PROTOCOL FULL TITLE:

Ex**tended-release **P**harmacotherapy for **O**pioid Use Disorder (EXPO): An Open Label Randomised Controlled Trial of Injectable Depot Maintenance Buprenorphine versus Standard-Of-Care Oral Maintenance Opioid Agonist/Partial Opioid Agonist Medication, with Personalised Psychosocial Intervention. **The EXPO study.

Protocol Short Title/Acronym

Extended-release **P**harmacotherapy for **O**pioid Use Disorder (**EXPO**)

Trial Identifiers

Protocol version (date): V5.1 (06/10/2021)

IRAS Project ID: 255522;
REC: London – Brighton and Sussex
REC Reference: 19/LO/0483

EudraCT number: 2018-004460-63

Co-Sponsors
King's College London (KCL) and South London & Maudsley NHS Foundation Trust (SLaM).

Chief Investigator and Principal Investigator (contract lead for academic partner: SLaM)
Mike Kelleher; South London and Maudsley NHS Foundation Trust.
Lambeth Addictions Consortium, 12-14 Brighton Terrace, London SW9 8DG
Telephone: 020 3228 1500; Fax: 020 3228 1585
Email: mike.kelleher@slam.nhs.uk

Lead (clinical scientific) Investigator (lead for academic partner: KCL)
John Marsden; Addiction Sciences Building; Institute of Psychiatry, Psychology and Neuroscience, 4 Windsor Walk, Denmark Hill, London SE5 8AF
Telephone: 0207 848 0830; 07710 327 876
Email: john.marsden@kcl.ac.uk

Co-Lead (clinical scientific) Investigator
Luke Mitcheson; South London and Maudsley NHS Foundation Trust; Lambeth Addictions Consortium. 12-14 Brighton Terrace, Brixton, London SW9 8DG
Telephone: 020 3228 1500; Fax: 020 3228 1585
Email: luke.mitcheson@slam.nhs.uk

1. Study Synopsis

Title of clinical trial	**Ex**tended-release **P**harmacotherapy for **O**pioid Use Disorder (EXPO): A Randomised Controlled Trial of Injectable Depot Buprenorphine with Personalised Psychosocial Intervention versus Oral Opioid Agonist/Partial Agonist Medication.
Short Title/acronym	**The EXPO trial**
Protocol Version (date)	Version 5.1 (06.10.2021)
Trial Phase	Phase III (CTIMP; IMP open-label, oral IMP comparators [no placebo])
Sponsors	King's College London and South London & Maudsley NHS Trust
EudraCT number	2018-004460-63
IRAS Project number	255522
NHS ethics committee	London – Brighton and Sussex
Medical condition	Opioid Use Disorder (OUD; moderate-severe; DSM5)
Primary objective	The primary objective is a clinical superiority effectiveness contrast to standard of care. Reported following SPIRIT and CONSORT standards, the study will determine whether extended-release injectable depot Buprenorphine (XR-Bup) maintenance therapy for OUD over six months is clinically superior to standard-of-care, oral medication.
Secondary objectives	To explore study group differences on the following measures: (1) Clinical superiority of XR-Bup plus personalised Psychosocial Intervention (PSI; offered across the treatment phase) versus Bup/Met plus PSI; (2) Safety of XR-Bup; (3) Treatment retention; (4) OUD and CUD remission status; (5) Clinician rated impression of patient response to treatment; (6) Patient reported recovery outcomes; (7) Mediation of craving, work and social adjustment, and cognitive function on outcome. Economic Objectives To estimate the cost-effectiveness of buprenorphine extended-release depot injection, based on the incremental cost per quality-adjusted life year (QALY) gained compared with standard-of-care, oral medication. Subject to securing research support, there will be analysis of data-registry indicators of mortality, convictions and health service utilisation (the later longer-term research aims). In preparation for this, participants will be asked for their consent.
Trial design	Multi-centre, pragmatic, open-label, phase 3, two-phase, open-label, randomised controlled trial.

Setting	Specialist community NHS addictions treatment clinics.
Endpoints	**Primary**: Count of days abstinent from illicit/non-medical opioids during weeks 2 to 24 (range: 0-161 days); combining self-report information from Time-Line Follow-Back interview adapted from the Treatment Outcomes Profile and incorporating data from 12 scheduled urine drug screens. **Secondary**: To explore study group differences on the following: (1) Clinical superiority of XR-Bup plus PSI versus Bup/Met plus PSI. (2) Safety of XR-Bup; (3) Time (days) enrolled in study treatment (retention) to week 24; (4) OUD and CUD remission status (DSM5 OUD and CUD severity; SCID-5-RV); (5) Clinician rating of severity, complexity and recovery strengths: ADAPT; (6) Clinician global impression of severity and improvement): CGI-S/I; (7) Count of days abstinent from cocaine and illicit/non-medical benzodiazepines during weeks 2 to 24 (range: 0-161 days); combining self-report information from Time-Line Follow-Back interview adapted from the Treatment Outcomes Profile and incorporating data from 12 scheduled urine drug screens. (8) Frequency of opioid (H) and cocaine (C) craving experience: CEQ-F(H) and CEQ-F(C); (9) Craving need and want strength for heroin and cocaine: VAS-N(H/C) and VAS-W(H/C); (10) Difficulties in Emotion Regulation (Short Form): DERS-SF; (11) Depression symptoms: QIDS-SR; (12) Work and social adjustment: WSAS; (13) Subjective recovery and improvement: SURE; (14) Patient rating of OUD severity and improvement: PRO-S/I; (15) Cognitive impairment: MoCA; (16) Alcohol consumption: typical quantity and frequency: (ALC-QFM); (17) Time (days) enrolled in study treatment (retention) from week 24 to date of last participant randomised plus 9 months; (18) Semi structured, topic guided interviews after week 24 (XR-Bup, XR-Bup +PSI & Bup/Met +PSI treatment arms) and after 12 months of enrolment within the trial (XR-Bup treatment arm only); (19) Among participants enrolled in longer term XR-Bup treatment: OUD and CUD remission status (SCID-5-RV); heroin, cocaine and illicit/non-medical benzodiazepine use in past 90 days (TLFB; UDS); somatic symptoms (PHQ-15), emotion regulation (DERS-SF), depression and anxiety symptoms (PHQ-4) and quality of life (OSTQOL). Economic: Costs based on responses to the ADSUS questionnaire and the EXPO keyworker contact form; and QALYs calculated from EQ-5D-5L scores and by applying the EQ-5D-3L crosswalk value set. This has no implications for the sample size calculation.

