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An open-label, multicentre, single-arm trial of monthly injections of depot buprenorphine in people with opioid dependence: Protocol for the CoLAB study

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ABSTRACT

Introduction: Opioid agonist treatment (OAT) is effective for opioid dependence and newer extended-release buprenorphine (BUP-XR) injections represent a significant development. The Community Long-Acting Buprenorphine (CoLAB) study aims to evaluate client outcomes among people with opioid dependence receiving 48 weeks of BUP-XR treatment, and examines the implementation of BUP-XR in diverse community healthcare settings in Australia.

Methods and analysis: The CoLAB study is a prospective single-arm, multicentre, open-label trial of monthly BUP-XR injections in people with opioid dependence. Participants are being recruited from a network of general practitioner and specialist drug treatment services located in the states of New South Wales, Victoria and South Australia in Australia. Following a minimum 7 days on 8-32mg of sublingual buprenorphine (+/- naloxone), participants will receive 12 monthly subcutaneous BUP-XR injections administered by a healthcare practitioner at intervals of 28 days (-2/+14 days). The primary endpoint is participant retention in treatment at 48 weeks after treatment initiation. Secondary endpoints will evaluate dosing schedule variations, craving, withdrawal, substance use, health and well-being, and client-reported treatment experience. Qualitative and costing sub-studies will examine implementation barriers and facilitators at the client and provider level.

Ethics and dissemination: The study has received ethics approval from the St Vincent's Hospital Sydney Human Research Ethics Committee (Ref. HREC/18/SVH/221). The findings will be disseminated via publication in peer-reviewed journals, presentations at national and international scientific conferences, and in relevant community organisation publications and forums.

Trial registration number: NCT03809143

Protocol Identifier: CoLAB1801, version 3.0 dated 02 May 2019

Keywords: opioid dependence, drug dependence, opiate medication assisted treatment, buprenorphine, extended release formulations

STRENGTHS AND LIMITATIONS

- This is an open-label trial with broad eligibility criteria and flexible extended-release buprenorphine (BUP-XR) dosing to more accurately reflect 'real-world' clinical practice compared with previous randomised controlled trials.
- The study will be conducted at a range of healthcare settings, including specialist opioid treatment services and general practice, publicly and privately operated facilities, in metropolitan and regional locations.
- The sample size for the clinical intervention cohort is relatively small with no comparison group; however, rich and detailed participant interview data will be collected to evaluate the impact of BUP-XR on people who are opioid dependent, including those participants who discontinue treatment early.
- This mixed-method protocol (clinical intervention cohort, qualitative research and costing) will focus on the barriers and facilitators to implementation, and will be used to inform models of care, clinical guidelines and training programs for health providers.

INTRODUCTION

The two main medications used in opioid agonist treatment (OAT), methadone and buprenorphine (buprenorphine;+/-naloxone), are well established as safe and effective treatments for opioid dependence (1, 2). OAT reduces illicit opioid use, crime, overdose, mortality risk, and risk of HIV and HCV acquisition (3-5). Despite these clear benefits, OAT carries some risks, including adverse events, injection of medication intended for oral/sublingual administration, diversion and overdose (e.g., (6-8).

In response to these risks, supervised daily dosing at a specialist clinic or pharmacy is a feature of OAT in many countries (e.g. (1-4) at least during the early stages of treatment. Attendance for daily dosing is burdensome for both clients and service providers. People in treatment often state that attendance for supervised dosing is restrictive on many aspects of daily life (5) especially if significant travel time, cost and inconvenience is involved in attending during limited clinic dosing hours . Additionally in Australia, people receiving OAT frequently pay the costs of pharmacy dispensing fees (6) which is a significant burden for many clients, and also a barrier to treatment access for many who are on income support payments or disability support pensions (6). In some Australian jurisdictions, publicly-funded specialist treatment services cover the costs of supervised dosing so there is no cost to the client, but this requires substantial staffing resources that may be alternatively utilised for case management or providing health-related and /or psychosocial interventions.

Recently developed extended-release buprenorphine (BUP-XR) injections represent a significant development in OAT. They are administered subcutaneously by a healthcare provider, releasing buprenorphine at a controlled rate over the dosing interval. Currently formulations enable weekly (9) or monthly administration (9, 10). Early studies indicate that they provide rapid onset and sustained release of buprenorphine (7, 8, 11), blockade at the mu-opioid receptors minimising the euphorigenic opioid effects of illicit opioid use (11, 12), sustained reductions in illicit opioid use and good treatment retention (13, 14). Once-monthly BUP-XR injections have been approved in the US (15), and once-weekly and once-monthly BUP-XR injections have been approved in Australia (16, 17) and Europe (18).

BUP-XR injections are expected to be associated with several potential benefits. Eliminating the need to attend for frequent dosing should increase convenience to clients, and may reduce the costs to clients and providers. Monthly BUP-XR injections may enhance treatment efficacy as a result of

fewer missed doses, more consistent buprenorphine plasma levels and improved treatment exposure (19). BUP-XR injections delivered by a healthcare professional may also reduce the diversion and use via unintended routes of administration observed with sublingual buprenorphine treatment (e.g., 20, 21, 22).

There is also substantial client interest in BUP-XR. A recent survey of people who used opioids regularly (23) found that two thirds of respondents believed BUP-XR was a good treatment option for them. Interest was high among those currently in OAT as well as those who were not, with no differences according to prior methadone vs. buprenorphine experience (23). The most common advantages endorsed by participants were less frequent service attendance, 'more time to do other things' and freedom to travel for work or holidays (23). Despite these potential advantages, it is important to understand how BUP-XR impacts on client outcomes and whether the outcomes observed with BUP-XR are similar to sublingual buprenorphine despite less frequent contact with treatment services.

Six-month retention on two BUP-XR formulations were 63% and 69% respectively (13, 14) in Phase III clinical trials. These retention levels are substantially higher than those observed in routine treatment with sublingual buprenorphine (e.g., 24), however the extent to which these trials reflect 'real-world' clinical practice is limited. The double-blind placebo-controlled designs of these trials required all participants to attend for dosing daily, which does not reflect the likely routine practice with injections of BUP-XR. Clients were a highly selected group, with a range of exclusions. There is limited data available on the adherence, retention and safety (adverse events) of BUP-XR injections over the longer-term, especially the potential for local injection site complications. One open-label safety study with flexible dosing with either weekly or monthly BUP-XR over 48 weeks found high levels of retention (73.6% at 48 weeks) and the treatment was well-tolerated with a safety profile consistent with that for sublingual buprenorphine (25). Additional studies conducted over such extended period of treatment and adverse event monitoring are needed.

Implementing BUP-XR in the diverse range of treatment settings in Australia and many other countries also presents challenges. Although specialist publicly-funded clinics with onsite pharmacies are available in some jurisdictions, the treatment models in other jurisdictions rely predominantly on primary care prescribers and community pharmacies. Implementing BUP-XR in these diverse settings has important service- and system-level implications, including the development of new models of care and new procedures for drug storage and administration.

The overarching aims of the CoLAB studies detailed in this protocol are:

1. To evaluate the client outcomes following the implementation of a monthly injection of BUP-XR for the treatment of opioid dependence in community-based treatment settings with a focus on retention in treatment, opioid and other illicit drug use, adherence with the administration schedule and participants' experiences of the implementation; and
2. To develop and document the implementation of a monthly injection of BUP-XR for the treatment of opioid dependence with an emphasis on the feasibility and practical clinical, regulatory and supply issues in settings representative of Australian clinical practice.

METHODS AND ANALYSIS

Study design

The CoLAB study is a prospective single-arm, multicentre, open-label trial of monthly BUP-XR in people with opioid dependence, with qualitative and costing sub-studies. The primary objective is to examine treatment retention at 48 weeks following initiation of BUP-XR injections in clients with opioid dependence transferred from a stable dose of sublingual buprenorphine.

A total of 100 people with opioid dependence will be enrolled from seven Australian study sites, which include a mix of service providers in community settings (e.g. primary care based general practitioners) and in specialist clinic settings. Participant recruitment commenced in May 2019 and is expected to reach completion in late 2019. Qualitative and costing sub-studies will also be conducted and are described here in brief. The CoLAB study protocol addresses all criteria in the 2013 SPIRIT guidelines (Appendix 1), and study findings will be reported in accordance with these criteria.

Participant eligibility

The study population is individuals with opioid dependence who are receiving sublingual buprenorphine treatment (for at least 7 days), express interest in receiving BUP-XR, and are deemed suitable for treatment with BUP-XR by the Site Investigator. Eligibility criteria are deliberately broad to allow enrolment of a diverse group of participants. Anyone with significant, medical or psychiatric conditions which would compromise compliance and/or client safety will be excluded. Specific conditions of interest include severe hepatic disease (Child-Pugh Class B), severe renal or respiratory disease, or severe cognitive impairment or psychiatric condition that impairs the ability to provide

informed consent (e.g. psychosis, delirium, hypomania, severe depression or suicidal ideation). Whilst potential drug-drug interactions for BUP-XR are similar to sublingual buprenorphine, any participant with a history or presence of allergic or adverse response to the ATRIGEL® Delivery System gel polymer component of Sublocade® BUP-XR will be excluded. Full eligibility criteria are described in Table 1.

Table 1 about here

Study schedule

The study consists of a screening phase (up to 4 weeks); treatment intervention phase (48 weeks); and follow up at 4 weeks after the last dose of study medication, as depicted in the study schema (Figure 1):

i. Screening: Following informed consent, screening assessments include: physical assessment, medical history, substance use and related treatment history, urine pregnancy test, urine drug screening, concomitant medication, and eligibility confirmation.

ii. Treatment: BUP-XR treatment will be provided over 44 weeks, involving study visits every 4 weeks. Each study visit consists: 1) clinical and safety assessments 2) Administration of BUP-XR injection and 3) research interviews.

iii. Post-treatment follow-up: 4 weeks after the last dose of BUP-XR, for collection of safety event and research interview data.

Figure 1 about here

The procedures conducted at each visit throughout the study are detailed in the CoLAB schedule of assessments (Table 2).

Table 2 about here

BUP-XR treatment

The protocol allows for participants to receive 12 injections of Sublocade® scheduled 28 days apart (-2/+14 days; Figure 1). Sublocade® contains a buprenorphine base in a precipitation delivery system (ATRIGEL®) of biodegradable polylactide-co-glycolide polymer and biocompatible solvent (N-methyl-pyrrolidone), which, in contact with aqueous interstitial fluid, solidifies in the subcutaneous space to

form a depot. This solid depot provides sustained release of buprenorphine over a minimum of 28 days through diffusion and polymer degradation (26, 27).

Participants will follow a dosing schedule aligned with the Australian Sublocade® product information (10). This involves two Sublocade® doses of 300 mg at baseline and week 4, reflecting 'loading' doses that elevate plasma buprenorphine levels. Thereafter (doses 3-12), doses are flexible with either 100 or 300 mg every four weeks, as decided by the Site Investigator in consultation with the participant (Figure 1). Relevant factors in dose consideration include client craving and withdrawal, client rating of dose adequacy, opioid and other substance use, and adverse events. All injections will be administered by a medical practitioner or nurse trained to perform the task. The product is administered by subcutaneous injection into the abdominal area only, with the injection site rotated each dose to avoid potential irritation.

Supplemental doses of up to 8 mg daily sublingual buprenorphine for 14 days are permitted, however after the first 2 BUP-XR doses additional doses will require approval by the study Chief Medical Officer, who is available to provide clinical advice site staff throughout the study. Treatment is to be discontinued in the event of pregnancy, non-adherence to dosing regimen (more than 56 days between injections), participant removal of the depot, or medical deterioration in clinical condition of the participant according to the site PI.

Participant interviews

Participants will complete interviews via telephone at intervals of 28 days (+/- 4 days) throughout the treatment period. After the first BUP-XR dose, the interview schedule is independent of the dosing schedule and participants who discontinue treatment will remain in follow up for interviews. The interviews are structured from a combination of validated tools and additional questions developed by the Protocol Steering Committee, collecting client-reported withdrawal, craving, substance use, overdose, health service utilisation, work attendance, pain, quality of life, and treatment satisfaction data. The questionnaires included in the interviews are described in Table 2. Participants are reimbursed $50 per completed interview as compensation for their time.

