment (IDAVE). Study investigators will perform analyses on IDAVE using statistical software. Research Data may not be copied or transferred from IDAVE. Only results derived from the Research Data that have been vetted for re-identification risk and approved by Institute for Clinical Evaluative Sciences may be released from IDAVE.

18.2 Retention

18.21 Strategies

Once a patient is enrolled or randomized, the RAAM clinics will make every reasonable effort to follow the patient for the entire study period. The RAAM clinics and their healthcare providers will utilize recommended clinical strategies as part of their usual standard of care to minimize loss-to-follow-up for any patient with OUD on opioid substitution therapy.[17]

In addition to these strategies, the RAAM clinic healthcare providers and study personnel will:

1) Direct contact by phone for each participant will take place 2 days in advance of a scheduled clinic visit as a reminder of the date and time of the scheduled visit, and to determine if there are any barriers to attendance. Incentives such as taxi chits will be provided to participants who have transportation barriers to attendance.

2) For those participants who require additional bloodwork or electrocardiograms, home lab services free-of-charge will be provided through LifeLabs™.

3) The study-specific questionnaires will be completed using interviews with study personnel as opposed to simply asking participants to complete the questionnaires on their own to maximize completion rates.

4) The study-specific questionnaire schedules will be flexible, with study personnel able to interview participants $\mp$ 2 weeks around the scheduled date.

18.22 Withdrawal

Participants may choose to withdraw from the study for any reason at any time. As part of the usual standard of care, the RAAM clinic healthcare providers may also withdraw participants from the study for clinical reasons such as failure to comply with opiate substitution treatment, failure to comply with urine drug testing or self-reports of drug use, failure to attend scheduled clinic visits, failure to comply with birth control or becoming pregnant after enrolment, or for any other reason that may jeopardize the safety of the participants or others. For those participants who choose to withdraw or are withdrawn by their healthcare providers, ongoing follow-up for the study period will continue for all outcomes measured using routinely collected data (such as healthcare utilization). For outcome measures that require study-specific data, such as the WHOQOL-BREF questionnaire, consent will be sought to permit ongoing assessment for the study period. Deviations from the study protocol (which do not result in withdrawal by the healthcare providers) or loss-to-follow-up for any reason will not be considered reasons for withdrawal from the study.

19 Data management

All routinely collected data will be entered electronically by the RAAM clinic healthcare providers at the RAAM clinics using the electronic health record system. Study personnel will extract the relevant routinely collected data from the electronic health record system and record the data into the electronic case report form stored in REDCap, a password-protected, Personal Health Information Protection Act (PHIPA)-compliant database stored on servers at the Royal Victoria Regional Health Centre that is used to support all the hospital's research activities and is supported and managed by the staff of the Royal Victoria Regional Health Centre Research Institute. Study personnel will record study-specific data directly into the REDCap electronic case report form (Medication Satisfaction Questionnaire and WHOQOL-BREF questionnaire) or extract study-specific data from the electronic health record system (Healthcare utilization) and record it in REDCap. The study personnel will access the questionnaires (Medication Satisfaction Questionnaire and WHOQOL-BREF questionnaire) in REDCap and complete them with the participants. This may be done either in-person at the RAAM clinics or remotely by telephone or videoconference.

When a patient is enrolled and randomized, a unique study number will be automatically generated in REDCap. This unique study number, along with the patient's name (first, middle, last), Ontario Health Insurance Plan number, date of birth, and unique electronic health record system number will be stored in a password-protected EXCEL computer file. This study EXCEL file will be stored in a dedicated, password-protected electronic shared drive located on the Royal Victoria Regional Health Centre Personal Health Information Protection Act (PHIPA)-compliant servers. This EXCEL file will permit linkage to the electronic case report form to enable study personnel to record repeated measurements over the study period for a participant. Real-time data quality rules will be implemented in REDCap that will display warning pop-up messages whenever the rules are violated during data entry. These quality rules will minimize missing values in required fields; prevent incorrect data type entry and out of range data entry; identify outliers for numerical fields; and prevent invalid data entry into multiple choice fields. The data quality rules will also be available to be executed at any time by a study monitor or study personnel. All electronic case report form entries and edits are associated with an electronic audit trail that identifies the user, date and time of entry, and entry type. The type of activity that study personnel may undertake in REDCap is regulated by privileges associated with their user identification and password. Incremental data back-ups of REDCap are routinely performed twice a day, with off-site storage of the backed-up files done on a monthly basis. Data status reports on missing data will be provided to the Data management committee on a biweekly schedule for review. All study data will be archived in REDCap for 25 years and subsequently permanently destroyed.