Sample size and justification	**Target total N=604** Group 1: XR-Bup (n=152); Group 2: Bup/Met (n=152); Group 3: XR-Bup and PSI (n=150); Group 4: Bup/Met and PSI (n=150). The target number of participants has been calculated using that required for a Poisson regression taking a baseline rate of 0.6 and assuming a 23% target difference in the count of days of abstinence from heroin over the study period of 161 days (reference study: ARC trial (ISRCTN69313751; 56.78% for the treatment-as-usual control group [i.e. assuming 17 abstinent days over a period of 28 days]). To obtain 90% power, for a Poisson regression model, with alpha at 5% and with 15% inflation for attrition, EXPO has a target total of 304 participants for the statistical comparison of the primary outcome recorded for Group 1 and Group 2 and a target total of 300 for the statistical comparison of Group 3 and Group 4. The statistical analysis plan will include a sensitivity check on this power calculation on the assumption of a greater response for the control groups. Following completion of these analyses, an analysis will be done of Group 1 and Group 3 to estimate the effect of XR-Bup and PSI compared to XR-Bup). This will be an exploratory but pre-registered analysis.
Participant eligibility criteria	Inclusion criteria 1. Aged ≥ 18 years (no upper age limit); 2. Current diagnosis of DSM-5 OUD via SCID-5-RV (moderate-severe at baseline for current episode); 3. Currently enrolled on Met (30mg/day or less) or sublingual Bup or Bup-NX (24mg/day or less) or Esp (18mg/day or less) and in the view of the clinician would be able to convert to XR-Bup within 7 days post randomisation; 4. Voluntarily seeking treatment and able to attend the clinic as required in the protocol; 5. Able to communicate in English to level required to accept standard care and psychosocial intervention; 6. Possession of a contactable personal mobile phone or landline telephone number and ability to nominate at least one locator individual with a verifiable address and a telephone number to assist with the arrangement of follow-up appointments; 7. Living circumstances judged to be of sufficient stability to be able to engage/adhere to the study protocol; 8. Is not pregnant (confirmed) or breast feeding and, if currently or intending to have potentially procreative intercourse, agrees to use a birth control method (either oral hormonal contraceptives, barrier

	[condom or diaphragm], or Nexplanon implant) for the duration of the study. Exclusion criteria 1. Clinically significant medical condition or observed abnormalities on physical examination or laboratory investigation, including but not limited to: (a) uncontrolled hypertension, significant heart disease (including angina and myocardial infarction in past 12 months), or any cardiovascular abnormality which is judged to be clinically significant; (b) severe alcohol dependence/withdrawal syndrome which is judged to be clinically significant and may constitute a risk to the patient's safety; (c) acute hepatitis taken as clinical jaundice on examination, or evidence of blood bilirubin level above the normal range for local reference criteria, or evidence of serum levels of aspartate aminotransferase, alanine aminotransferase levels that are more than three-times the upper limit of the normal range; 2. History of allergic or adverse reactions to Bup or the proprietary ATRIGEL delivery system for XR-Bup (Sublocade®)*; 3. Clinically significant or uncontrolled mental health problems (including but not limited to psychosis, bipolar disorder, schizoaffective disorder), or history or evidence of organic brain disease or dementia that may compromise safety or compliance with the study protocol; 4. Current (past 30 day) suicide plan or suicide attempt in past six months; 5. Current criminal justice involvement with legal proceedings, which in the opinion of a medically qualified investigator indicates a risk that the patient would fail to complete the study protocol due to re-incarceration or move away from the centre's catchment area. 6. Currently taking oral or depot naltrexone therapy or enrolment in any form of naltrexone therapy within 90 days prior to study screening; 7. Any contraindication to Bup* . **Participant is ineligible if they have any allergic or adverse reactions or contraindication to Buprenorphine. If participant has any allergic or adverse reaction or contraindication to Met or naloxone, or excipients of Bup-NX or Esp they can be prescribed Bup within the trial.*
IMP, dosage and route of administration	Buprenorphine extended-release depot injection (USA Sublocade®; XR-Bup) is administered by subcutaneous injection into abdominal tissue. XR-Bup is available as a 100mg/0.5ml and 300mg/1.5ml pre-filled syringe. In EXPO, the drug is administered as two initial doses of 300mg given a minimum of 21 days apart, followed by 4 x 100 mg monthly maintenance doses. Within the regimen and if the benefits are judged to outweigh the risks: (1) The 100 mg maintenance dose may be increased and maintained to 300mg if there is unsatisfactory clinical response (i.e. dose 3-6); (2) A 300 mg maintenance dose (i.e. dose 4 and 5) may be reduced to 100 mg according to clinical assessment; (3) Bup will be given on a rescue

	basis for patients who do not achieve a satisfactory clinical response to XR-Bup.
Active comparator product(s)	(1) Bup (sublingual [tablet] Bup, or substitute 4:1 ratio Bup/naloxone 'Suboxone' [Bup- NX]) usual dose 12-24mg/day; or substitute oral lyophilisate Espranor (Esp) usual dose 8-18mg/day) are longstanding standard-of-care maintenance pharmacotherapy for OUD in the NHS. (2) Met (oral methadone hydrochloride; usual dose 60-120mg/d), longstanding standard-of-care maintenance pharmacotherapy for OUD in the NHS.
Maximum duration of treatment for participant	40 months
Electronic CRF	InferMED MACRO (programmed by King's Clinical Trials Unit [KCTU])
Clinical trials unit	KCTU (on-line randomisation)
Study Phases	Data lock 1: target quarter 3, 2022 for analysis of XR-Bup vs. Bup/Met. Data lock 2: target quarter 3, 2022 for analysis of XR-Bup + PSI vs. Bup/Met + PSI.
Target duration of study	48 months
Protocol Amendments	Detailed in Section 25 of the protocol