Outcome measures and analysis

The primary objective of the CoLAB trial is to examine treatment retention at 48 weeks following initiation of monthly BUP-XR injections in clients with opioid dependence transferred from a stable dose of sublingual buprenorphine. Secondary objectives include evaluation of dosing schedule

variations, craving, withdrawal, substance use, health and well-being, and client-reported treatment experience over the treatment period. Study endpoints are described in Table 3.

Table 3 about here

Safety event reporting

In addition to standard adverse events and serious adverse event data collection and reporting to the ethics committee, regulatory authority and Indivior pharmacovigilance, information on adverse events of special interest (AESI) will be collected. AESI include: pregnancy, buprenorphine overdose, severe hepatic impairment, depot removal, and severe precipitated withdrawal. A medical monitor independent of UNSW, the CoLAB study, and Indivior will review all SAEs for relatedness to BUP-XR and/or study participation. A Data Safety Monitoring Board will review interim safety data once the first 20 participants have reached month 6 of the study, with subsequent review commensurate with its risk assessment.

Sample size

Existing clients of participating general practice and public specialist drug and alcohol services will be approached and following informed consent will be screened for enrolment. A total of 100 participants will be enrolled and receive at least one dose of BUP-XR. The sample will allow estimation of the retention primary endpoint with adequate precision, and evaluation of factors impacting implementation at a variety of site types (specialist and primary care; public and private). Estimates of retention are based on phase III trials with BUP-XR products (Estimated retention: 69% (14); Confidence interval: 60.0% to 77.9%). Exact 95% confidence intervals around the potential estimates of retention, calculated by the Epitools package of R, are tabled below.

Data management

Clinical data will be collected by participating sites and entered into a web-based electronic case report form, OpenClinica, an open-source clinical trial software for electronic data capture and clinical data management. On-site monitoring and source data verification will be completed at regular intervals by the sponsor for data quality assurance and to ensure compliance with the study protocol, ICH-GCP, ethics approvals, and sponsor standard operating procedures. Interviews will be conducted via telephone by UNSW researchers, not involved in the participants' clinical care or study team located at the site. Data will be entered by interviewers into the OpenClinica database. Multiple contact methods (e.g. mobile, email, social media accounts) and those for participants'

family or friends will be collected at baseline to facilitate intensive follow up and maximise retention in research interviews.

Qualitative research sub-study

The qualitative sub-study aims to examine factors impacting BUP-XR implementation from the client, service provider, clinician and policy maker perspective. Clients and providers will be interviewed to explore clients' interests, expectations and experiences of receiving BUP-XR treatment, providers' experiences of administering BUP-XR treatment in their service, and the organisational implications of implementing BUP-XR in service settings with varied characteristics in terms of model of care, staffing and policy. Qualitative interview data will be generated to examine factors that clients, service providers, clinicians and policy makers perceive as important in the implementation and delivery of BUP-XR for the treatment of opioid dependence in community-based general practice and specialist treatment settings; how this new treatment is translated and made to work in its implementation contexts and practices; how the introduction of this treatment may impact treatment experience and shape service provision; and the possibilities of, and challenges posed by, this new treatment. Purposive sampling will be used to recruit consenting participants to participate in semi-structured interviews, conducted either in person (where possible) or via telephone. Clients will be sampled to maximise diversity in gender, previous treatment experience, and duration on BUP-XR, including those who discontinue treatment early.

Costing sub-study

A costing sub-study will be undertaken to evaluate the impact of BUP-XR treatment on both participating services and participants. Resource use will be identified at both the client and facility level and will include process measures obtained through participant records (e.g. medication charts), facility records (e.g., appointment records) and interviews with individual clinical team members (e.g. Site Principal Investigator, other treating staff and pharmacist)to document procedures related to drug storage, drug administration and client care. A bottom-up or activity-based costing will be used, where each of the resources utilised will be identified, measured and valued. This will include (but is not limited to) the implementation or start-up costs; staff training; treatment costs including time to prescribe, order/transport medication, dispense and administer; monitor drug storage (e.g. refrigeration, temperature incursions and wastage); cost of the medication; any counselling or other health care costs, and any other consumables/supplies. Costs will be obtained from state-based salary and wage schedules, the Medicare Benefits Scheme (diagnostics, consultations etc.), and other standard unit costs where relevant. Any relevant

overhead and on-costs will be included. Monthly participant interviews will include collection of travel costs for BUP-XR treatment, changes in work hours, and health service utilisation unrelated to the facility providing BUP-XR.

DISCUSSION

BUP-XR injections have been established as efficacious in licensing randomised controlled trials (13, 14) however, client outcomes observed in these trials may not directly translate to real-world clinical practice in diverse client populations, particularly with respect to adherence with the dosing schedule and retention. One open-label safety study of weekly and monthly BUP-XR provides positive indications, with high levels of treatment retention (25); the CoLAB study will provide further data that reflect the 'real world' patient reported outcome and experience measures through detailed monthly patient interviews with independent researchers not involved in clinical care. There are also a number of clinical, regulatory and supply issues that may affect the feasibility of delivering this treatment in Australian clinical practice settings. The multicomponent CoLAB study will provide important data on effectiveness and safety outcomes collected in a context as close to routine clinical care as possible, while also providing important data on costs, client and provider perspectives, and implementation facilitators and barriers. These data will further inform models of care, clinical guidelines and training programs for health providers.

Although a recent survey conducted in Australia found that the majority of people who use opioids regularly anticipated that BUP-XR would be a good treatment option for them (23), criteria for effective BUP-XR client selection have not been established. One concern is that reduced clinician contact may impact treatment outcomes for some clients, through loss of daily structure and engagement with support services. Qualitative studies of potential clients found that 'longer' BUP-XR formulations (e.g., monthly or six-monthly) were viewed as beneficial for clients who wanted to avoid thinking about drugs and their networks of people who use drugs, wanted to reduce stigma, and desired 'normality' and 'recovery' (28). 'Shorter' BUP-XR formulations (.g., weekly) were viewed as beneficial to clients who were new to OAT, worried about the safety and reliability/effectiveness of OAT, want a 'break' from illicit opioids, and those who need more regular contact with services to monitor/support them (28). It is important to note, however, that the interest in a hypothetical treatment may not translate into actual experience and uptake of monthly BUP-XR injections.

Reduced frequency of clinic attendance also has implications for services providing OAT. Whilst it may potentially free up resources for providing other services, the impact on clients' other healthcare needs during BUP-XR treatment is unknown. OAT for opioid dependence in Australia is incorporated into a broader treatment model of care involving regular clinical reviews, case management and psychosocial interventions, with services individualised for each client (29). In the CoLAB study, the minimum frequency of scheduled clinical reviews with a Site Investigator (or delegated clinician) is every 42 days. Participation in psychosocial services (e.g. counselling) is encouraged, but not mandated, in the study protocol to more accurately reflect 'real world' clinical practice. The CoLAB study will provide important data on how clients receiving monthly BUP-XR injections utilise psychosocial and healthcare interventions in the periods between injections.

The study will also explore implementation issues related to management and administration of the BUP-XR medication. Sublocade® must be stored and managed consistent with jurisdictional requirements for Schedule 8 (an Australian classification of drugs of dependence that are subject to additional regulatory controls regarding their manufacture, supply, distribution, possession and use (30)). Sublocade® must also be stored under refrigerated conditions (2-8°C) and is supplied via cold chain to participating clinics, however, is stable at ambient temperature for up to 7 days. The process of BUP-XR management, including distribution, receipt, storage and temperature control, permits and accountability in accordance with Schedule 8 requirements will be documented to identify barriers. Sites with and without onsite Schedule 8 compliant refrigerated storage have been included to examine these issues.

Although the study schedule of dosing and assessments is designed to allow flexibility and mimic 'real world' clinical scenarios, there are many that will not be evaluated within the context of this research protocol. For example, all participants must be stable on a daily dose of 8-32 mg sublingual buprenorphine for at least seven days immediately prior to the first BUP-XR injection. The study will therefore not provide answers to clinical questions such as initiation of Sublocade® in patients using methadone or illicit heroin, treatment of clients on low sublingual buprenorphine doses (less than 8 mg daily) with BUP-XR, and transfer of clients between the two current BUP-XR products (Sublocade® and Buvidal®). Clinical Guidelines regarding these specific scenarios have been developed in Australia (31), with recommendations based on the available evidence and expert consensus, though further research is required. A further limitation is the single arm design. The relatively small sample size and lack of comparator limits the ability to evaluate effectiveness and cost-effectiveness of BUP-XR compared to the sublingual buprenorphine standard of care; however, the CoLAB study will provide

important information on the client retention, tolerability, and acceptability of BUP-XR, as well as the cost and key considerations involved in integrating this formulation into clinical practice in Australia.

The introduction of depot buprenorphine formulations is likely to have significant benefits for some clients and their service providers. BUP-XR may not suit all OAT clients, and some will prefer methadone or sublingual buprenorphine treatment. Current treatment guidelines recommend that medication choice is guided by client factors such as prior experience with medications, adverse events, drug-drug interactions, overdose risks, and in some cases logistic factors such as travel requirements. It is also possible that prescribers may prefer BUP-XR where there are concerns regarding a client's non-medical use (e.g. injecting, hoarding, diversion to others) of sublingual buprenorphine, or a client has a number of risk factors for unsupervised dosing that are difficult to mitigate, such as homelessness, high risk substance use, or history of medication diversion. Uptake and experience of clients will also be impacted by the way in which the medication is incorporated into existing OAT policies (e.g., 31), education on delivering BUP-XR for healthcare professionals, communication strategies and engagement of consumer groups and peers. The CoLAB study will provide important data to inform these activities.

ETHICS AND DISSEMINATION

The study is sponsored and managed by the National Drug and Alcohol Research Centre (NDARC), UNSW Sydney, Sydney, Australia. Oversight is provided by a Protocol Steering Committee (PSC) composed of clinical specialists in addiction medicine, epidemiologists with expertise in opioid dependence and drug user research, qualitative researchers, health economist, NDARC research and clinical trials operational staff, and representatives from participating clinic sites. The protocol was informed by a survey of over 400 consumers evaluating attitudes and preferences for OAT. The PSC includes representatives of community organisations advocating for people who use drugs. This study has received ethics approval from the St Vincent's Hospital Sydney Human Research Ethics Committee (Ref. HREC/18/SVH/221), and site specific assessments have been approved by the local research governance offices of participating sites. Future amendments will be similarly submitted for approval. The study was registered on clinicaltrials.gov on 16 January 2019 (NCT03809143). The study will be conducted in accordance with ICH-GCP guidelines, the Declaration of Helsinki, and all applicable local ethical and regulatory requirements. All participants must provide written informed consent. The findings will be disseminated via publication in a peer-reviewed journal and relevant scientific conference presentations. In addition to the primary clinical study report, we aim to publish a series of secondary papers describing the various components of the study, including implementation issues, qualitative and costing sub-studies, and clinical guidance development. The

authors will disseminate findings to the affected community by engaging organisations representing users.

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COLLABORATORS

The CoLAB Study Team are Michael Farrell (Chief Investigator; PSC), Louisa Degenhardt (PSC), Nicholas Lintzeris (Chief Medical Officer; PSC), Briony Larance (PSC), Suzanne Nielsen (PSC), Jason Grebely (PSC), Gregory Dore (PSC), Robert Ali (PSC), Kari Lancaster (PSC), Marian Shanahan (PSC), Carla Treloar (PSC), Marianne Byrne (Clinical Trials Manager; PSC), Jeyran Shahbazi (Trial Coordinator; PSC), Stella Nalukwago (health economic analyses), Craig Rodgers (Site Investigator; PSC), Adrian Dunlop (Site Investigator; PSC), Michael McDonough (Site Investigator) , Jon Cook (Site Investigator), Mark Montebello (Site Investigator), Michael Aufgang (Site Investigator) and Robert Weiss (Site Investigator), Madeline News (interview data collection), Zoe Griffin (research data collection).