20 Statistical methods

20.1 Outcomes

The intervention arm (Sublocade®) will be compared against the active comparator (Suboxone®) for all primary and secondary analyses. All analyses will be done according to original patient allocation regardless of whether they received the randomized treatment or were compliant with the study protocol (Intention-to-treat). All analyses will be conducted using STATA/MP 17.0 for Mac.

20.11 Primary

20.11a Opioid positivity

We will use a 3-level hierarchical design to model the relapse-free weeks data where the observation for each week (Level 1) will be coded as binary; relapse-free week if urine drug screen and self-report is negative for non-prescribed opioid use, and otherwise relapse week if either is positive for non-prescribed opioid use. As described in Section 12.11, imputation of missing data will occur for those weeks in which a urine drug screen/self-report was not scheduled according to the results of the subsequent week's urine drug screen/self-report. Level 1 observations are clustered within individual participants (Level 2) , which are nested within RAAM clinic sites (Level 3). We will analyse the outcome data using multi-level, mixed-effects logistic regression analysis with random effects estimated for the variance in the intercepts of both participant and clinic levels. The model will also include a random slope on the indicator for OUD severity (moderate versus severe) in the Level 2 random effects equation using an unstructured covariance structure between intercept and slope. We will also include clinic visit (week) and an interaction term between clinic visit and treatment. A sensitivity analysis will be conducted to compare this baseline model with an extended model that includes any baseline demographic or clinical variables that appear to be unbalanced at Level 1. The models will be compared using the likelihood-ratio comparison test for superiority. Post-regression analyses using *margins* command will be used to estimate difference in proportions of RFWs between treatment groups.

20.11b Healthcare utilization

We will model the days of healthcare utilization as count data, with the period of follow-up while alive during the study period as the exposure period. We will analyse the data using a Poisson regression model. We will include an indicator for OUD severity. We will include any baseline demographic or clinical variables that are unbalanced at Level 1.

20.12 Secondary outcomes

We will use a 3-level hierarchical design to model all the repeated measures outcomes (Medications Satisfaction Questionnaire and the WHOQOL-BREF) where the outcomes will be coded as continuous. Level 1 observations are clustered within individual participants (Level 2), which are nested within RAAM clinic sites (Level 3). We will analyse the data using multi-level, mixed-effects linear regression analysis with random effects estimated for the variance in the

intercepts of both participant and clinic levels. We will include a random slope on the indicator for OUD severity (moderate versus severe) in the Level 2 random effects equation using an unstructured covariance structure between intercept and slope. We will also include clinic visit and an interaction term between clinic visit and treatment, along with any baseline demographic or clinical variables that are unbalanced at Level 1.

Both clinic retention and mortality will be coded as binary outcomes. We will conduct unadjusted analyses for both using a chi-squared test (with continuity correction) or Fisher's exact test depending on cell sizes.

21 Monitoring

21.1 Trial management committee

This comparative effectiveness study involves the use of two opiate substitution medications that are Health Canada-approved for use in moderate- to severe-OUD. In addition, the study RAAM clinics are accredited facilities with trained personnel in the use of both study treatments for the treatment of moderate- to severe-OUD. As such, an informal trial management committee will be created to ensure that all privacy requirements for data collection, storage and dissemination are met. In addition, this committee will meet biannually to review data quality, including amount and reasons for missing data, and provide guidance to investigators on these issues.