2. Study Contacts

Michael Kelleher (Chief Investigator [CI] and Principal Investigator) Clinical Lead Lambeth Addictions SLaM Drug and Alcohol Service (Lambeth) Lorraine Hewitt House 12-14 Brighton Terrace, Brixton London SW9 8DG w: 020 322 81500; m: 0781 3 055 783 email: Mike.Kelleher@slam.nhs.uk	**John Marsden (Co-Lead Investigator [Co-LI])** Research Lead Lambeth Addictions Institute of Psychiatry, Psychology & Neuroscience Box 48, Addiction Sciences Building 4 Windsor Walk, London SE5 8AF w: 020 7848 0830; m: 07710 327 876 f: 020 7848 5966; email: john.marsden@kcl.ac.uk
Luke Mitcheson (Co-LI) Clinical Lead Lambeth Addictions SLaM Drug and Alcohol Service (Lambeth) Lorraine Hewitt House, 12-14 Brighton Terrace, Brixton, London SW9 8DG w: 020 322 81512 m: 0781 3 055 783 email: Luke.Mitcheson@slam.nhs.uk	**Jatinder Bisla (EXPO Trial Manager)** Institute of Psychiatry, Psychology & Neuroscience Box 48, Addiction Sciences Building 4 Windsor Walk, London SE5 8AF w: 020 7848 0830; f: 020 7848 5966 email: jatinder.bisla@kcl.ac.uk
Zoë Hoare (Trial Statistician) NWORTH Clinical Trials Unit, School of Health Sciences, Bangor University, Bangor, Gwynedd, LL57 2DG; w: 01248 388840; email: z.hoare@bangor.ac.uk	**Caroline Murphy (Operational Director KCTU)** Institute of Psychiatry, Psychology & Neuroscience PO64, De Crespigny Park, London SE5 8AF w: 020 7848 0532; f: 020 7848 5229 email: caroline.murphy@kcl.ac.uk
Angela Cape (EXPO Trial Pharmacist) Institute of Psychiatry, Psychology & Neuroscience PO64, De Crespigny Park, London SE5 8AF w: 020 7848 0532; f: 020 7848 5229 email: angela.cape@kcl.ac.uk	**Joanna Kelly (Strategic Data Management Lead KCTU)** Institute of Psychiatry, Psychology & Neuroscience PO64, De Crespigny Park, London SE5 8AF w: 020 7848 0532; f: 020 7848 5229 email: joanna.kelly@kcl.ac.uk
Eilish Gilvarry (Principal Investigator [PI]) Consultant Psychiatrist in Addictions Northumberland, Tyne & Wear NHS Foundation Trust Newcastle Addictions Service, Plummer Court, Carliol Place, Newcastle upon Tyne, NE1 6UR w: 0191 206 1123 (Personal Assistant) email: eilish.gilvarry@ntw.nhs.uk	**Ed Day (Principal Investigator)** Consultant in Addiction Psychiatry, Birmingham & Solihull Mental Health NHS Foundation Trust 25 Vincent Drive, Birmingham B15 2FG w. 0121 301 2355; f: 0121 301 2351 email: e.j.day@bham.ac.uk
Jonathan Dewhurst (Principal Investigator) Clinical Lead consultant psychiatrist Greater Manchester Mental Health NHS Foundation Trust, Chapman Barker Unit, Bury New Road, Prestwich, Manchester, M25 3BL w: 0161 358 1599 email: jonathan.dewhurst@gmmh.nhs.uk	**Fiona Cowden (Principal Investigator)** Consultant Psychiatrist Dundee Drug & Alcohol Recovery Service Constitution House 55 Constitution Road Dundee, DD1 1LB w: 01382 424518 email: fcowden@nhs.net
Dyfrig Hughes (Health Economics Lead) Centre for Health Economics and Medicines Evaluation Bangor University, Bangor, Gwynedd, LL57 2PZ w: 01248 382950 email: d.a.hughes@bangor.ac.uk	

3. List of abbreviations

Abbreviation	Definition
ADAPT	Addiction Dimensions for Assessment and Personalised Treatment
ADSUS	Alcohol and Drug Service Use Schedule
AE	Adverse Event
AEL	Adverse Event Log
ALC-QFM	Alcohol - Quantity, Frequency and Maximum Consumption
ALT	Alanine Aminotransferase
AMRI	Albany Molecular Research
AR	Adverse Reaction
AST	Aspartate Aminotransferase
ATRIGEL	Proprietary Extended-Release Bup Delivery Technology
BP	Blood Pressure
Bup	Buprenorphine
Bup-NX	Buprenorphine-Naloxone (Suboxone®)
CBT	Cognitive Behavioural Therapy
CDF	Cumulative Distribution Function (for primary outcome)
CEQ-F(H/C)	Craving Experience Questionnaire (frequency version) (Heroin/Cocaine)
CI	Chief Investigator
CGI-S and I	Clinical Global Impression (severity and improvement)
CHEERS	Consolidated Health Economics Evaluation Reporting Standards
COVID-19	Coronavirus Disease 2019
CRA	Clinical Research Associate
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medical Product
CUD	Cocaine Use Disorder
DERS-SF	Difficulties in Emotion Regulation Scale – Short Form
DMC	Data Monitoring Committee
DSM-5	Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEA QPPV	European Economic Area Qualified Person Responsible for Pharmacovigilance
Esp	Espranor®
EQ-5D-5L	EuroIQol Health Status (5 level)
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HEAP	Health Economics Analysis Plan
IB	Investigators Brochure
IME	Important Medical Events
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
KCF	Keyworker Contact Form
KCTU	King's Clinical Trials Unit
KHP-CTO	King's Health Partners – Clinical Trials Office
LFT	Liver Function Tests (AST, ALT, albumin and bilirubin)
Met	Methadone (oral)
Mg	Milligrams
Mg/day	Milligrams per day
MoCA	Montreal Cognitive Assessment
MHRA	Medicines and Healthcare Product Regulatory Agency
NICE	National Institute for Health and Care Excellence
OSTQOL	Opioid Substitution Treatment Quality of Life scale
OUD	Opioid Use Disorder
PDA	Percentage Days Abstinent
PHE	Public Health England
PHQ-4	Patient Health Questionnaire Anxiety and Depression
PHQ-15	Patient Health Questionnaire
PI	Principal Investigator
PNC	Police National Computer