AUTHOR CONTRIBUTIONS

BL, SN, MS, LD, KL, JG, GD, RA and MF conceived the original study concept, contributed to the study design and obtained funding. BL, NL, MB, JS, SN, MS, LD, JG and MF participated in survey development, design of data collection and contributed to the detailed trial protocol. MB and BL drafted the manuscript with input from all authors. All authors meet the International Committee of Medical Journal Editors criteria for authorship and have read and approved the final manuscript.

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COMPETING INTERESTS STATEMENT

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Farrell, Suzanne Nielsen, Robert Ali, Adrian Dunlop); Mundipharma (Briony Larance, Louisa Degenhardt, Nicholas Lintzeris, Michael Farrell); and Seqirus (Briony Larance, Louisa Degenhardt, Michael Farrell, Suzanne Nielsen).

EXECUTIVE LICENCE

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Table 1. Participant inclusion and exclusion criteria for the CoLAB study

Inclusion criteria	*Exclusion criteria*
• Aged 18 to 65 years • Opioid-dependent currently receiving treatment • Has been receiving 8-32mg sublingual buprenorphine +/- naloxone tablets/film for at least 7 days • Negative pregnancy test at screening and baseline in females of childbearing potential	• Currently lactating or pregnant, or of childbearing potential and not willing to avoid becoming pregnant during the study • History or presence of allergic or adverse response (including rash or anaphylaxis) to buprenorphine or the ATRIGEL® Delivery System • Significant, medical or psychiatric conditions which would compromise compliance with the protocol and/or client safety. Specific conditions of interest include severe hepatic disease (Child-Pugh Class B), severe renal or respiratory disease, or severe cognitive impairment or psychiatric condition that impairs the ability to provide informed consent • Subjects who are currently participating in any other clinical study involving investigational medication(s) • Inability or unwillingness to provide informed consent or abide by the requirements of the study

Table 2. CoLAB study schedule of assessments

Study week	Screening -4 to 0	Treatment 0	4	8	12	16	20	24	28	32	36	40	44	Post-Tx 48
Clinical assessments														
Medical history and physical examination	X													
Substance use and treatment history	X													
Australian Treatment Outcome Profile (ATOP)	X													
Past 7 day sublingual buprenorphine dose		X												
Eligibility confirmation[1]		X												
Pregnancy test and contraception counselling[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine drug screening (UDS)[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X
Dose adequacy		X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Opiate Withdrawal Scale (COWS)		X	X	X	*When participant reports BUP-XR dose inadequacy or withdrawal, only*									
BUP-XR treatment														
300mg BUP-XR injection		X	X											
100 or 300 mg BUP-XR injection[4]				X	X	X	X	X	X	X	X	X	X	
Telephone interviews														
Demographics		X												
Subjective Opiate Withdrawal Scale (SOWS)		X			X						X			X
Opioid Craving Visual Analogue Scale		X	X	X	X	X	X	X	X	X	X	X	X	X
Dose Adequacy			X	X		X	X	X	X	X		X	X	
Australian Treatment Outcomes Profile (ATOP)		X	X	X	X	X	X	X	X	X	X	X	X	X
Overdose (self-report)		X	X	X	X	X	X	X	X	X	X	X	X	X
Health service utilisation		X			X						X			X
Assessment of Quality of Life 4 (AQoL-4D)		X			X						X			X

PEG (Pain assessment)		X	X	X	X
Patient Health Quality 9 (PHQ-9)		X	X	X	X
WHO Absenteeism and Presenteeism		X	X	X	X
Treatment Satisfaction Questionnaire for Medication (TSQM)		X	X	X	X
Treatment Perceptions Questionnaire (TPQ)		X	X	X	X
End of Treatment Questionnaire					X
Early Cessation Questionnaire		*When participant has discontinued BUP-XR treatment early, for any reason*			

[1] Includes routine clinical tests where needed to confirm eligibility, e.g. suspected severe hepatic or renal impairment

[2] In women of childbearing potential

[3] At 3 selected sites, for validation of participant-reported drug use during interviews

[4] From the 3rd BUP-XR injection, the dose prescribed can be either 100 or 300 mg, at the discretion of the treating Investigator

Table 3. Primary and secondary endpoints of the CoLAB study

Primary objective	*Primary endpoint*
To examine BUP-XR treatment retention at 48 weeks	Percentage of participants completing 12 injections within the scheduled administration windows.
Secondary objective	*Secondary endpoint*
1. To evaluate opioid craving, withdrawal, opioid and other drug use	1.1. Change in clinically assessed (urinary drug screen) and client-reported use of opioids and other drugs and opioid craving
2. To evaluate client utilisation of buprenorphine medication during the study, including BUP-XR dose variation, adherence with dosing schedule, and dose supplementation	2.1 Percentage of participants requiring dose adjustments with sublingual buprenorphine / buprenorphine-naloxone (and dose) during treatment 2.2 Percentage of participants maintained on 300 mg per month and 100 mg per month after the initial 2x300mg injection 2.3 Mean duration of continuous treatment (weeks); 2.4 Reasons for drop-out among non-completers; 2.5 Percentage of participants presenting to receive treatment within 7 and 14 days of the next scheduled injection; 2.6 Mean duration (days) between administered injections
1. To evaluate treatment safety and tolerability by monitoring adverse events, and events of clinical interest such as drug-drug interactions and pain management in clients treated with BUP-XR	3.1 Percentage of participants with different types of special events of interest'; 3.2 Percentage of participants with common adverse events (reported in greater than 5%); 3.3 Percentage of participants with at least one severe or potentially life threatening (grade 3 or 4) adverse event; 3.4 Percentage of participants withdrawn from treatment due to unacceptable adverse events
4. To describe client-reported changes to health and social well-being	4.1. Health service utilisation during treatment and estimated costs (including client travel); 4.2. Hours worked in paid employment/study; 4.3. Other changes in health and social well-being (as measured by BPI-SF, EQ-5D, ATOP client surveys)
5. To evaluate demographic, drug use and treatment factors associated with treatment outcomes	5.1 Demographic, drug use and treatment characteristics associated with treatment outcomes, e.g. participant retention
6. To evaluate client-reported experience of treatment	6.1 Client-reported treatment satisfaction measures

7. Percentage of participants completing 6 injections within the scheduled administration windows.	7.1 Number of clients completing the 6 injections over 24 weeks
8. To document the cost of the treatment at different settings	8.1 Using process measures identify the resource use at both client and facility level

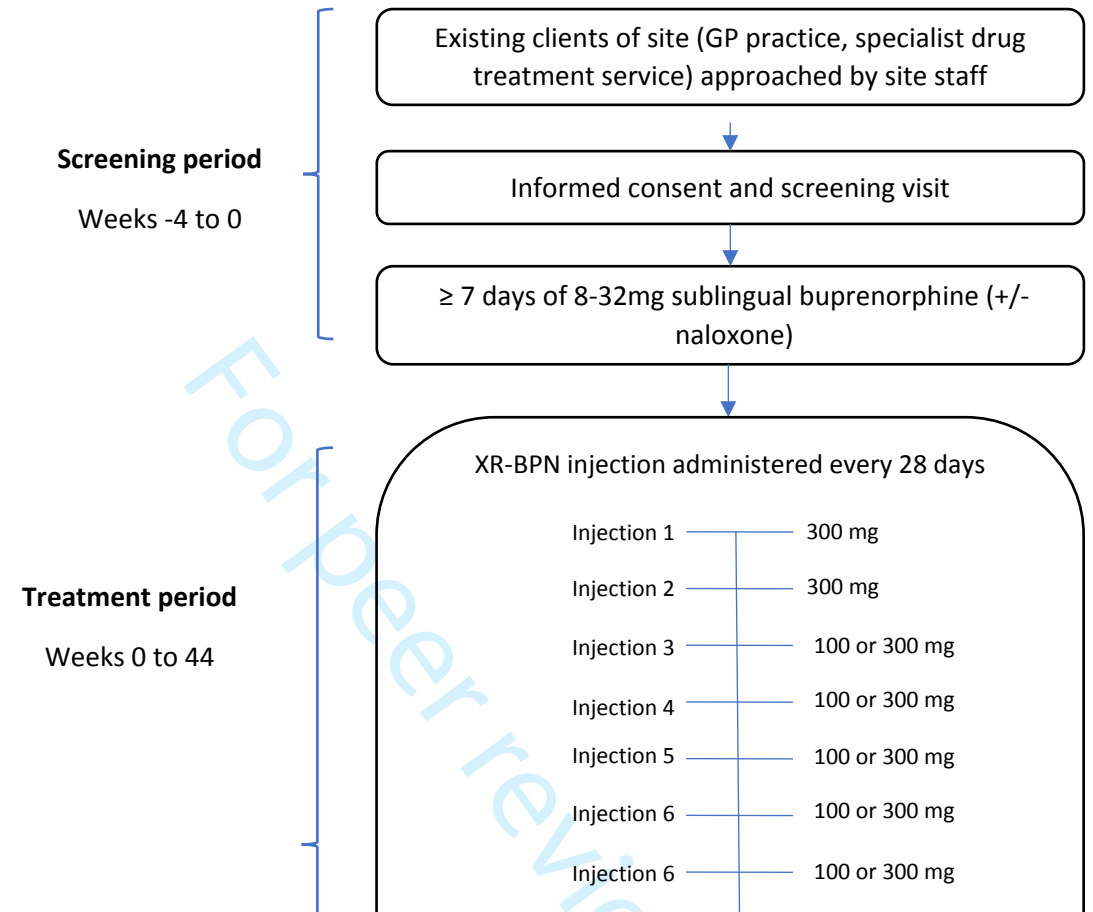

Figure 1. CoLAB study schema

SUPPLEMENTARY APPENDIX 1:

SPIRIT Checklist: Recommended items to address in a clinical trial protocol and related documents

Section/ item	Item No	Description	Included in protocol?
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Y
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Y
	2b	All items from the World Health Organization Trial Registration Data Set	Y
Protocol version	3	Date and version identifier	Y
Funding	4	Sources and types of financial, material, and other support	Y
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Y
	5b	Name and contact information for the trial sponsor	Y
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Y
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Y
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Y
	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	Y

Trial design	8	Description of trial design including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, noninferiority, exploratory)	Y
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Y
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (e.g., surgeons, psychotherapists)	Y
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Y
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)	Y
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests)	Y
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Y
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Y
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Y
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Y
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Y
Methods: Assignment of interventions (for controlled trials)			

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	17a	Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Y
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Y
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Y
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Y
	20b	Methods for any additional analyses (e.g., subgroup and adjusted analyses)	Y
	20c	Definition of analysis population relating to protocol non-adherence (e.g., as randomised analysis), and any statistical methods to handle missing data (e.g., multiple imputation)	Y

Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Y
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Y
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Y
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Y
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Y
Protocol amendments	25	Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Y
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Y
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Y
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Y
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Y
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Y
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Y

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Y
	31b	Authorship eligibility guidelines and any intended use of professional writers	Y
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Y
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Y
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Y

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	16
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	16
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	16
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	9, 13

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	8
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	8
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8

Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	7
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
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Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	N/A

		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9

Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9
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Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	8
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	8
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further	9

		details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9
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Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	8
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	13
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

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An open-label, multicentre, single-arm trial of monthly injections of depot buprenorphine in people with opioid dependence: Protocol for the CoLAB study

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An open-label, multicentre, single-arm trial of monthly injections of depot buprenorphine in people with opioid dependence: Protocol for the CoLAB study

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ABSTRACT

Introduction: Opioid agonist treatment (OAT) is effective for opioid dependence and newer extended-release buprenorphine (BUP-XR) injections represent a significant development. The Community Long-Acting Buprenorphine (CoLAB) study aims to evaluate client outcomes among people with opioid dependence receiving 48 weeks of BUP-XR treatment, and examines the implementation of BUP-XR in diverse community healthcare settings in Australia.