An informal trial management committee will be created to ensure study recruitment and retention is optimized. The committee will be composed of members of the study RAAM clinics' administration and members of the Research Institute. The members of the committee will perform quarterly audits on a random sample of 5% of enrolled participants, and these audits will involve, but not be limited to, the following:
(i) Documentation of consent and consistent application of inclusion and exclusion criteria
(ii) Adherence to study treatment allocation
(iii) Completeness and accuracy of the electronic case report forms
(iv) Protocol deviations and reporting
This committee will submit quarterly reports to the data management committee as part of their responsibilities.

21.2 Interim analysis

There will be no interim analysis or premature termination of the study.

22 Harms

In this pragmatic, comparative effectiveness study, the RAAM clinic healthcare providers will document adverse events that occur during the study according to their clinical judgement and

usual standard of care. The subsequent clinical decisions and actions to any adverse event will be left up to the discretion of the healthcare providers. The only adverse event that will be considered serious will be any healthcare utilization for any reason during the 12-month study period, defined as any emergency room visit, admission to hospital, mental health facility or detoxification centre. Screening for these events will occur with each clinic visit by soliciting the information from the participant but will also occur unsolicited by screening the electronic health record system between visits. These healthcare utilization events will be reported to the Trial and Data management committees on a quarterly basis, along with the Research Ethics Board according to local regulatory standards.

23 Auditing

23.1 Investigator responsibilities

The investigators agree to perform the clinical trial in accordance with this clinical trial protocol, International Council for Harmonisation guideline for Good Clinical Practice (https://ichgcp.net/) and all applicable regulatory requirements.

23.2 Coordinating centre responsibilities

The RVH Research Institute will be responsible for taking all reasonable steps to ensure proper conduct of the clinical trial protocol.

23.3 Site initiation

Prior to the initiation of the study at each study RAAM clinic, the RVH Research Institute will be responsible for providing adequate training to the clinic healthcare providers and study personnel. The training will cover all aspects of the study protocol and procedures and will include practical training on the use of the randomisation system, electronic case report forms and study materials such as questionnaires. The site initiation visit will be conducted by either teleconference, video conference or face-to-face meetings at the participating study RAAM clinic. Written and electronic materials will be supplied for study personnel and for the education of the study RAAM clinic healthcare providers at each site.

23.4 Monitoring during the study

An independent study monitor for the RVH Research Institute will visit each participating RAAM clinic biannually during the study period. This will ensure that the study is conducted according to the protocol, good clinic practice guidelines and relevant regulatory requirements. The main duty of the study monitor is to help the principal investigators and the RVH Research Institute maintain a high level of ethical, scientific, technical and regulatory quality throughout all aspects of the trial.

The principal investigators, healthcare providers and study personnel will assist the study monitor by providing all appropriate documentation and being available to discuss the study. These monitoring visits will include, but not be limited to, review of the following aspects:

1) Adherence to the protocol including consistency with inclusion and exclusion criteria
2) Study treatment allocation
3) The completeness and accuracy of the electronic case report forms and electronic medical records
4) Participant recruitment
5) Adverse event documentation and reporting
6) Compliance with the study treatment regimen for enrolled participants
7) Study drug storage, administration, accountability and reconciliation
8) Compliance with regulations

23.5 Site close-out

At the completion of the trial, a final monitoring and close out visit will be conducted by the study monitor.

23.6 Source documents

The study monitor will check the source documents to confirm the existence of the participant and the integrity of the study data. Source documents refer to the electronic medical records of the participants used by the study RAAM clinic healthcare providers during episodes of care related to the study. Adequate and accurate source documents allow the principal investigators and the study monitor to verify the reliability and authenticity of data recorded on the electronic case report forms and ultimately to validate that the study was carried out in accordance with the protocol.

23.7 Study treatment

The principal investigator (PW) or delegate at each study RAAM clinic site will be responsible for receiving, inspecting and documenting Sublocade® acquired prior to placement in storage. The principal investigator (PW) or delegate will inventory and acknowledge receipt of all shipments of the study drug. Documentation of study drug, distribution, receipt, use and disposal will be kept enabling comprehensive tracking and reconciliation of all study treatments, used or unused.