PRO-S and I	Patient Reported Outcome (severity and improvement)
PSI	Personalised Psychosocial Intervention
QALY	Quality-adjusted life year
QIDS-SR	Quick Inventory of Depressive Symptomatology
QP	Qualified Person
REC	Research Ethics Committee
RR	Relative Risk
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction (SAR)
SCID-5-RV	Standard Clinical Interview for Dependence – Research Version (DSM-5)
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SURE	Substance Use Recovery Evaluator
SUSAR	Suspected Unexpected Serious Adverse Reaction
TLFB	Timeline Follow Back
TMG	Trial Management Group
TOP	Treatment Outcomes Profile
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
UDS	Urine Drug Screen
VAS-(N/W)	Visual Analogue Craving Rating (Need/Want; 0-100 Point)
WSAS	Work and Social Adjustment Scale
XR-Bup	Extended-Release Buprenorphine (US Sublocade®; prev. RBP-60000)

Contents

4. Introduction

4.1 Background

In England, there are ~260,000 people with primary opioid use disorder (OUD) [1], with 150,000 people enrolled in front-line standard-of-care sublingual tablet buprenorphine (Bup) and oral liquid methadone (Met) in 1,000 public clinics in the National Health Service (NHS) and third-sector services.

Initially commercially developed as an analgesic, Bup is a lipophilic thebaine derivative with a high binding affinity at the *mu*-opioid receptor where it has partial agonist effects, and at the kappa opioid receptor where it is a competitive antagonist. Approved for detoxification and maintenance medication treatment for OUD, generic sublingual tablet Bup is available in the NHS; along with Bup combined with naloxone (Bup-NX) as alternatives to Met in standard-of-care treatment. In the EXPO trial, the effectiveness of extended-release subcutaneous injectable Bup (Sublocade®; RBP-6000 during development; XR-Bup herein) will be determined in comparison to standard-of-care opioid agonist or partial opioid agonist medication (Met or Bup; Met/Bup herein).

4.2 Rationale

OUD is a debilitating psychiatric condition with a high global burden of disease [1] and substantial social costs (£4.7 billion in England and Wales associated with drug-related acquisitive crime in 2010/11) [2]. Internationally, in recent years there has been a rapid and substantial increase in the prevalence of OUD and the rate of fatal opioid deaths [3]. Bup and Met are the first-line maintenance medication treatments for OUD. In the English public treatment system, these medications are dispensed by community pharmacists (by direct observation in the early phase of treatment and then for self-administration contingent on satisfactory progress).

The average treatment effect from randomised controlled trials shows that Bup and Met supress illicit and non-medical opioid use [4,5]. In treatment systems, follow-up studies of these medications have reported substantial average reductions in drug use [6] and opioid overdose mortality [7]. Systematic review evidence from maintenance trials of Bup and Met for illicit OUD [5] suggests that flexible dose Met is more effective than flexible dose Bup maintenance at retaining patients (six trials with 837 participants; relative risk [RR] 0.82, 95% confidence interval [CI] 0.69 to 0.96), but with no statistical difference for the suppression of heroin (mean difference -0.12 days, 95% CI -0.32 to 0.12). For OUD involving licit or illicit pharmaceutical products [6], there is no statistically significant difference between Bup and Met for retention (three studies, 360 participants, RR 0.69, 95% CI 0.39 to 1.22) or suppression of non-prescribed opioid use (mean difference -1.41 days, 95% CI -3.37 to 0.55). Observational follow-up studies suggest that retention in Bup and Met maintenance is associated with a reduction in the risk of fatal overdose [7,8], blood-borne viral infections [9] and crime [10].

There are three issues of concern about these two standard-of-care medications for OUD. Despite efforts to select the best medication and dose for each patient, many discontinue treatment [11]. Other patients are retained but either fail to take their prescription as directed [12] or continue to use illicit or non-prescribed pharmaceutical opioids (herein

'opioids') or relapse to pre-treatment levels. For example, in an English study of 12,745 patients enrolled for 12-26 weeks, 64% were using opioids on 10 or more of the past 28 days at clinical review [13]. Cocaine use disorder (particularly with the base form *crack*) [14], and co-occurring anxiety [15] and depressive disorders [16] are prevalent in the clinical OUD population and can moderate treatment adherence and response [17]. Family relationships and social networks can either support or hinder recovery [18].

Technological advances in the formulation of Bup have potential to address the lack of effectiveness for some patients. Using the polymer ATRIGEL® delivery system, Indivior has developed an extended-release formulation of Bup. Injected subcutaneously into abdominal tissue, this medication forms a depot and releases Bup for a minimum of 28 days by diffusion and as the polymer biodegrades. Development studies of RBP-6000 showed that a relatively high dose of Bup is stably released and this (in comparison with placebo Bup) is associated with attenuated craving for opioids and drug use. This medication (Sublocade® [XR-Bup] now approved by the Food and Drug Administration (FDA) and from March 2018 has been available to US prescribers. XR-Bup has the potential to enable patients to derive enhanced benefit from treatment – but there has been no head-to-head comparison to date with standard-of-care Bup and Met. This is a crucial comparison to inform clinical practice.