Methods and analysis: The CoLAB study is a prospective single-arm, multicentre, open-label trial of monthly BUP-XR injections in people with opioid dependence. Participants are being recruited from a network of general practitioner and specialist drug treatment services located in the states of New South Wales, Victoria and South Australia in Australia. Following a minimum 7 days on 8-32mg of sublingual buprenorphine (+/- naloxone), participants will receive monthly subcutaneous BUP-XR injections administered by a healthcare practitioner at intervals of 28 days (-2/+14 days). The primary endpoint is participant retention in treatment at 48 weeks after treatment initiation. Secondary endpoints will evaluate dosing schedule variations, craving, withdrawal, substance use, health and well-being, and client-reported treatment experience. Qualitative and costing sub-studies will examine implementation barriers and facilitators at the client and provider level.

Ethics and dissemination: The study has received ethics approval from the St Vincent's Hospital Sydney Human Research Ethics Committee (Ref. HREC/18/SVH/221). The findings will be disseminated via publication in peer-reviewed journals, presentations at national and international scientific conferences, and in relevant community organisation publications and forums.

Trial registration number: NCT03809143

Protocol Identifier: CoLAB1801, version 3.0 dated 02 May 2019

Keywords: opioid dependence, drug dependence, opiate medication assisted treatment, buprenorphine, extended release formulations

STRENGTHS AND LIMITATIONS

- This is an open-label trial with broad eligibility criteria and flexible extended-release buprenorphine (BUP-XR) dosing to more accurately reflect 'real-world' clinical practice compared with previous randomised controlled trials.
- The study will be conducted at a range of healthcare settings, including specialist opioid treatment services and general practice, publicly and privately operated facilities, in metropolitan and regional locations.
- The sample size for the clinical intervention cohort is relatively small with no comparison group; however, rich and detailed participant interview data will be collected to evaluate the impact of BUP-XR on people who are opioid dependent, including those participants who discontinue treatment early.
- This mixed-method protocol (clinical intervention cohort, qualitative research and costing) will focus on the barriers and facilitators to implementation, and will be used to inform models of care, clinical guidelines and training programs for health providers.

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INTRODUCTION

The two main medications used in opioid agonist treatment (OAT), methadone and buprenorphine (buprenorphine;+/-naloxone), are well established as safe and effective treatments for opioid dependence (1, 2). OAT reduces illicit opioid use, crime, overdose, mortality risk, and risk of HIV and HCV acquisition (3-5). Despite these clear benefits, OAT carries some risks, including adverse events, injection of medication intended for oral/sublingual administration, diversion and overdose (e.g., (6-8).

In response to these risks, supervised daily dosing at a specialist clinic or pharmacy is a feature of OAT in many countries (e.g. (1-4) at least during the early stages of treatment. Attendance for daily dosing is burdensome for both clients and service providers. People in treatment often state that attendance for supervised dosing is restrictive on many aspects of daily life (5) especially if significant travel time, cost and inconvenience is involved in attending during limited clinic dosing hours . Additionally in Australia, people receiving OAT frequently pay the costs of pharmacy dispensing fees (6) which is a significant burden for many clients, and also a barrier to treatment access for many who are on income support payments or disability support pensions (6). In some Australian jurisdictions, publicly-funded specialist treatment services cover the costs of supervised dosing so there is no cost to the client, but this requires substantial staffing resources that may be alternatively utilised for case management or providing health-related and /or psychosocial interventions.

Recently developed extended-release buprenorphine (BUP-XR) injections represent a significant development in OAT. They are administered subcutaneously by a healthcare provider, releasing buprenorphine at a controlled rate over the dosing interval. Currently formulations enable weekly (9, 10) or monthly administration (9-11). Early studies indicate that they provide rapid onset and sustained release of buprenorphine (7, 8, 12), blockade at the mu-opioid receptors minimising the euphorigenic opioid effects of illicit opioid use (13, 14), sustained reductions in illicit opioid use and good treatment retention (15, 16). Once-monthly BUP-XR injections have been approved in the US, Canada and Australia (17), and once-weekly and once-monthly BUP-XR injections have been approved in Australia (18, 19) and Europe (20).

BUP-XR injections are expected to be associated with several potential benefits. Eliminating the need to attend for frequent dosing should increase convenience to clients, and may reduce the costs to clients and providers. Monthly BUP-XR injections may enhance treatment efficacy as a result of

fewer missed doses, more consistent buprenorphine plasma levels and improved treatment exposure (21). BUP-XR injections delivered by a healthcare professional may also reduce the diversion and use via unintended routes of administration observed with sublingual buprenorphine treatment (e.g., 22, 23, 24).

There is also substantial client interest in BUP-XR. A recent survey of people who used opioids regularly (25) found that two thirds of respondents believed BUP-XR was a good treatment option for them. Interest was high among those currently in OAT as well as those who were not, with no differences according to prior methadone vs. buprenorphine experience (25). The most common advantages endorsed by participants were less frequent service attendance, 'more time to do other things' and freedom to travel for work or holidays (25). Despite these potential advantages, it is important to understand how BUP-XR impacts on client outcomes and whether the outcomes observed with BUP-XR are similar to sublingual buprenorphine despite less frequent contact with treatment services.

Six-month retention on two BUP-XR formulations were 63% and 69% respectively (15, 16) in Phase III clinical trials. These retention levels are substantially higher than those observed in routine treatment with sublingual buprenorphine (e.g., 26), however the extent to which these trials reflect 'real-world' clinical practice is limited. The double-blind placebo- or active-controlled designs of these trials required all participants to attend clinics on a weekly basis, which does not reflect the likely routine practice with injections of monthly BUP-XR. Clients were a highly selected group, with a range of exclusions. There is limited data available on the adherence, retention and safety (adverse events) of BUP-XR injections over the longer-term, especially the potential for local injection site complications. One open-label safety study with flexible dosing with either weekly or monthly BUP-XR over 48 weeks found high levels of retention (73.6% at 48 weeks) and the treatment was well-tolerated with a safety profile consistent with that for sublingual buprenorphine (27). Additional studies conducted over such extended period of treatment and adverse event monitoring are needed.

Implementing BUP-XR in the diverse range of treatment settings in Australia and many other countries also presents challenges. Although specialist publicly-funded clinics with onsite pharmacies are available in some jurisdictions, the treatment models in other jurisdictions rely predominantly on primary care prescribers and community pharmacies. Implementing BUP-XR in these diverse settings

has important service- and system-level implications, including the development of new models of care and new procedures for drug storage and administration.

The overarching aims of the CoLAB studies detailed in this protocol are:

1. To evaluate the participant outcomes following the implementation of a monthly injection of BUP-XR for the treatment of opioid dependence in community-based treatment settings with a focus on retention in treatment, opioid and other illicit drug use, adherence with the administration schedule and participants' experiences of the implementation; and
2. To develop and document the implementation of a monthly injection of BUP-XR for the treatment of opioid dependence with an emphasis on the feasibility and practical clinical, regulatory and supply issues in settings representative of Australian clinical practice.

METHODS AND ANALYSIS

Study design

The CoLAB study is a prospective single-arm, multicentre, open-label trial of monthly BUP-XR (Sublocade™) in people with opioid dependence, with qualitative and costing sub-studies. The primary objective is to examine treatment retention at 48 weeks following initiation of BUP-XR injections in clients with opioid dependence transferred from a stable dose of sublingual buprenorphine.

A total of 100 people with opioid dependence will be enrolled from seven Australian study site locations, which include a mix of service providers in community settings (e.g. primary care based general practitioners) and in specialist clinic settings. Sites were selected to be representative of the range of treatment service models typical in Australia, to facilitate efficient capture of implementation issues. All site Principal Investigators are current OAT prescribers, either addiction specialists (n=6) or general practitioners with experience in delivering OAT (n=1), and were provided additional training by the study team on BUP-XR administration and management. Participant recruitment commenced in May 2019 and is expected to reach completion in late 2019. Qualitative and costing sub-studies will also be conducted and are described here in brief. The CoLAB study protocol addresses all criteria in the 2013 SPIRIT guidelines (Appendix 1), and study findings will be reported in accordance with these criteria.

Participant eligibility

The study population is individuals with opioid dependence who are receiving 8-32mg sublingual buprenorphine treatment (for at least 7 days), express interest in receiving BUP-XR, and are deemed suitable for treatment with BUP-XR by the Site Investigator. Eligibility criteria are deliberately broad to allow enrolment of a diverse group of participants. Anyone with significant, medical or psychiatric conditions which would compromise compliance and/or client safety will be excluded. Specific conditions of interest include hepatic disease (Child-Pugh Class B or C), severe renal or respiratory disease, or severe cognitive impairment or psychiatric condition that impairs the ability to provide informed consent (e.g. psychosis, delirium, hypomania, severe depression or suicidal ideation). Whilst potential drug-drug interactions for BUP-XR are similar to sublingual buprenorphine, any participant with a history or presence of allergic or adverse response to the ATRIGEL® Delivery System gel polymer component of Sublocade™ BUP-XR will be excluded. Full eligibility criteria are described in Table 1.

Table 1. Participant inclusion and exclusion criteria for the CoLAB study

Inclusion criteria	*Exclusion criteria*
• Aged 18 to 65 years • Opioid-dependent currently receiving treatment • Has been receiving 8-32mg sublingual buprenorphine +/- naloxone tablets/film for at least 7 days • Negative pregnancy test at screening and baseline in females of childbearing potential	• Currently lactating or pregnant, or of childbearing potential and not willing to avoid becoming pregnant during the study • History or presence of allergic or adverse response (including rash or anaphylaxis) to buprenorphine or the ATRIGEL® Delivery System • Significant, medical or psychiatric conditions which would compromise compliance with the protocol and/or client safety. Specific conditions of interest include hepatic disease (Child-Pugh Class B or C), severe renal or respiratory disease, or severe cognitive impairment or psychiatric condition that impairs the ability to provide informed consent • Subjects who are currently participating in any other clinical study involving investigational medication(s)

	• Inability or unwillingness to provide informed consent or abide by the requirements of the study

Study schedule

The study consists of a screening phase (up to 4 weeks); treatment intervention phase (48 weeks); and follow up at 4 weeks after the last dose of study medication, as depicted in the study schema (Figure 1):

i. Screening: Following informed consent (please refer to supplementary file), screening assessments include: physical assessment, medical history, substance use and related treatment history, urine pregnancy test, urine drug screening, concomitant medication, and eligibility confirmation.

ii. Treatment: BUP-XR treatment will be provided over 44 weeks, involving study visits every 4 weeks. Each study visit consists: 1) clinical and safety assessments 2) Administration of BUP-XR injection and 3) research interviews via telephone.

iii. Post-treatment follow-up: 4 weeks after the last dose of BUP-XR, for collection of safety event and research interview data.

Figure 1 about here

The procedures conducted at each visit throughout the study are detailed in the CoLAB schedule of assessments (Table 2).