Study drug will be kept in a secure area with restricted access. The study drug must be stored and handled in accordance with the manufacturer's instructions. The principal investigator (PW) or delegate will also keep accurate records of the quantities of the study drug dispensed, used and unused by each participant.

All unused or partially used study drug should be returned to the principal investigator (PW) or delegate once the treatment period has ended. The study personnel will cross check the study drug that are identified on the accountability log against the study drug that has been dispensed/administered to the participant.

Following verification from the RVH Research Institute, study drug may be destroyed providing documentation of destruction with a complete and accurate account of study drug destroyed be available for verification by the study monitor and filed in the principal investigator study file.

At the conclusion of the study, all unused study drug (which has not been allocated to a participant) will be destroyed unless other arrangements have been approved by the RVH Research Institute or RAAM clinics. Final destruction of unallocated study drug must only occur following written authorisation from the RVH Research Institute or RAAM clinics. The RVH Research Institute will verify that a final report of study treatment accountability is prepared and maintained in the principal investigator study file.

23.8 Direct access to data and documents

The study may be audited by Health Canada, the RVH Research Ethics Board, or qualified representatives of the RVH Research Institute as permitted by regulations. Therefore, access to medical records, other source documents and other study related files will be made available at all study sites for monitoring and audit purposes during the study and after its completion.

Participants will not be identified by name, and confidentiality of information in medical records will be preserved. The confidentiality of the participant will be maintained unless disclosure is required by regulations.

24 Ethics approval

This protocol and appendices will be reviewed and approved by the RVH Research Institute and the Clinical Trials Ontario-accredited RVH Research Ethics Board with respect to scientific content and compliance with applicable research and human subjects' regulations.

The protocol and informed consent form, other requested documents, and any subsequent modifications, also will be reviewed and approved by the RVH Research Ethics Board.

Subsequent to initial review and approval, the RVH Research Ethics Board will review the protocol at least annually. The Principal investigators will make safety and progress reports to the RVH Research Ethics Board at least annually and within three months of study termination. These reports will include the total number of participants enrolled, completed the study, in

follow-up, lost-to-follow-up, and withdrawn; total number of adverse events; protocol and informed consent deviations and modifications.

25 Protocol amendments

All modifications to the protocol which may impact on the conduct of the study, potential benefit of the participant or may affect participant safety, including changes of study objectives, study design, participant population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendments will be agreed upon by the Principal investigators, the RVH Research Institute, and approved by the RVH Research Ethics Board prior to implementation.

Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be agreed upon by the Principal investigators, the RVH Research Institute, and will be documented in a Note to File to the RVH Research Ethics Board.

26 Consent

This pragmatic, comparative effectiveness study involves the random assignment of Sublocade® or Suboxone® to participants who meet the Health Canada-approved indications for their use. This study fulfils the criteria for a low intervention clinical trial in that the drug treatments are Health Canada-approved, the drug treatments are being used in accordance with the terms of the Health Canada-marketing authorization, and any additional study-related assessments (Medication Satisfaction and WHOQOL-BREF questionnaires) and follow-up (12-month healthcare utilization) do not pose more than minimal additional risk or burden to the safety of the participants compared with normal clinical practice.[33] As such, eligible participants will be briefly informed by their RAAM clinic healthcare providers about the main features of the trial that are not part of the usual standard of care, notably, randomisation; the Medical Satisfaction and WHOQOL-BREF questionnaires, and healthcare utilization follow-up at 12-months from enrollment. A ***modified*** written informed consent describing ***only*** the process and rationale for randomization and the description, need for and schedule of the Medication Satisfaction and WHOQOL-BREF questionnaires will be obtained prior to enrolment by the Principal investigators or their nominated delegates. The written informed consent will not contain any information about the study drugs, administration, side effects or duration of treatment as verbal consent will be obtained by the healthcare providers as part of the usual standard of care.[33] In addition, the written informed consent will not contain any information about the 12-month healthcare utilization follow-up as this is routinely collected data that will be de-identified and analysed in aggregate thus posing no additional burden or risk to the safety of the participants.