EXPO will be a superiority evaluation. In comparison to Bup and Met, the study will evaluate two potential patient benefits arising from treatment with XR-Bup: (1) delivery of stable and effective dose of Bup to facilitate opioid blockade (and attenuate reinforcing effects of non-medical opioids) while giving protection against opioid overdose; and (2) by avoiding the need to attend for daily dosing, the facilitation of the patient's recovery activities and independence. As dosing of XR-Bup is done in the clinic, there will be no risk of medication diversion.

Another potential avenue to enhance the medication-assisted treatment for OUD is the provision of adjunctive PSI. Unfortunately, a Cochrane review has concluded that no single PSI is effective [8]. OUD is a complex phenotype and an alternative approach is to use a clinical formulation to personalise (tailor) elements for a PSI that best meet the needs and preferences of the patient. A completed pragmatic randomised controlled trial by the EXPO coordinators successfully targeted Bup and Met-resistant patients with a tailored PSI, drawing on a toolkit of change methods indicated by a patient-collaborative, measurement-based care and clinical formulation model [9]. The PSI toolkit included: CBT for coping strategies, Contingency Management to reinforce recovery; facilitation to attend 12-step groups; cognitive behavioural therapy (CBT)/Behavioural Activation for depression; and techniques to engage partners and family members in the participant's treatment. In this context, the EXPO co-ordinating centre will determine whether a tailored PSI intervention will help the patient to attenuate illicit drug use and improve their personal and social functioning and thereby give an adjunctive beneficial effect to XR-Bup on outcome.

In summary, the EXPO study will determine the effectiveness of XR-Bup in a head-to-head superiority comparison with Bup and Met and with an adjunctive PSI (offered during the 24-week treatment phase) in the pragmatic context of specialist community setting addiction treatment programmes in England provided by the NHS.

The EXPO protocol will be published following the SPIRIT standard. The statistical analysis plans will be published on the Centre for Open Science. The results of EXPO will be reported in adherence with CONSORT and other relevant standards and extensions.

5. Trial Objectives and Design

5.1. Trial objectives and primary endpoint

During six months of active trial treatment, the primary objective of this superiority study is to determine the difference in effectiveness (in terms of reduced use of heroin and illicit opioids) of XR-Bup and Met or Bup. Study participation will be offered to patients already enrolled in Bup and Met maintenance treatment and also new admissions of patients seeking this treatment.

With a 1-week measurement grace period from randomisation, the primary endpoint is the count of days abstinent from heroin and illicit opioids during six months of treatment combined with urine drug screen samples which are negative for non-medical opioids.

5.2. Trial design, blinding overview

EXPO is a pragmatic, multi-centre, open-label, superiority randomised controlled trial in NHS specialist addiction clinics delivering standard-of-care oral opioid medication for adults with OUD. The study will be implemented in five clinically recruiting sites (NHS trusts) across England and Scotland: in the coordinating centre in South London, the West Midlands, Greater Manchester, Newcastle and Tayside. The target randomised sample size is 604 patients. Recruitment will be in two study phases, as follows:

In **Phase I** (all sites and with enrolment timed to start at approximately the same time), informed consenting participants will be allocated to one of two groups:

Group 1: XR-Bup (n=152; approx. n=38 at each site)
Group 2: Bup/Met (n=152; approx. n=38 at each site)

Participants in group 2 will receive Bup or Met following the local NHS clinical process of medical assessment and informed by any patient expressed preference for Bup or Met. All participants in groups 1 and 2 will receive standard case and medication management with general drug counselling (fortnightly, one-to-one at the clinic; ~30 minutes). The study plan is to aim to commence recruitment for groups 1 and 2 in July 2019 with all participants completing follow-ups in Q1 2020 (n=76 participants in each NHS trust)*.

During Phase 1 at the EXPO co-ordinating centre only, there will be allocation of participants to two additional groups:

Group 3: XR-Bup + PSI (South London site only)
Group 4: Bup/Met + PSI (South London site only)

All participants in groups 3 and 4 will receive standard case/medication management and general drug counselling, as usual. The PSI will be a tailored PSI (adapted from the co-ordinating centre's successful previous trial to development this therapy (ARC Trial; ISRCTN69313751) and offered to participants across the treatment phase. At the co-ordinating centre, recruitment to groups 1-4 will commence in July 2019 using a 4:1 allocation ratio in favour of groups 1 and 2 (given local resource capacity)*.

In **Phase II** (co-ordinating centre only) there will be continued recruitment of groups 3 and 4 following completion of Phase I using a 1:1 allocation ratio until target quarter 3 2021, at which point it is aimed that all participants will have completed this phase*.

Group 3: XR-Bup + PSI (Total from Phase I and Phase II 150 South London site only)
Group 4: Bup/Met + PSI (Total from Phase I and Phase II 150 South London site only)

The senior statistician will be blinded. The junior statistician is unblinded so that reports can be prepared. Research and clinical team will also be unblinded.

*Due to the Coronavirus 2019 (COVID-19) pandemic and slower than anticipated recruitment rate, recruitment into Phase I and Phase II will be completed at the same time; target quarter 4 2021.

5.3. Primary endpoint analysis overview

Analysis of EXPO primary outcome data will be done in two phases, as follows:

In phase I (planned data lock: quarter 3 2020), there will be a comparison of group 1 versus group 2. This comparison will include data from all 4 sites. In phase II (planned data lock: October 2021) there will be a comparison group 3 versus group 4 (data from the co-ordinating centre only).*

Following completion of the phase I and II analysis, there will be an exploratory analysis of group 1 and group 3 to compare XR-Bup and XR-Bup + PSI.