Table 2. CoLAB study schedule of assessments

Study week	Screening -4 to 0	Treatment 0	4	8	12	16	20	24	28	32	36	40	44	Post-Tx 48
Clinical assessments														
Medical history and physical examination	X													
Substance use and treatment history	X													
Australian Treatment Outcome Profile (ATOP)	X													
Past 7 day sublingual buprenorphine dose		X												
Eligibility confirmation[1]		X												
Pregnancy test and contraception counselling[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine drug screening (UDS)[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X
Dose adequacy		X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Opiate Withdrawal Scale (COWS)		X	X	X	*When participant reports BUP-XR dose inadequacy or withdrawal, only*									
BUP-XR treatment														
300mg BUP-XR injection		X	X											
100 or 300 mg BUP-XR injection[4]				X	X	X	X	X	X	X	X	X	X	
Telephone interviews														
Demographics		X												
Subjective Opiate Withdrawal Scale (SOWS)		X			X						X			X
Opioid Craving Scale		X	X	X	X	X	X	X	X	X	X	X	X	X
Dose Adequacy			X	X		X	X		X	X		X	X	
Australian Treatment Outcomes Profile (ATOP)		X	X	X	X	X	X	X	X	X	X	X	X	X
Overdose (self-report)		X	X	X	X	X	X	X	X	X	X	X	X	X
Health service utilisation		X			X						X			X
Australian Quality of Life (AQoL-4D)		X			X						X			X

Pain, Enjoyment, General Activity (PEG) scale		X	X	X	X
Patient Health Questionnaire (PHQ-9)		X	X	X	X
WHO Absenteeism and Presenteeism		X	X	X	X
Treatment Satisfaction Questionnaire for Medication (TSQM)		X	X	X	X
Treatment Perceptions Questionnaire (TPQ)		X	X	X	X
End of Treatment Questionnaire					X
Early Cessation Questionnaire			*When participant has discontinued BUP-XR treatment early, for any reason*		

[1] Includes routine clinical tests where needed to confirm eligibility, e.g. suspected severe hepatic or renal impairment

[2] In women of childbearing potential

[3] At 3 selected sites, for validation of participant-reported drug use during interviews

[4] From the 3rd BUP-XR injection, the dose prescribed can be either 100 or 300 mg, at the discretion of the treating Investigator

BUP-XR treatment

The protocol allows for participants to receive injections of Sublocade™ scheduled 28 days apart (-2/+14 days; Figure 1). Sublocade™ contains a buprenorphine base in a precipitation delivery system (ATRIGEL®) of biodegradable polylactide-co-glycolide polymer and biocompatible solvent (N-methyl-pyrrolidone), which, in contact with aqueous interstitial fluid, solidifies in the subcutaneous space to form a depot. This solid depot provides sustained release of buprenorphine over a minimum of 28 days through diffusion and polymer degradation (28, 29).

Participants will follow a dosing schedule aligned with the Australian Sublocade™ product information (11). This involves two Sublocade™ doses of 300 mg at baseline and week 4, reflecting 'loading' doses that elevate plasma buprenorphine levels. Thereafter (doses 3-12), doses are flexible with either 100 or 300 mg every four weeks, as decided by the Site Investigator in consultation with the participant (Figure 1). Relevant factors in dose consideration include client craving and withdrawal, client rating of dose adequacy, opioid and other substance use, and adverse events. In general, doses should be maintained (on 100mg or 300mg) if no clinically significant opioid withdrawal, cravings, or dose-related adverse events are identified, and the patient is satisfied with his/her current dose. Doses should generally be reduced from 300mg to 100mg if the patient reports dose-related adverse events (e.g. sedation, lethargy, headaches, nausea), the patient is seeking to ultimately withdraw from OAT, or the patient reports the dose is 'too high'. Doses should be increased from 100mg to 300mg if the patient is not achieving treatment goals (e.g. persistent unsanctioned opioid use, withdrawal symptoms or cravings), no dose-related adverse events to buprenorphine are identified, or the patient reports the dose is inadequate and there are no significant clinical safety concerns. All injections will be administered by a medical practitioner or nurse trained to perform the task. The product is administered by subcutaneous injection into the abdominal area only, with the injection site rotated each dose to avoid potential irritation.

Supplemental doses of up to 8 mg daily sublingual buprenorphine for 14 days are permitted, however after the first 2 BUP-XR doses additional doses will require approval by the study Chief Medical Officer, who is available to provide clinical advice to site staff throughout the study. Treatment is to be discontinued in the event of pregnancy, non-adherence to dosing regimen (more than 56 days between injections), participant removal of the depot, or medical deterioration in clinical condition of the participant according to the site PI. Where XR-BUP treatment is discontinued for any reason, individualised advice is provided by the study Chief Medical Officer, typically to reintroduce sublingual buprenorphine based on first principles.

Participant interviews

Participants will complete interviews via telephone at intervals of 28 days (+/- 4 days) throughout the treatment period. After the first BUP-XR dose, the interview schedule is independent of the dosing schedule and participants who discontinue treatment will remain in follow up for interviews. The interviews are structured from a combination of validated tools and additional questions developed by the Protocol Steering Committee, collecting client-reported withdrawal, craving, substance use, overdose, health service utilisation, work attendance, pain, quality of life, and treatment satisfaction data. The questionnaires included in the interviews are described in Table 2. Participants are reimbursed $50 per completed interview as compensation for their time.

Outcome measures and analysis

The primary objective of the CoLAB trial is to examine treatment retention at 48 weeks following initiation of BUP-XR injections at intervals of 28 days (-2/+14 days) in clients with opioid dependence transferred from a stable dose of sublingual buprenorphine. Secondary objectives include evaluation of dosing schedule variations, craving, withdrawal, substance use, health and well-being, and client-reported treatment experience over the treatment period. Study endpoints are described in Table 3.

Table 3. Primary and secondary endpoints of the CoLAB study

Primary objective	*Primary endpoint*
1. To examine BUP-XR treatment retention at 48 weeks	1.1 Proportion of participants retained in treatment at 48 weeks following initiation of monthly depot buprenorphine injections. Treatment retention is defined as remaining on active depot buprenorphine medication at 48 weeks.
Secondary objective	*Secondary endpoint*
1. To examine BUP-XR treatment retention and engagement in ongoing clinical care at 48 weeks	1.1 Proportion of participants retained in treatment at 48 weeks following initiation of monthly depot buprenorphine injections and engaged in ongoing clinical care. Treatment retention is defined as remaining on active depot buprenorphine medication AND completing a clinical assessment at 48 weeks.
2. To evaluate opioid craving, withdrawal, opioid and other drug use	2.1 Change in clinically assessed (urinary drug screen) and client-reported use of opioids 2.2 Change in clinically assessed (urinary drug screen) and client-reported use of other drugs 2.3 Change in clinically assessed opioid craving

3. To evaluate client utilisation of buprenorphine medication during the study, including BUP-XR dose variation, adherence with dosing schedule, and dose supplementation	3.1 Percentage of participants who completed 12 injections (per protocol) during the 48 week study period. 3.2 Percentage of participants requiring dose adjustments with sublingual buprenorphine / buprenorphine-naloxone (and dose) during treatment 3.3 Percentage of participants maintained on 300 mg per month and 100 mg per month after the initial 2x300mg injection 3.4 Mean duration of continuous treatment (weeks); 3.5 Reasons for drop-out among non-completers; 3.6 Percentage of participants presenting to receive treatment within 7 and 14 days of the next scheduled injection; 3.7 Mean duration (days) between administered injections
4. To evaluate treatment safety and tolerability by monitoring adverse events, and events of clinical interest such as drug-drug interactions and pain management in clients treated with BUP-XR	4.1 Percentage of participants with different types of 'special events of interest'; 4.2 Percentage of participants with common adverse events (reported in greater than 5%); 4.3 Percentage of participants with at least one severe or potentially life threatening (grade 3 or 4) adverse event; 4.4 Percentage of participants withdrawn from treatment due to unacceptable adverse events
5. To describe client-reported changes to health and social well-being	5.1. Health service utilisation during treatment and estimated costs (including client travel); 5.2. Hours worked in paid employment/study; 5.3. Other changes in health and social well-being (as measured by PEG, AQol-4D, ATOP client surveys)
6. To evaluate demographic, drug use and treatment factors associated with treatment outcomes	6.1 Demographic, drug use and treatment characteristics associated with treatment outcomes, e.g. participant retention
7. To evaluate client-reported experience of treatment	7.1 Client-reported treatment satisfaction measures
8. To examine BUP-XR treatment retention at 24 weeks	8.1 Percentage of participants retained in treatment at 24 weeks following initiation of monthly depot buprenorphine injections. Treatment retention is defined as remaining on active depot buprenorphine medication at 24 weeks.
9. To document the cost of the treatment at different settings	9.1 Using process measures identify the resource use at both client and facility level

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Safety event reporting

In addition to standard adverse events and serious adverse event data collection and reporting to the ethics committee, regulatory authority and Indivior pharmacovigilance, information on adverse events of special interest (AESI) will be collected. AESI include: pregnancy, buprenorphine overdose, severe hepatic impairment, depot removal, and severe precipitated withdrawal. A medical monitor independent of UNSW, the CoLAB study, and Indivior will review all SAEs for relatedness to BUP-XR and/or study participation. A Data Safety Monitoring Board will review interim safety data once the first 20 participants have reached month 6 of the study, with subsequent review commensurate with its risk assessment.

Sample size

Existing clients of participating general practice and public specialist drug and alcohol services will be approached and following informed consent will be screened for enrolment. A total of 100 participants will be enrolled and receive at least one dose of BUP-XR. The sample will allow estimation of the retention primary endpoint with adequate precision, and evaluation of factors impacting implementation at a variety of site types (specialist and primary care; public and private). Estimates of retention are based on phase III trials with BUP-XR products (Estimated retention: 69% (16); Confidence interval: 60.0% to 77.9%). Exact 95% confidence intervals around the potential estimates of retention, calculated by the Epitools package of R, are tabled below.

Data management

Clinical data will be collected by participating sites and entered into a web-based electronic case report form, OpenClinica, an open-source clinical trial software for electronic data capture and clinical data management. On-site monitoring and source data verification will be completed at regular intervals by the sponsor for data quality assurance and to ensure compliance with the study protocol, ICH-GCP, ethics approvals, and sponsor standard operating procedures. Interviews will be conducted via telephone by UNSW researchers, not involved in the participants' clinical care or study team located at the site. Data will be entered by interviewers into the OpenClinica database. Multiple contact methods (e.g. mobile, email, social media accounts) and those for participants' family or friends will be collected at baseline to facilitate intensive follow up and maximise retention in research interviews.

Qualitative research sub-study

The qualitative sub-study aims to examine factors impacting BUP-XR implementation from the client, service provider, clinician and policy maker perspective. Clients and providers will be interviewed to explore clients' interests, expectations and experiences of receiving BUP-XR treatment, providers' experiences of administering BUP-XR treatment in their service, and the organisational implications of implementing BUP-XR in service settings with varied characteristics in terms of model of care, staffing and policy. Qualitative interview data will be generated to examine factors that clients, service providers, clinicians and policy makers perceive as important in the implementation and delivery of BUP-XR for the treatment of opioid dependence in community-based general practice and specialist treatment settings; how this new treatment is translated and made to work in its implementation contexts and practices; how the introduction of this treatment may impact treatment experience and shape service provision; and the possibilities of, and challenges posed by, this new treatment. Purposive sampling will be used to recruit consenting participants to participate in semi-structured interviews, conducted either in person (where possible) or via telephone. Clients will be sampled to maximise diversity in gender, previous treatment experience, and duration on BUP-XR, including those who discontinue treatment early. Interviews will capture a range of treatment timepoints including early BUP-XR experience soon after the first dose, and follow up interviews after at least 6 months of treatment.

Costing sub-study

A costing sub-study will be undertaken to evaluate the impact of BUP-XR treatment on both participating services and participants. Resource use will be identified at both the client and facility level and will include process measures obtained through participant records (e.g. medication charts), facility records (e.g., appointment records) and interviews with individual clinical team members (e.g. Site Principal Investigator, other treating staff and pharmacist)to document procedures related to drug storage, drug administration and client care. A bottom-up or activity-based costing will be used, where each of the resources utilised will be identified, measured and valued. This will include (but is not limited to) the implementation or start-up costs; staff training; treatment costs including time to prescribe, order/transport medication, dispense and administer; monitor drug storage (e.g. refrigeration, temperature incursions and wastage); cost of the medication; any counselling or other health care costs, and any other consumables/supplies. Costs will be obtained from state-based salary and wage schedules, the Medicare Benefits Scheme (diagnostics, consultations etc.), and other standard unit costs where relevant. Any relevant overhead and on-costs will be included. Monthly participant interviews will include collection of

travel costs for BUP-XR treatment, changes in work hours, and health service utilisation unrelated to the facility providing BUP-XR.