27 Confidentiality

All participant data pertaining to the study will be stored in a computer database maintaining confidentiality in accordance with PHIPA regarding privacy and use of health data. When archiving or processing data pertaining to the investigators and/or to the participants, the RVH Research Institute will take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

The investigators will maintain the confidentiality of all study documentation and take measures to prevent accidental or premature destruction of these documents. After the completion or discontinuation of the study the investigators will retain the study documents twenty-five (25) years in Canada as required by regulation. The investigators must notify the RVH Research Institute prior to destroying any study documents following study completion or discontinuation. If the investigators' situation is such that archiving can no longer be ensured, the investigators will inform the RVH Research Institute, and the relevant records will be transferred to a mutually agreed designee.

If any of the investigators retire, relocate, or otherwise withdraw from conducting the study, the responsibility for maintaining records may be transferred to the RVH Research Institute or another investigator. The RVH Research Institute must be notified of and agree to the change. All associated documentation must also be updated.

28 Declaration of Interests

GD and PW have never received any salary support or grants, honoraria, paid consultancies or service on advisory boards and medical education companies, receipt of patents or patents pending, ownership of stocks or options from INDIVIOR.

29 Access to data

The RVH Research Institute will oversee the intra-study data sharing process, with input from the Data Management Committee.

The Principal Investigators will be given access to the cleaned data sets. Study data sets will be housed on the RVH REDCap web-site created for the study, and all data sets will be password protected. The Principal Investigators will have direct access to the data sets. To ensure confidentiality, any data dispersed to the study RAAM clinic healthcare providers or study personnel will be de-identified participant information and aggregated whenever feasible.

30 Post-trial care

Should this study provide evidence of the superior effectiveness of Sublocade® compared to Suboxone®, it will be critical to provide ongoing access to this drug for those study participants who were allocated to Sublocade® and for those who were allocated to Suboxone®. For those patients who do not qualify for the Ontario Drug Benefit plan or do not have private health insurance to cover the ongoing costs of treatment or cannot afford to pay out-of-pocket for Sublocade®, discussions will be initiated with other RAAM clinic healthcare providers across Canada, along with federal and provincial health agencies, to encourage the bulk purchase of Sublocade® and provision at low or no cost to RAAM clinics for use in uninsured patients with OUD eligible for opiate substitution therapy with long-acting buprenorphine.

31 Trial results and authorship

The study will be conducted in the name of the 'STOP-IT Trial Investigators'. Overall project coordination and data management will be provided by the RVH Research Institute. Study results will be disseminated via abstracts, trial registry, journal publication and RVH Research Institute and RAAM clinic websites regardless of the magnitude or direction of effect.

Authorship of publications arising from the study will be consistent with current International Committee of Medical Journal Editors' recommendations (http://www.icmje.org/recommendations/) with full credit assigned to all collaborating investigators, healthcare providers, study personnel and institutions. Responsibility for the content of manuscripts will rest with the Principal Investigators, and where listed, Philip Wong will be listed as first author and Giulio DiDiodato will be listed as corresponding author, with all other subsequent members listed alphabetically following Philip Wong and preceding Giulio DiDiodato.

Funding bodies will be acknowledged in all publications.

32 Reproducible research

The trial protocol, full study report, de-identified participant-level dataset, and statistical code for generating the results will be made publicly available no later than 3 years after study closure to an appropriate data archive for sharing purposes.