Further details of the statistical approach for these analyses is outlined in section 10 and will be specified in detail in the Statistical Analysis Plan ([SAP] to be summarised in the published protocol paper and on the Open Science Framework before data-lock).

*Due to the Coronavirus 2019 (COVID-19) pandemic and slower than anticipated recruitment rate, data lock for Phase I and Phase II will be completed at the same time; target quarter 3 2022.

6. Trial Medication

The drugs used in the trial are controlled drugs. Sites are expected to comply with the storage and supply requirements set out in the Misuse of Drugs Regulations 2001 (as amended) and the UK Controlled Drug Regulations, in addition to the trial requirements.

6.1 Investigational medicinal product

Bup extended-release injection (XR-Bup in this protocol) is licenced in the USA under the name Sublocade®. It is used for the treatment of moderate to severe OUD in patients who have initiated treatment with a transmucosal Buprenorphine product. The product is currently unlicensed in the EU. The injection is presented as a sterile, clear, viscous,

colourless to yellow amber solution in a single dose, pre-filled syringe with a 19 gauge 5/8th inch safety needle.

Bup in XR-Bup is dissolved in the ATRIGEL® delivery system. This system delivers the drug at a controlled rate over a 1-month period. The depot injection provides sustained plasma levels of Bup sufficient to block the subjective effects of exogenous opioids after a single dose and even more complete blockade after two monthly doses. The product is available in dosage strengths of 100mg/0.5ml and 300mg/1.5ml Bup. It is administered as a monthly subcutaneous injection into abdominal tissue.

Indivior will be responsible for the manufacture of the product and import into the UK. Sharp Clinical Services (UK) are contracted by Indivior to label and final Qualified Person (QP) release the product prior to distribution to investigational sites. The Simplified Investigational Medicinal Product Dossier (sIMPD), US Prescribing Information and Investigator Brochure (IB) provides further information.

6.2 Active comparators

The active comparator drugs sublingual Bup; (including sublingual Bup/Naloxone, oromucosal Bup) and oral Met will be dispensed by community pharmacies on receipt of a valid prescription, as per standard NHS practice. The drugs will be labelled with a normal dispensing label in accordance with Schedule 5 to The Medicines for Human Use (Marketing Authorisations etc) Regulations 1994. This activity is covered by Regulation 46 (2) of SI 2004/1031 of the Medicines for Human Use (Clinical Trials) Regulations (as amended).

Bup is licenced for the treatment of opioid use disorder. The tablets are available as 0.4mg, 2mg and 8mg strengths. The Summary of Product Characteristics (SmPC) for Subutex® provides further information.

Bup-NX (as hydrochloride) and naloxone (as hydrochloride dihydrate) sublingual tablets (Suboxone®) is licenced for the treatment of opioid use disorder. Suboxone® is manufactured by Indivior UK Limited. Buprenorphine is the active component of Bup/naloxone when taken sublingually. Naloxone is a deterrent to diversion and injection of the tablet and is prescribed in an identical fashion to Bup. Research sites are permitted to prescribe Bup-NX as a replacement to Bup if that is the local prescribing procedure. The tablets are available as 16mg/4mg, 8mg/2mg and 2mg/0.5mg strengths. The SmPC provides further information on this product.

Espranor® (Esp) oral lyophilisate containing (Buprenorphine as hydrochloride) and aspartame is licenced for the treatment of opioid use disorder. Buprenorphine is the active component of Esp and administration is oromucosal. Research sites are permitted to prescribe Esp as a replacement to Bup if that is the local prescribing procedure. Esp oral lyophilisate is available in 2mg/0.5mg and 8mg/2mg strengths. The SmPC provides further information on this product.

As Buprenorphine is the active component of Bup-NX and Esp they will be categorised under Bup within the protocol guidance and analysis between trial arms.

Methadone is available as a 1mg/ml solution and is licenced for the treatment of opioid use disorder. The SmPC provides further information on the product.

Participant is ineligible if they have any allergic or adverse reactions or contraindication to Buprenorphine. If participant has any allergic or adverse reaction or contraindication to Met or naloxone, or excipients of Bup-NX or Esp they can be prescribed Bup within the trial. Participants randomised to group 2 and group 4 are permitted to change between the active comparator drugs whilst enrolled in the trial by following the prescribing guidelines as detailed in the SmPC and if there are no known allergic, adverse reactions or contraindications to the drug.

6.3 Dosing regimen

Bup (active sublingual comparator): The usual dose is 8-24mg/day (Esp usual dose 8-18mg/day). Clinical practice in NHS clinics is supervised (directly observed dosing) in a community pharmacy followed by provision of patient self-administered 'take home' doses according to clinical response (i.e. informed by negative urine drug screens [UDS]; adherence to prescription; retention in treatment).

Met (active oral comparator): The recommended dose is 60-120mg/day. Clinical practice in NHS clinics is supervised (directly observed dosing) in a community pharmacy followed by provision of patient self-administered 'take home' doses according to clinical response (i.e. informed by negative UDS; adherence to prescription; retention in treatment).

In the event patients in the Met/Bup arm fail to adhere to daily dosage regime they will need to follow standard clinical protocol for that clinic.

XR-Bup (IMP active injectable comparator): The recommended dose of Sublocade® (which will be adhered to in the EXPO trial) is a 300mg loading dose, administered monthly for the first 2 months, followed by a 100mg maintenance dose for the remaining 4 months. The scheduled dosing interval is 28 days and, in EXPO, the minimum interval between the two initial loading doses is 21 days to provide increased flexibility for the participant to ensure that the loading doses are achieved. All injections will be by the site investigator, medical practitioner, nurse, or nurse practitioner who has received training in the procedure. XR-Bup is for abdominal injection into adipose tissue only (not intramuscularly). The specific area is on the abdomen between the transpyloric and trans-tubercular planes with adequate subcutaneous tissue below the waistline and above the hip bone, which is free from any lesion, mole or other skin mark.