Patient and public involvement

Design of the CoLAB implementation study was informed by a survey (n=402) evaluating patients' priorities and concerns regarding BUP-XR (25). The research question, study design, participant information sheet and survey tools were reviewed by a community reference panel which included individuals with a history of or current drug use. Findings of the study will be disseminated through a lay language summary posted to participants, as well as publications distributed by advocacy agencies representing people who use drugs.

DISCUSSION

BUP-XR injections have been established as efficacious in licensing randomised controlled trials (15, 16) however, further data are limited (27). The CoLAB study will provide data that reflect the 'real world' patient reported outcome and experience measures in a context as close to routine clinical care as possible, while also providing important data on costs, client and provider perspectives, and implementation facilitators and barriers. These data will further inform models of care, clinical guidelines and training programs for health providers.

Although a recent survey conducted in Australia found that the majority of people who use opioids regularly anticipated that BUP-XR would be a good treatment option for them (25), criteria for effective BUP-XR client selection have not been established. One concern is that reduced clinician contact may impact treatment outcomes for some clients, through loss of daily structure and engagement with support services. Qualitative studies of potential clients found that 'longer' BUP-XR formulations (e.g., monthly or six-monthly) were viewed as beneficial for clients who wanted to avoid thinking about drugs and their networks of people who use drugs, wanted to reduce stigma, and desired 'normality' and 'recovery' (30). 'Shorter' BUP-XR formulations (.g., weekly) were viewed as beneficial to clients who were new to OAT, worried about the safety and reliability/effectiveness of OAT, want a 'break' from illicit opioids, and those who need more regular contact with services to monitor/support them (30). It is important to note, however, that the interest in a hypothetical treatment may not translate into actual experience and uptake of monthly BUP-XR injections.

Reduced frequency of clinic attendance also has implications for services providing OAT. Whilst it may potentially free up resources for providing other services, the impact on clients' other healthcare needs during BUP-XR treatment is unknown. OAT for opioid dependence in Australia is incorporated into a broader treatment model of care involving regular clinical reviews, case management and psychosocial interventions, with services individualised for each client (1). In the CoLAB study, the minimum frequency of scheduled clinical reviews with a Site Investigator (or delegated clinician) is every 42 days. Participation in psychosocial services (e.g. counselling) is encouraged, but not mandated, in the study protocol to more accurately reflect 'real world' clinical practice. The CoLAB study will provide important data on how clients receiving monthly BUP-XR injections utilise psychosocial and healthcare interventions in the periods between injections.

The study will also explore implementation issues related to management and administration of the BUP-XR medication. Sublocade™ must be stored and managed consistent with jurisdictional requirements for Schedule 8 (an Australian classification of drugs of dependence that are subject to additional regulatory controls regarding their manufacture, supply, distribution, possession and use (31)). Sublocade™ must also be stored under refrigerated conditions (2-8°C) and is supplied via cold chain to participating clinics, however, is stable at ambient temperature for up to 7 days. The process of BUP-XR management, including distribution, receipt, storage and temperature control, permits and accountability in accordance with Schedule 8 requirements will be documented to identify barriers. Sites with and without onsite Schedule 8 compliant refrigerated storage have been included to examine these issues.

Although the study schedule of dosing and assessments is designed to allow flexibility and mimic 'real world' clinical scenarios, there are many that will not be evaluated within the context of this research protocol. For example, all participants must be stable on a daily dose of 8-32 mg sublingual buprenorphine for at least seven days immediately prior to the first BUP-XR injection. The study will therefore not provide answers to clinical questions such as initiation of Sublocade™ in patients using methadone or illicit heroin, treatment of clients on low sublingual buprenorphine doses (less than 8 mg daily) with BUP-XR, and transfer of clients between the two current BUP-XR products (Sublocade™ and Buvidal™). Clinical Guidelines regarding these specific scenarios have been developed in Australia (31), with recommendations based on the available evidence and expert consensus, though further research is required. A further limitation is the single arm design. The relatively small sample size and lack of comparator limits the ability to evaluate effectiveness and cost-effectiveness of BUP-XR compared to the sublingual buprenorphine standard of care; however, the CoLAB study will provide

important information on the client retention, tolerability, and acceptability of BUP-XR, as well as the cost and key considerations involved in integrating this formulation into clinical practice in Australia.

The introduction of depot buprenorphine formulations is likely to have significant benefits for some clients and their service providers. BUP-XR may not suit all OAT clients, and some will prefer methadone or sublingual buprenorphine treatment. Current treatment guidelines recommend that medication choice is guided by client factors such as prior experience with medications, adverse events, drug-drug interactions, overdose risks, and in some cases logistic factors such as travel requirements. It is also possible that prescribers may prefer BUP-XR where there are concerns regarding a client's non-medical use (e.g. injecting, hoarding, diversion to others) of sublingual buprenorphine, or a client has a number of risk factors for unsupervised dosing that are difficult to mitigate, such as homelessness, high risk substance use, or history of medication diversion. Uptake and experience of clients will also be impacted by the way in which the medication is incorporated into existing OAT policies (e.g., 31), education on delivering BUP-XR for healthcare professionals, communication strategies and engagement of consumer groups and peers. The CoLAB study will provide important data to inform these activities.

ETHICS AND DISSEMINATION

The study is sponsored and managed by the National Drug and Alcohol Research Centre (NDARC), UNSW Sydney, Sydney, Australia. Oversight is provided by a Protocol Steering Committee (PSC) composed of clinical specialists in addiction medicine, epidemiologists with expertise in opioid dependence and drug user research, qualitative researchers, health economist, NDARC research and clinical trials operational staff, and representatives from participating clinic sites. The protocol was informed by a survey of over 400 consumers evaluating attitudes and preferences for OAT. The PSC includes representatives of community organisations advocating for people who use drugs. This study has received ethics approval from the St Vincent's Hospital Sydney Human Research Ethics Committee (Ref. HREC/18/SVH/221), and site specific assessments have been approved by the local research governance offices of participating sites. Future amendments will be similarly submitted for approval. The study was registered on clinicaltrials.gov on 16 January 2019 (NCT03809143). The study will be conducted in accordance with ICH-GCP guidelines, the Declaration of Helsinki, and all applicable local ethical and regulatory requirements. All participants must provide written informed consent. The findings will be disseminated via publication in a peer-reviewed journal and relevant scientific conference presentations. In addition to the primary clinical study report, we aim to publish a series of secondary papers describing the various components of the study, including implementation issues, qualitative and costing sub-studies, and clinical guidance development. The

authors will disseminate findings to the affected community by engaging organisations representing users.

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COLLABORATORS

The CoLAB Study Team are Michael Farrell (Chief Investigator; PSC), Louisa Degenhardt (PSC), Nicholas Lintzeris (Chief Medical Officer; PSC), Briony Larance (PSC), Suzanne Nielsen (PSC), Jason Grebely (PSC), Gregory Dore (PSC), Robert Ali (PSC), Kari Lancaster (PSC), Marian Shanahan (PSC), Carla Treloar (PSC), Marianne Byrne (Clinical Trials Manager; PSC), Jeyran Shahbazi (Trial Coordinator; PSC), Stella Nalukwago (health economic analyses), Craig Rodgers (Site Investigator; PSC), Adrian Dunlop (Site Investigator; PSC), Michael McDonough (Site Investigator) , Jon Cook (Site Investigator), Mark Montebello (Site Investigator), Michael Aufgang (Site Investigator) and Robert Weiss (Site Investigator), Madeline News (interview data collection), Zoe Griffin (research data collection).

AUTHOR CONTRIBUTIONS

BL, SN, MS, LD, KL, JG, GD, RA and MF conceived the original study concept, contributed to the study design and obtained funding. BL, NL, MB, JS, SN, MS, LD, JG and MF participated in survey development, design of data collection and contributed to the detailed trial protocol. MB and BL drafted the manuscript with input from all authors. All authors meet the International Committee of Medical Journal Editors criteria for authorship and have read and approved the final manuscript.

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COMPETING INTERESTS STATEMENT

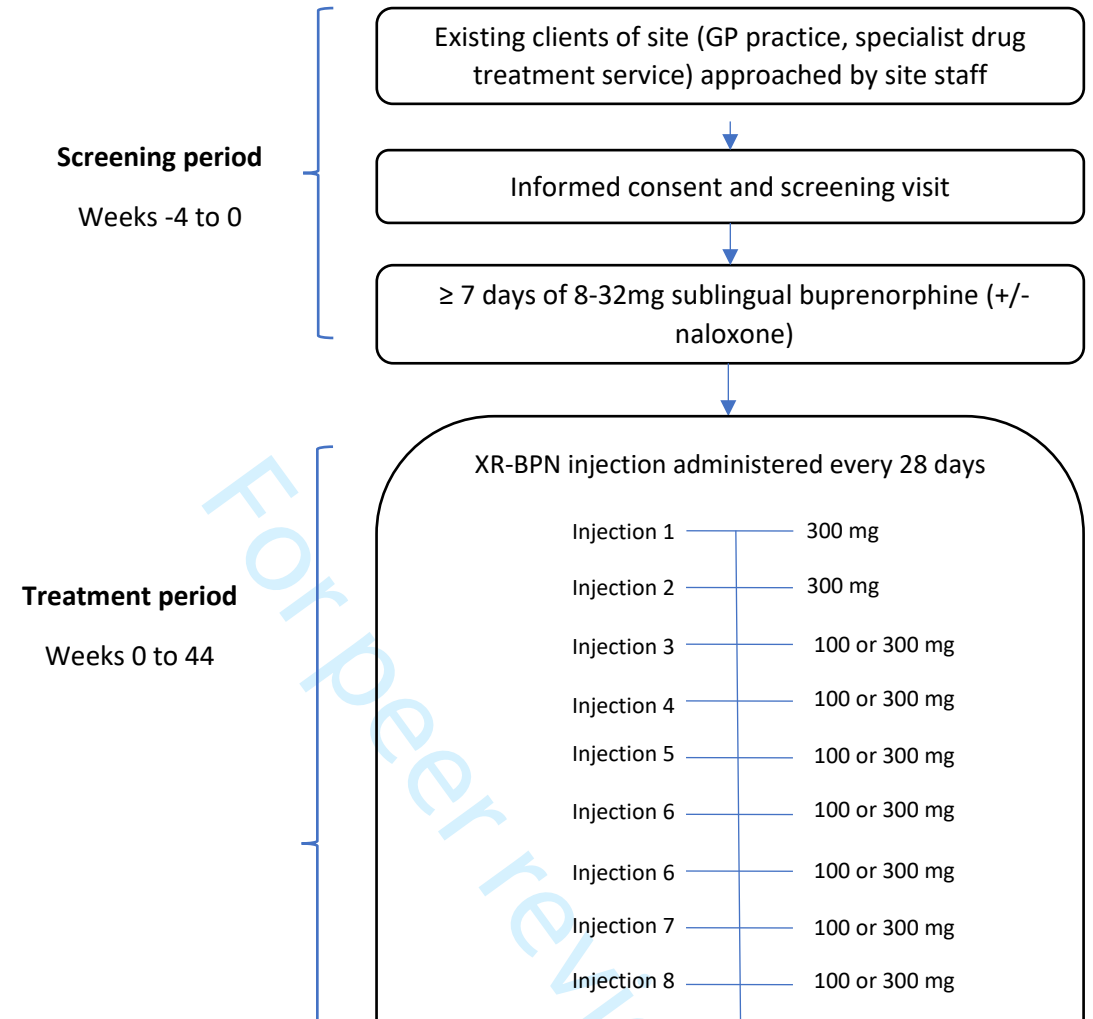
Many of the investigators have received investigator-initiated, untied educational grants for opioid-related studies from: Indivior (Briony Larance, Louisa Degenhardt, Nicholas Lintzeris, Michael Farrell, Suzanne Neilsen); Reckitt Benckiser (Briony Larance, Louisa Degenhardt, Nicholas Lintzeris, Michael

Farrell, Suzanne Nielsen, Robert Ali, Adrian Dunlop); Mundipharma (Briony Larance, Louisa Degenhardt, Nicholas Lintzeris, Michael Farrell); and Seqirus (Briony Larance, Louisa Degenhardt, Michael Farrell, Suzanne Nielsen).