33 References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (5th ed.)*. (American Psychiatric Publishing, Inc., 2013).
2. Ontario Agency for Health Protection and Promotion. *Opioid mortality surveillance report: analysis of opioid-related deaths in Ontario July 2017-June 2018.* (2019).
3. Special Advisory Committee on the Epidemic of Opioid Overdoses. *Opioid and Stimulant-related Harms in Canada*. https://health-infobase.canada.ca/substance-related-harms/opioids-stimulants/ (2021).
4. Public Health Ontario. Opioid-related Morbidity and Mortality in Ontario. https://www.publichealthontario.ca/en/data-and-analysis/substance-use/interactive-opioid-tool#/trends (2021).
5. Nielsen, S. *et al.* Opioid agonist treatment for pharmaceutical opioid dependent people. *Cochrane database Syst. Rev.* CD011117 (2016) doi:10.1002/14651858.CD011117.pub2.
6. Bruneau, J. *et al.* Management of opioid use disorders: a national clinical practice guideline. *Can. Med. Assoc. J.* **190**, E247–E257 (2018).
7. Sordo, L. *et al.* Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *BMJ* **357**, j1550 (2017).
8. Bahji, A., Cheng, B., Gray, S. & Stuart, H. Reduction in mortality risk with opioid agonist therapy: a systematic review and meta-analysis. *Acta Psychiatr. Scand.* **140**, 313–339 (2019).
9. Galanter, M., Femino, J., Hunter, B. & Hauser, M. Buprenorphine Treatment for Opioid Use Disorder in Community-Based Settings: Outcome Related to Intensity of Services and Urine Drug Test Results. *Am. J. Addict.* **29**, 271–278 (2020).
10. Wiercigroch, D., Sheikh, H. & Hulme, J. A rapid access to addiction medicine clinic facilitates treatment of substance use disorder and reduces substance use. *Subst. Abuse Treat. Prev. Policy* **15**, 4 (2020).
11. Koehl, J. L., Zimmerman, D. E. & Bridgeman, P. J. Medications for management of opioid use disorder. *Am. J. Heal. Pharm.* **76**, 1097–1103 (2019).
12. Lofwall, M. R. *et al.* Weekly and monthly subcutaneous buprenorphine depot formulations vs daily sublingual buprenorphine with naloxone for treatment of opioid use disorder a randomized clinical trial. *JAMA Intern. Med.* **178**, 764–773 (2018).
13. Rosenthal, R. N. *et al.* Buprenorphine implants for treatment of opioid dependence: randomized comparison to placebo and sublingual buprenorphine/naloxone. *Addiction* **108**, 2141–2149 (2013).
14. Rosenthal, R. N. *et al.* Effect of buprenorphine implants on illicit opioid use among abstinent adults with opioid dependence treated with sublingual buprenorphine a randomized clinical trial. *JAMA - J. Am. Med. Assoc.* **316**, 282–290 (2016).
15. Ontario Drug Policy Research Network. Ontario Opioid Prescription Tool. https://odprn.ca/ontario-opioid-drug-observatory/ontario-prescription-opioid-tool/ (2018).
16. Canadian Agency for Drugs and Technologies in Health. *Pharmacoeconomic Review*