After the two 300mg loading doses, the aim is to maintain the patient on a 100mg monthly dose if they achieve:

- no unsanctioned use of opioids
- no clinically significant opioid withdrawal
- no distressing craving for opioids and the patient is satisfied with their current dose, and requesting the dose be maintained at this level.

As a clinical guide, the maintenance dose should be increased from 100mg to 300mg under the following conditions:

- The patient is not achieving desired treatment goals (e.g. persistent unsanctioned opioid use, opioid withdrawal symptoms or distressing cravings);
- the patient does not report dose-related adverse events related to the 100mg dose (e.g. sedation or lethargy, persistent headaches, nausea);
- the patient reports that 100mg is too low and they would like a dose increase, and there are no significant clinical safety concerns.

As a clinical guide, the dose should be reduced from 300 to 100mg under the following conditions:

- The patient reports XR-Bup dose-related adverse events (e.g. sedation or lethargy, persistent headaches, nausea);
- the patient is seeking to reduce their dose in an attempt to ultimately withdraw from opioid agonist treatment;
- the patient reports that 300mg is 'too high' and they would like a dose decrease, and there are no significant concerns regarding deterioration in clinical condition (e.g. substance use, physical or mental health symptoms) that may arise with a dose reduction.)

On the basis of patient report and clinical judgement of the risks and benefits, rescue dosing of Bup can be provided at any point after the first dose of XR-Bup. This will be recorded as concomitant medication.

Whilst maintenance doses will be routinely scheduled to occur every 28 days, flexibility was included in the development research for Sublocade® and this will be followed in the EXPO trial to accommodate patients who need to attend other appointments or have travel problems attending the clinic.
In summary, the protocol allows for:

(1) the second 300mg loading dose of XR-Bup to be given after a minimum of 21 days;
(2) each planned 100mg maintenance doses can be administered up to 2 days ahead of the scheduled dose (i.e. 26 days since the last injection); and
(3) all subsequent doses after the first dose to be given up to 14 days after the 28-day scheduled dose (i.e. to 42 days).

Unexpected delays of up to 14 days are not anticipated to have any clinical impact on treatment response given the reported extended-release profile of the IMP.

Following the 6th dose, there is an optional consent for participants who are randomised to XR-Bup to continue receiving doses every 28 days until the date that the last participant is randomised within the EXPO Trial plus 9 months.

In summary, the dosing schedule for EXPO is shown below:

Dose	Day	Visit	Window	XR-BUP dose
1	1	Baseline	-	300mg
2	28	Week 4	21-42	300mg
3	56	Week 8	54-70	100mg or 300mg
4	84	Week 12	82-98	100mg or 300mg
5	112	Week 16	110-126	100mg or 300mg
6	140	Week 20	138-168	100mg or 300mg
7 onwards	168 onwards	Week 24 onwards (every 28 days)	Up to 42 days since previous dose	100mg or 300mg

If the participant misses a scheduled maintenance of XR-Bup no adjustment in dose is required, if they receive this dose within 60 days of their last injection. If the participant does not receive an XR-Bup dose within 60 days of their last injection, the participant is not withdrawn from study treatment; but a clinical assessment by the principal investigator (PI) is needed to determine if there has been any illicit opioid use and the optimal starting dose.

6.4 IMP administration

XR-Bup will be administered by subcutaneous injection into abdominal adipose tissue by the site investigator, medical practitioner, nurse, or nurse practitioner who have received training in the procedure and are delegated to perform this task. The drug will be prescribed for administration following local hospital requirements.

The specific area for administration is below the waist line and above the hip bone (specifically, in the region where the body curves at the side to about 2 inches from the middle of the abdomen i.e. between the transpyloric and trans tubercular planes), selecting a clear needle insertion point with adequate amounts of subcutaneous tissue that does not have excessive pigment, nodules, lesions, or hair or areas with brawny or fibrous subcutaneous tissue or locations that could be rubbed or compressed (i.e. with a belt or clothing waistband).

To avoid irritation, the injection site will be recorded and rotated across four different injection points for subsequent doses (with the patient's head pointing north), these will be, from the patient's perspective:

(1) right upper (RU); (2) left upper (LU); (3) left lower (LL) and (4) right lower (RL).

A cold press can be administered for up to 10 seconds prior to the injection.

6.5 IMP risks

The Reference Safety Information (RSI) for all information pertaining to IMP risk for the XR-Bup will be set out in the manufacturer's Investigators Brochure (IB). The SmPC will be the reference document for Bup/Met.

Adverse reactions (commonly associated in 5% or more of patients) receiving XR-Bup are: (a) constipation; (b) nausea; (c) vomiting; (d) headache; (e) fatigue; (f) increased hepatic enzymes; (g) injection site pain; (h) injection site pruritis.

Drug-drug interactions potentially relevant to the IMP (with Bup and XR-Bup) are as follows:

Drug Class	**Drug(s) within Class**	**Clinical effect and suggested management**
Benzodiazepines and Other Central Nervous System (CNS) Depressants	Alcohol, non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anaesthetics, antipsychotics, and other opioids	- Increases the risk of respiratory depression, profound sedation, coma, and death. - Use of these substances should be stabilised during treatment with Bup products. Patients should be advised of the danger of concomitant use of sedatives while participating in the trial.
CYP3A4 inhibitors:	Macrolide antibiotics (e.g. erythromycin) Azole-antifungal agents (e.g. ketoconazole) Protease inhibitors (e.g. ritonavir)	- Effects of CYP3A4 inhibitors on Bup exposure in participants treated with XR-Bup have not been studied with Bup, however, such interactions have been established. - In the presence of CYP3A4 inhibitors, monitor for signs and symptoms of Bup toxicity or overdose. - Monitor for Bup withdrawal if the concomitant medication is discontinued after the patient is stable on. - The dose of either Bup or the CYP3A4 inhibitor may need to be adjusted accordingly.
CYP3A4 Inducers	Rifampin Carbamazepine Phenytoin	- Effects of CYP3A4 inducers on Bup exposure in participants treated with XR-Bup have not been studied, however, CYP3A4 inducers may induce its metabolism and lead to decrease in Bup plasma concentrations. - Monitor for signs and symptoms of Bup toxicity or overdose, if the CYP3A4 inducers is discontinued after the patient is stable on XR-Bup. The dose of either Bup or the CYP3A4 inducer may need to be adjusted accordingly.
Antiretrovirals: Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Efavirenz, nevirapine, etravirine, delavirdine	- Significant pharmacokinetic interactions between NNRTIs and Bup have been shown, but these pharmacokinetic interactions did not result in any significant pharmacodynamic effects. - Monitor for increase or decrease in therapeutic effects of NNRTIs.