EXECUTIVE LICENCE

FIGURES

Figure 1. CoLAB study schema



[INSERT LETTERHEAD]

Participant Information Sheet/Consent Form

[Insert site name]

Title	An open-label, multicentre, single-arm trial of monthly injections of extended release buprenorphine in people with opioid dependence
Short Title	CoLAB
Protocol Number	SVH No: 18/194
Project Sponsor	University of New South Wales (UNSW) Sydney
Co-ordinating Principal Investigator	Prof Michael Farrell
Location	[INSERT HOSPITAL NAME & LOCATION]

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project. This is because you are in opioid substitution therapy (buprenorphine) for opioid dependence; which is the term used by the World Health Organization to describe the symptoms where a person has difficulty controlling their use of opioids, and continues to use opioids despite experiencing negative consequences.

The research project is testing whether a new treatment of monthly buprenorphine injection is acceptable and effective for people with opioid dependence. The new treatment is called 'Sublocade®'.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:
- Understand what you have read
- Consent to take part in the research project
- Consent to have the tests and treatments that are described
- Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

Sublocade® is a new form of buprenorphine administered by injection under the skin in the abdominal area. The buprenorphine is combined with a gel-like substance called ATRIGEL® so

that it forms a small mass under the skin, which slowly releases buprenorphine into the bloodstream over at least 28 days. Studies where people have been treated with Sublocade® show that it maintains blood levels of buprenorphine that are enough to control cravings and withdrawal symptoms, and that it is well tolerated by clients, with possible side effects similar to buprenorphine taken sublingually, underneath the tongue

The purpose of this study is to evaluate how feasible and acceptable Sublocade® is for treatment of people with opioid dependence, in particular whether people continue with this treatment. Participants will be people already receiving sublingual buprenorphine, and will be asked by their doctor if they would like to have the new treatment. All participants in the study will receive treatment with Sublocade® for 12 months.

The study will assess how acceptable the new treatment is by looking at the proportion of people who continue on Sublocade® for 12 months. It will also assess the percentage of people completing 6 monthly injections. It will examine people's experience of the treatment, how people use the medication (e.g. doses used), and its impact upon substance use, health and social conditions.

Sublocade® has been recently approved by the Food and Drugs Administration (FDA) in the United States, and is currently being considered for approval by the Therapeutic Goods Administration (TGA) in Australia.

This study is sponsored by the National Drug and Alcohol Research Centre (NDARC) at the University of New South Wales (UNSW) in Sydney. The study is an investigator initiated or so called collaborative study and funding for the study (together with supply of Sublocade®) is from the pharmaceutical company Indivior Pty Ltd.

3 What does participation in this research involve?

If you agree to participate in this project, you will be asked to sign the Participant Consent Form prior to any study assessments being performed. This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way.

If you agree to take part, your participation would be for up to 13 months. Below is an outline of the clinic visits you would be required to attend, and what would happen at the visits. There are three phases of the study: screening (seeing whether you are eligible and want to take part in the study, lasting up to a 1month period); treatment (12 months); and follow up after the last study treatment visit (1 month). Only participants who meet all eligibility criteria assessed during screening will be able to enter the treatment phase of the study. Participants who aren't eligible for treatment can continue treatment with sublingual buprenorphine. Participants who stop study treatment for any reason before the end of the study will be asked to remain in the study and continue research assessments.

SCREENING PHASE

Your study doctor will do some assessments (history, physical and mental health examination, blood and urine tests) to see if you are eligible to enter the treatment phase of the study. You will have the following tests and procedures over one or more clinic visits within a four-week period:

- the study doctor will take a medical history from you and complete a mental health assessment over the past 12 month
- the study doctor will perform an examination (this may require you to partially undress)
- you may be asked to provide a urine sample for an urine test. This is a research sample to tests for the presence of certain drugs including opiates, amphetamines, cannabis, cocaine, oxycodone, ecstasy, fentanyl and benzodiazepines. You and the study doctor

and nurse will not receive the results from this test. The results of the urine drug test will not affect whether or not you can participate in the study.
- a pregnancy test (urine) will be done for females who can fall pregnant
- the study doctor will ask you about any medications you are using

TREATMENT PHASE

The Baseline Visit

If you meet all the requirements and want to continue in the study, you will commence treatment at the Baseline visit. This will take place within four weeks of screening assessments (when your doctor has all of your results from screening). This visit will approximately take approximately half an hour to complete.

The following assessments will be performed at the baseline visit:

- you may be asked to provide a urine sample for an urine test. This is a research sample to tests for the presence of certain drugs including amphetamines, cocaine and opiates. A positive drug test will not affect whether or not you can participate in the study.
- a pregnancy test (urine) will be done for females who can fall pregnant
- the study doctor will ask you about any illness or injury, and any medications you are taking since the last visit
- Additionally, your study doctor will assess your symptoms of opiate withdrawal
- The study doctor or nurse will administer your first dose of Sublocade® by injecting it into the skin on your stomach

Within 7 days prior to your clinic visit, a researcher will conduct an interview with you. The interview usually takes about 60 minutes to complete. The researcher will ask you questions about:

- Your recent drug and alcohol use, and whether you have been craving drugs
- How happy you are with your recent buprenorphine treatment
- How you are feeling in your health and quality of life
- Whether you have needed to use other health services or miss work recently, due to your health

On-treatment Visits

You will be required to attend the clinic every 4 weeks to receive your next Sublocade® injection. The study doctor or nurse will perform the tests and procedures below:

- the study doctor or nurse will perform a clinical assessment asking you about your treatment, adequacy of the dose, any side effects and use of other medications
- you may be asked to provide a urine sample for an urine test. This is a research sample to tests for the presence of certain drugs including amphetamines, cocaine and opiates. A positive drug test will not affect whether or not you can continue in the study and the results will not be made available to your treatment team
- a pregnancy test (urine) will be done for females who can fall pregnant

your study doctor will assess your symptoms of opiate withdrawal.

- The study doctor or nurse will administer your dose of Sublocade® by injecting it into the skin on your stomach

Within 4 days of each clinic visit, a researcher will conduct an interview with you. The interview should take about 60 minutes to complete at baseline and week 12, 24, 36 and 48. The interview should take about 20 minutes to complete at week 4, 8, 16, 20, 28, 32, 40 and 44 . The researcher will ask you questions about:

- Your recent drug and alcohol use, and whether you have been craving drugs
- How happy you are with your recent buprenorphine treatment

- How you are feeling, physically and mentally and if you have been experiencing any pain
- Whether you have needed to go to the doctor or miss work recently, due to your health

If you decide that you want to stop treatment before week 44, or your study doctor decides it is unsafe for you to continue in the study, you will be asked to complete the tests and procedures that are part of the ' Clinical Safety follow up visit, then carry on with research interview at defined time points during the study.

End of Study Visit

You will be required to attend the clinic 4 weeks after the last Sublocade® injection you receive as part of the study (this visit could be 48 weeks after the first dose). The study doctor or nurse will perform the tests and procedures below:

The following assessments will be performed:

- you may be asked to provide a urine sample for an urine test. This is a research sample to tests for the presence of certain drugs including amphetamines, cocaine and opiates. A positive drug test will not affect whether or not you can continue in the study and the results will not be made available to your treatment team

- the study doctor or nurse will perform an examination (this may require you to partially undress), to check if you have any irritation at the injection sites
- a urine pregnancy test will be done (for females of child bearing potential)
- the study doctor or nurse will ask you about any illness or injury, and any medications you are using

Within 4 days of each clinic visit, a researcher will conduct an interview with you which should take about 60 minutes to complete.

The researcher will ask you questions about:

- Your recent drug and alcohol use, and whether you have been craving drugs
- How happy you are with your recent buprenorphine treatment
- How you are feeling, physically and mentally and if you have been experiencing any pain
- Whether you have needed to go to the doctor or miss work recently, due to your health

What is the study treatment?

All participants will receive injections of the same treatment, called Sublocade® every 4 weeks. This is a new form of buprenorphine combined with a gel-like substance that means when it is injected into the skin of the stomach it is released slowly into the bloodstream over one month or more. All participants will receive a dose of 300mg at the baseline visit and week 4 visit. From the third dose onwards, patients and their doctor will be able to choose between a dose of 100mg or 300mg. Previous experience suggests some patients may prefer the higher dose, and others the lower dose.

Whilst the doses are scheduled to occur every 4 weeks, there will be some flexibility about dosing, allowing for doses to be given 2 days earlier or two week after the usual 4 week dose .In exceptional circumstances, the study doctor may authorise a short period of treatment with sublingual buprenorphine if required.

Will I receive payment for being part of this project?

Participation in this study (including clinic visits and medications) will be provided free of charge. You will be reimbursed for your time participating in research assessments and reasonable travel expenses up to the amount of $50 per visit, and $60 for the week 48 visit. Reimbursement will be organised by the researchers following completion of each research interview.

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions.

4 What do I have to do?

If you decide to be in this study, there are certain rules you must follow before, during, and after the study period. Some are listed below, but there could be others that the study doctor will discuss with you:

- You must be able to provide written consent to be in this study.
- It is possible that taking the study drug with your regular medications or supplements may change how the study drug, your regular medications, or your regular supplements work. It is very important that you tell the study doctor about all medications or supplements you are taking during the study including those you take as needed or which you take only occasionally.
- You must check with your study doctor before you take any new medications during the study.
- If you decide to take part in this study, it is very important that you attend all visits as scheduled.
- You must follow all instructions given to you while you are participating in this study. If you do not, you may be removed from the study. If you are unsure about what you are supposed to do, ask the study doctor.
- You must not be pregnant, become pregnant or father a child during this study. Please see the Pregnancy section below for more information.
- It is desirable that your local doctor be advised of your decision to participate in this research project. If you have a local doctor, we strongly recommend that you inform them of your participation in this research project.

If you cannot follow these restrictions, you should not be in this study.

It is important that you attend study visits every month. If you miss a visit and are more than 4 weeks overdue for a Sublocade® injection, the study doctor cannot continue your Sublocade® treatment. If this happens, you will be offered alternative treatments for your opioid dependence.

5 Other relevant information about the research project

The study is sponsored by the University of New South Wales Sydney, and supported by a grant from Indivior, the company that manufactures Sublocade®.

The study will involve a total of 100 participants in different states in Australia.

6 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage. If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with UNSW Sydney, the clinic you attend, or medical or other staff caring for you.

7 What are the alternatives to participation?

You do not have to take part in this research project to receive buprenorphine treatment at this clinic. Sublocade® is currently only available in Australia by participating in this study, however other treatment options for opioid dependence are available. These include continuing on sublingual buprenorphine. Your study doctor will discuss these options with you before you decide whether or not to take part in this research project. You can also discuss the options with your local doctor.

8 What are the possible benefits of taking part?

There is no guarantee that you will receive personal benefit from taking part in this study. It is hoped that Sublocade® may effectively and safely manage your opioid dependence, and allow you to attend the clinic and take buprenorphine less frequently (for monthly Sublocade® injection instead of daily sublingual buprenorphine). However, it is possible that you may still need sublingual buprenorphine. Your participation may provide valuable information to improve the management of people with opioid dependence in the future.

9 What are the possible risks and disadvantages of taking part?

Medical treatments often cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get. Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. At each study visit, the study doctor or nurse will check on how you are feeling and to see if you have had any side effects. They will discuss with you the best way to manage mild side effects. If a severe side effect or reaction occurs, you may need to attend the clinic for review by the study nurse or study doctor. The study doctor may need to stop your treatment. Your study doctor will discuss the best way of managing any side effects with you.

In studies with this treatment most of the side effects experienced by patients taking Sublocade® were similar to patients taking sublingual buprenorphine, and the side effects were considered mild. Safety of Sublocade® has been characterised in 8 clinical studies to date in which 484 participants have taken Sublocade® ,The most common side effects were constipation (11%), headache (9%), nausea (10%), vomiting (6%) and abnormal liver enzymes (10%).