Report: Buprenorphine extended-release injection (Sublocade). https://www.cadth.ca/sites/default/files/cdr/pharmacoeconomic/sr0579-sublocade-pharmacoeconomic-review-report.pdf (2019).
17. Addictions & Mental Health Ontario. *Ontario Provincial Standards for Withdrawal Management Services: 2021 Standards Manual*. https://amho.ca/wp-content/uploads/AMHO-Final-WMS-Ontario-Provincial-Standards-for-Withdrawal-Management-Services-September-2021-AMHO-FINAL.pdf (2021).
18. Brens, C., Swoboda-Geen, C. & Gill, S. *Simcoe Muskoka Opioid Strategy: An Action Plan for Our Communities*. http://preventod.ca/Shared Documents/SMOS/SMOS Final Report - An Action Plan for Our Communities.pdf (2018).
19. Wesson, D. R. & Ling, W. The Clinical Opiate Withdrawal Scale (COWS). *J. Psychoactive Drugs* **35**, 253–259 (2003).
20. McMillan, D. E. & Gilmore-Thomas, K. Stability of opioid craving over time as measured by visual analog scales. *Drug Alcohol Depend.* **40**, 235–239 (1996).
21. Fals-Stewart, W., O'Farrell, T. J., Freitas, T. T., McFarlin, S. K. & Rutigliano, P. The Timeline Followback reports of psychoactive substance use by drug-abusing patients: Psychometric properties. *J. Consult. Clin. Psychol.* **68**, 134–144 (2000).
22. Reith, F. C. M., Van den Brande, R., Synnot, A., Gruen, R. & Maas, A. I. R. The reliability of the Glasgow Coma Scale: a systematic review. *Intensive Care Med.* **42**, 3–15 (2016).
23. Institute for Clinical Evaluative Sciences. Data Dictionary. *ICES Data Holdings Obligations for ICES Projects* https://datadictionary.ices.on.ca/Applications/DataDictionary/Default.aspx?viewmode=DataAccess (2021).
24. Appropriate Use of Drug Testing in Clinical Addiction Medicine. *J. Addict. Med.* **11**, 1–56 (2017).
25. Fals-Stewart, W., O'Farrell, T. J., Freitas, T. T., McFarlin, S. K. & Rutigliano, P. The Timeline Followback reports of psychoactive substance use by drug-abusing patients: Psychometric properties. *Journal of Consulting and Clinical Psychology* vol. 68 134–144 (2000).
26. Dennis, B. B. *et al.* A call for consensus in defining efficacy in clinical trials for opioid addiction: combined results from a systematic review and qualitative study in patients receiving pharmacological assisted therapy for opioid use disorder. *Trials* **21**, 30 (2020).
27. Vernon, M. K. *et al.* Psychometric evaluation of the Medication Satisfaction Questionnaire (MSQ) to assess satisfaction with antipsychotic medication among schizophrenia patients. *Schizophr. Res.* **118**, 271–278 (2010).
28. Ling, W. *et al.* Patient-centered Outcomes in Participants of a Buprenorphine Monthly Depot (BUP-XR) Double-blind, Placebo-controlled, Multicenter, Phase 3 Study. *J. Addict. Med.* **13**, 442–449 (2019).
29. World Health Organization. The World Health Organization Quality of Life (WHOQOL). *WHOQOL BREF* (2012).
30. Harris, P. A. *et al.* The REDCap consortium: Building an international community of software platform partners. *J. Biomed. Inform.* **95**, 103208 (2019).
31. Harris, P. A. *et al.* Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics

support. *J. Biomed. Inform.* **42**, 377–381 (2009).
32. Ministry of Health & Long-Term Care. Personal Health Information Protection Act. https://www.ontario.ca/laws/statute/04p03 (2004).
33. Dal-Ré, R. *et al.* Low risk pragmatic trials do not always require participants' informed consent. *BMJ* **364**, l1092 (2019).

34 Appendices

All data collection tools described in this section will be created and stored in REDCap. The links to the tools are solely intended to provide the REB committee members easy access to the contents of these tools for their review.

34.1 OUD DSM-V Diagnostic Criteria for OUD

Source for review of contents:

https://www.asam.org/docs/default-source/education-docs/dsm-5-dx-oud-8-28-2017.pdf?sfvrsn=70540c2_2

34.2 Clinical Opiate Withdrawal Scale

Source for review of contents:

https://www.mdcalc.com/cows-score-opiate-withdrawal

34.3 Opiate Craving Visual Analog Scale

Linear scale is 10 cm long, anchored at the left end by the phrase “no craving at all” and at the right end by “strongest craving ever”. Slider is moved by the participant to mark the location on the linear scale that most closely measures the intensity of the strongest craving experienced during the previous 24 hours.

34.4 Timeline Followback questionnaire

Source for review of contents:

https://cde.drugabuse.gov/sites/nida_cde/files/TimeLineFollowBack_2014Mar24.pdf

34.5 World Health Organization Quality of Life (Brief) Questionnaire

Source for review of contents:

https://neurotoolkit.com/whoqol-bref/

34.6 ICES Support Letter

ICES Central
G1 06, 2075 Bayview Avenue
Toronto, Ontario M4N 3M5
www.ices.on.ca

Monday, November 15, 2021

Dr. Giulio DiDiodato
Royal Victoria Regional Health Centre
201 Georgian Drive
Barrie, Ontario, L4M6M2

Dear Dr. DiDiodato,

Re: Confirmation of Feasibility

The Institute for Clinical Evaluative Sciences (ICES) and ICES Data & Analytic Services (DAS) is pleased to provide conditional confirmation of feasibility for the research submitted by you and your colleagues, entitled **"A pragmatic, multi-centre, open-label, randomized, 12-month, parallel group, superiority study to compare the effectiveness of subcutaneous buprenorphine depot (Sublocade®) vs daily sublingual buprenorphine with naloxone (Suboxone®) for the treatment of opioid use disorder"** and the associated data and analytic services as outlined in Appendix A ("Research Plan").

Funding for ICES DAS comes in part through support from the Ontario Ministry of Health and Long Term Care, the Ministry of Research and Innovation, and the Canadian Institutes for Health Research. ICES DAS provides in-kind support for upfront consultation required to determine feasibility and ongoing administrative services associated with managing your research. An estimate of the total cost for providing your research team with virtual access to ICES data and the analytic consultation and support for ICES to provide data cut and analytic services is attached. These figures are included in Appendix B ("Services Quote") and are intended to aid in applying for research funding. Please note that this Services Quote is subject to change if there are any changes to the scope, funding or feasibility at any point during your engagement with ICES Data & Analytic Services.

While the research meets the eligibility criteria for accessing ICES DAS, research initiation will only occur upon receipt of an approval letter from a valid Research Ethics Board (REB) (see Appendix C) and corresponding application. It is the responsibility of the Principal Investigator to complete the Research Plan in its entirety prior to submission. The REB application must include this document as supporting documentation in order to ensure that the REB is authorizing the intended research.

ICES policy will require that the Principal Investigator confirms how and when the funds are used to support this research are derived from public or publicly-funded sources, that your interest in the disclosure of the data for your research purpose will not result in actual, perceived or potential conflict of interest. If you have any questions please contact das@ices.on.ca or 416-480-4092 (toll-free 1-844-848-9855).

Once you provide all conditional requirements ICES will provide you with an ICES Data & Analytic Services Agreement that governs the research and, upon execution allows the research to be activated.

We look forward to working with you and your colleagues.

Yours sincerely,

Refik Saskin
Staff Scientist

35 Budget

All costs will be supported by in-kind funding from the Centre for Education & Research and the RAAM clinics.

Cost Component	Persons Involved	Total time (hours)	Cost per hour	Total Cost ($)
Study-related products & training				
Enrollment logs/Participant master files Randomization module Electronic case report form Standard operating procedures Training manuals Delegation logs	Centre for Education & Research (CER) RAAM Clinic Research coordinator	100 20 100	150 100 40.50	15 000 2 000 4 050
Healthcare provider engagement & training	Research coordinator Study nurse	40 20	40.50 48.50	1620 970
Study brochures Study posters Patient instructions Research personnel business cards	Research coordinator Study nurse Materials	10 10 N/A	40.50 48.50 N/A	405 485 1000
Research ethics board application	Study nurse RAAM clinic	40 20	48.50 100	1 940 2 000
Protocol review prior to research ethics board submission	Research manager	N/A	N/A	700
Research Ethics Board Fee	Research Ethics Board	N/A	N/A	500
Subtotal				**30 670**
Trial Management				
Eligibility screening Informed consent Enrollment Randomization	Study nurse	328 (2 hr/pt)	48.50	15 908
MSQ WHOQOL-BREF UDS	Research coordinator	328 (2 hr/patient)	40.50	13 284

Case report form completion	Research coordinator	328 (2 hr/patient)	40.50	13 284
Site/data audit/close out	Research coordinator	180 (15 hr/month)	40.50	7 290
Drug storage Dispensation Study drug logs	Pharmacist	120 (10 hr/month)	72.10	8 652
Subtotal				**58 418**
Data Analysis				
Validation	Study monitor	20 (1 hr/patient)	37.50	750
Cleaning Statistical analysis Data report	CER	40	150	6 000
Healthcare utilization data	ICES	N/A	N/A	12 587
Subtotal				**19 337**
Report				
Publication costs (protocol and final publication)	Journal fees	N/A	N/A	5 000
Subtotal				**5 000**
Final Costs				***113 425***