However, having a drug injected may cause some discomfort, bruising, minor infection or bleeding. If this happens, it can be easily treated. In research with Sublocade® so far, injection site pruritus (itchiness) was experienced by 7% of people, and 8% of people had pain at the site of injection.

It is not expected that you will have any or all of these side effects. Other side effects may occur that are not listed here or were not seen before. Please speak to your study doctor for more information. Side effects are usually temporary and can often be treated. However, it is very important that you report all side effects to your study nurse at any time during the study as it is possible that side effects may suggest a serious or fatal health problem.

Pregnancy:
Care must be taken to avoid pregnancy in female participants during this study and for up to 6 months following completion of study treatment. The effects of Sublocade® on the unborn child and on the newborn baby are not known. Because of this, it is important that research project participants are not pregnant or breast-feeding and do not become pregnant during the course of the research project. You must not participate in the research if you are pregnant or trying to become pregnant, or breastfeeding. If you are male, you should not father a child or donate sperm for at least 6 months after the last dose of study medication.

Female Participants only: Throughout the study women who are able to have children will have regular pregnancy tests to check that they have not fallen pregnant since their last visit. These will be performed at screening, baseline, and every four weeks during treatment. You must notify your study doctor or nurse immediately if you suspect you might be pregnant. Your study doctor may withdraw you from the study and advise on further medical attention should this be necessary.

[APPLICABLE FOR NON-CATHOLIC INSTITUTIONS delete or include as applicable]

This study has very specific instructions regarding birth control and pregnancy which should be adhered to during participation to this study.

Please ask your doctor if you have any questions about the birth control methods below.

From screening until 6 months after the last dose of Sublocade®, you and your partner must agree to use 1 effective method of contraception when having sexual intercourse.

The method can be a non-hormonal barrier method that prevents transmission of fluids or hormonal methods such as the oral contraception pill, the hormonal implant, the hormonal injection, the hormonal or copper IUD, the vaginal ring and the transdermal contraceptive patch. Other acceptable methods are tubal sterilisation or vasectomy in males.

[APPLICABLE FOR CATHOLIC INSTITUTIONS delete or include as applicable]

Female participants need to avoid pregnancy during the course of the study and for a period of 6 months after the last dose of study medication. Male participants with female partners need to avoid fathering a child during the course of the study and for a period of 6 months after last dose of study medication. You should speak to the study doctor about the need to avoid pregnancy during this study.

Other risks or discomforts of the study
Occasionally, people have allergic reactions (including life-threatening reactions) when taking any medication. Symptoms of any allergic reaction can include: rash, hives, itching and/or trouble breathing, closing of the throat, swelling of the lips, tongue or face, and rarely death. Immediately get emergency medical care if you have any of these symptoms. Stop taking your study drugs and let your study doctor know.

In general, allergic reactions to medicines are more likely to occur in people who already have allergies. If you are allergic to other drugs, foods or things in the environment, such as dust or grass, you should let your study doctor know. Also, if you have asthma, let your study doctor know.

Blood draws
Drawing blood may cause local pain, bruising, occasional light-headedness, fainting, and very rarely, infection at the site of the blood draw.

Drug use

This research project involves the collection of information about your use of drugs. Participation in the research project includes urine analysis to determine the presence of various drugs (marijuana (THC), methamphetamines, amphetamines, opiates, cocaine benzodiazepines, oxycodone, fentanyl, ecstasy, methadone and alcohol). The tests are used for research purposes only and the results will not be available to your treatment team. The results will in no way affect your treatment. If your treating doctor wants a urine drug test for clinical purposes, they will let you know that a separate urine specimen will be collected. Drug use information collected for this study will be stored in a re-identifiable (or coded) format. In the event that UNSW is required to disclose that information, it may be used against you in legal proceedings or otherwise.

10 What will happen to my test samples?

Urine samples

If you are female and able to fall pregnant you will have urine samples collected at screening, baseline and each study visit. Your study doctor or nurse will use the urine sample to test for pregnancy before administering the next Sublocade® injection.

You may be asked to provide a urine sample at some visits to check for recent drug use. The urine sample is for research purposes only. It allows the researchers to check whether overall drug use reported by participants in the research interviews matches drugs detected in urine. The urine will be sent to the laboratory working with the clinic, and identified by will only be identified with a unique study identification number, your initials and date of birth. The test will check for the presence of different drugs, marijuana, methamphetamines, amphetamines, opiates, cocaine, benzodiazepines, oxycodone, ecstasy, methadone and fentanyl. Your study doctor or nurse will not receive the results. If drugs are detected in your urine this will not affect your ability to stay in the study and continue treatment with Sublocade®. Any leftover urine not needed for this testing will be destroyed by the laboratory.

11 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, he/ she will explain the reasons and arrange for your regular health care to continue.

12 Can I have other treatments during this research project?

Whilst you are participating in this research project, you may not be able to take some or all of the medications or treatments you have been taking for other health conditions. It is important to tell your study doctor and the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the research project. Your study doctor should also explain to you which treatments or medications need to be stopped for the time you are involved in the research project.

13 What if I withdraw from this research project?

You can withdraw from treatment at any time, but the researchers will want to continue to follow you up for research interviews for the 12 month period.

If you decide to withdraw from the research project, please notify a member of the research team before you withdraw. This notice will allow that person to discuss any health issues or complications. Special requirements linked to withdrawals are safety reasons, pregnancy, removal of depot and you not adhering to study procedures.
If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the sponsor up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

14 Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:
• Unacceptable side effects
• Sublocade® being shown not to be effective
• Sublocade® being shown to work and not need further testing
• Decisions made by local regulatory/health authorities

15 What happens when the research project ends?

Once the research project ends you may be able to continue treatment with Sublocade®. Near the end of the study, your doctor will talk with you about continuing the treatment after the study ends.
If by then Sublocade® is approved by Therapeutic Goods Administration (TGA) and is accessible via the Pharmaceutical Benefits Scheme (PBS), your doctor will be able to arrange for continuation as part of your routine care; otherwise your study doctor may be able to access it from the company. If you prefer, you can be treated with sublingual buprenorphine instead of Sublocade®. Please ask your study doctor or nurse for more information about what the treatment options are after the research project ends

Part 2 How is the research project being conducted?

16 What will happen to information about me?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. When you enrol in the study you will be given a unique study identification number. This number will be used throughout the study and all samples and data collected from you will be identified by this ID number, your initials and your date of birth not your name. Your personal information may be collected to contact you for research interviews (name, phone number). This will be stored separately from study data and only authorised researchers will have access to the code linking this to your study ID number. All of your samples and data will be stored securely and

only authorised study personnel including monitors, auditors, ethics committees and inspectors will have access to them. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the study team accessing health records if they are relevant to your participation in this research project.

Your health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and authorised representatives of the Sponsor, UNSW Sydney, the institution relevant to this Participant Information Sheet, St Vincent's Hospital Sydney Human Research Ethics Committee, or as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission. Your unique study identification number will ensure your confidentiality.

Information about your participation in this research project may be recorded in your health records.

In accordance with relevant Australian and/or [NAME OF STATE/TERRITORY] privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

Any information obtained for the purpose of this research project that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

17 Complaints and compensation

Complaints

This study has been approved by the St Vincent's Hospital Sydney Human Research Ethics Committee. Any person with concerns or complaints about the conduct of this study should contact the Research Office who is nominated to receive complaints from research participants. You should contact them on 02 8382 4960 and quote reference number (HREC/18/SVH/221)

The conduct of this study at the [NAME OF SITE] has been authorised by the [NAME OF ORGANISATION]. Any person with concerns or complaints about the conduct of this study should refer to Section 20 for details of who to contact.

Compensation

If you suffer any injuries or complications as a result of this study, you should contact the study doctor as soon as possible and you will be assisted in arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

In the event of loss or injury, the parties involved in this research project have agreed that you may have a right to take legal action to obtain compensation for any injuries or complications resulting from the study. Compensation may be available if your injury or complication is sufficiently serious and is caused by unsafe drugs or equipment, or by the negligence of one of the parties involved in the study (for example, the researcher, the hospital, or the treating doctor). If you receive compensation that includes an amount for medical expenses, you will be required to pay for your medical treatment from those compensation monies. You do not give up any legal rights to compensation by participating in this study. If you are not eligible for compensation for your injury or complication under the law, but are eligible for Medicare, then you can receive any medical treatment required for your injury or complication free of charge as a public patient in any Australian public hospital.

18 Who is organising and funding the research?

The study is a collaborative study conducted by the UNSW Sydney and supported by funding and provision of drug from the pharmaceutical company Indivior Pty Ltd. No member of the research team will receive a personal financial benefit from their involvement in this research project (other than their ordinary wages).

19 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of St Vincent's Hospital Sydney. The HREC Reference Number is (HREC/18/SVH/221)

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

20 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor on [INSERT NUMBER] or any of the following people:

Clinical contact person

Name	[Name]
Position	[Position]
Telephone	[Phone number]
Email	[Email address]

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Position	[Research Office Manager]
Telephone	[(02) 8382 4960] SVHS.research@SVHA.org.au

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	St Vincent's Hospital Sydney HREC
Telephone	02 8382 4960
Email	SVHS.Research@svha.org.au

[INSERT LETTERHEAD]

Consent Form

Title	An open-label, multicentre, single-arm trial of monthly injections of extended release buprenorphine in people with opioid dependence
Short Title	CoLAB
Protocol Number	SVH No. 18/194
Project Sponsor	University of New South Wales (UNSW) Sydney
Co-ordinating Principal Investigator	Prof Michael Farrell
Location	[INSERT HOSPITAL NAME & LOCATION]

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to [INSERT SITE NAME] concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please _____

Signature _____ Date _____

Name of Witness* to Participant's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/ Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

I understand that, if I decide to discontinue the study treatment, I may be asked to attend follow-up visits to allow collection of information regarding my health status. Alternatively, a member of the research team may request my permission to obtain access to my medical records for collection of follow-up information for the purposes of research and analysis.

[INSERT LETTERHEAD]

Form for Withdrawal of Participation

Title	An open-label, multicentre, single-arm trial of monthly injections of extended release buprenorphine in people with opioid dependence
Short Title	CoLAB
Protocol Number	SVH No; 18/194
Project Sponsor	University of New South Wales (UNSW) Sydney
Co-ordinating Principal Investigator	Prof Michael Farrell
Location	[INSERT HOSPITAL NAME & LOCATION]

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with [INSERT SITE NAME].

I wish to withdraw my research samples from the above research project.

Name of Participant (please print) _____

Signature _____ Date _____

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.

SUPPLEMENTARY APPENDIX 1:

SPIRIT Checklist: Recommended items to address in a clinical trial protocol and related documents

Section/ item	Item No	Description	Included in protocol?
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Y
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Y
	2b	All items from the World Health Organization Trial Registration Data Set	Y
Protocol version	3	Date and version identifier	Y
Funding	4	Sources and types of financial, material, and other support	Y
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Y
	5b	Name and contact information for the trial sponsor	Y
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Y
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Y
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Y
	6b	Explanation for choice of comparators	N/A
Objectives	7	Specific objectives or hypotheses	Y

Trial design	8	Description of trial design including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, noninferiority, exploratory)	Y
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Y
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (e.g., surgeons, psychotherapists)	Y
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Y
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)	Y
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests)	Y
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Y
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Y
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Y
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Y
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Y
Methods: Assignment of interventions (for controlled trials)			

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	17a	Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Y
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Y
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Y
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Y
	20b	Methods for any additional analyses (e.g., subgroup and adjusted analyses)	Y
	20c	Definition of analysis population relating to protocol non-adherence (e.g., as randomised analysis), and any statistical methods to handle missing data (e.g., multiple imputation)	Y

Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Y
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Y
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Y
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Y
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Y
Protocol amendments	25	Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Y
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Y
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Y
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Y
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Y
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Y
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Y

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Y
	31b	Authorship eligibility guidelines and any intended use of professional writers	Y
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Y
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Y
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Y