Antiretrovirals: Protease inhibitors (PIs)	Atazanavir, ritonavir	- Treatment with atazanavir or atazanavir/ritonavir may result in elevated levels of Bup (and the metabolite nor-Bup). - If atazanavir +/- ritonavir is initiated once the patient is stable on XR-Bup, monitor for signs and symptoms of over-medication with Bup. If necessary, reduce XR-Bup dose from 300 to 100mg, or discontinue XR-Bup and treat with Bup to enable rapid dose adjustments.
Selective serotonin reuptake inhibitors (SSRIs) Serotonin and norepinephrine reuptake inhibitors (SNRIs) Tricyclic antidepressants (TCAs) Triptans 5-HT3 receptor antagonists Drugs that affect the serotonin neurotransmitter system inhibitors Monoamine oxidase (MAO)	e.g. mirtazapine, trazodone, tramadol e.g. linezolid and intravenous methylene blue	- May result in serotonin syndrome in high doses (e.g. overdose). Monitor for signs and symptoms of serotonin syndrome, particularly during treatment initiation, and during dose adjustment of the serotonergic drug.
Monoamine Oxidase Inhibitors (MAOIs)	e.g. Phenelzine, tranylcypromine, linezolid	- MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma). - It is recommended that patients receiving Bup and MAOI should be closely monitored.
Diuretics		- May reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. - Intervention: Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.
Anticholinergic Drugs		- May increase the risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. - Monitor for signs of urinary retention or reduced gastric motility.
Opioid antagonists	Naltrexone, naloxone	- Opioid antagonists should generally not be used outside of emergency situations in patients in opioid agonist treatment, including XR-Bup. - Naloxone may be administered in response to an opioid overdose.

Opioid analgesics	Opioids	- Bup may reduce the effects of opioid analgesics trough receptor blockade. Patients requiring analgesia should include non-opioid approaches (e.g. NSAIDs, ketamine). Opioids may be used with caution, but as higher doses may be required for analgesic effect, there may be a higher potential for toxicity with opioid administration, requiring close monitoring of opioid effects.

6.6 Treatment discontinuation

A participant is discontinued from the study medications for any of the following reasons:

- Participant safety reasons, including adverse events (AEs) or significant concomitant illness, injury, or urgent surgeries/procedures that would, in the opinion of the Investigator, compromise treatment safety or deterioration in the patient's clinical condition.
- Participant request to discontinue study intervention. A participant is free to withdraw to withdraw from study intervention at any time for any reason (they do not need to state a reason). Their participation is to be terminated upon his/her request, and the reason(s) for discontinuation appropriately documented.
- At the request of the Sponsor, regulatory agency, or Ethics Committee.
- Pregnancy. If not terminating, participant to discuss with clinician and continue with oral medication or withdraw following usual practice. Participants receiving IMP will not receive further injections and will receive oral medication or withdrawal according to usual practice.
- Administrative discharge due to non-adherence with site policies (e.g. violence towards other clients or staff).

In the event of an emergency, or if clinically indicated, a decision to surgically remove depot (up to 14 days from injection) may be made by the CI or PI, following discussion with the participant. An appropriately skilled medical practitioner may perform the surgical procedure, as follows:

1. Palpate the depot and surrounding area to confirm location.
2. Cleanse the area with an antiseptic solution.
3. Infiltration the area with local anaesthesia and wait for it to take effect.
4. Cover the area with sterile drape.
5. Incise the skin up to the subcutaneous tissues using a scalpel.
6. Using blunt and sharp dissection, identify the plane between the depot and surrounding subcutaneous tissues. Once the plane is identified, separate the superficial 25% of the circumference of the depot with blunt dissection.
7. Gently lift the incised ellipse of skin and depot with forceps.
8. Once the depot is removed, ensure haemostasis, and close the skin with non-absorbable sutures.

Removal of the depot is to be recorded as an Important Medical Event (IME).

6.7 Drug accountability

6.7.1 XR-Bup

XR-Bup will be distributed to each site following the final QP release, and once all regulatory and local approvals are in place.

The pharmacy clinical trials team must maintain accurate accountability records for XR-Bup, including, but not limited to, the number of kits received, the number of kits dispensed to which patient, batch number, expiry date, and the date of the transaction, in addition to the quantity of unused investigational product and empty packaging returned to pharmacy for each patient. Trial specific prescriptions must be filed in the pharmacy trial file for audit purposes.

Sites must use a transfer log to record the transfer of:

- Dispensed XR-Bup from pharmacy to clinics
- Return of unused syringes and empty packaging from clinics back to pharmacy

The research team (clinic staff) must maintain accurate accountability records for XR-Bup, including, but not limited to, the number of kits received and administered for each individual patient and the date of the transaction, in addition to the number of unused kits returned to pharmacy. Administration records in clinics will be retained and monitored by the KHP-CTO during monitoring visits to ensure appropriate handling and storage of the IMP.

Unused XR-Bup and empty packaging (post dose) must be returned to pharmacy by the research team for reconciliation on the accountability log. The returns will be verified by the CRA prior to disposal at site. Destruction of XR-Bup must follow the site IMP destruction SOP and local hospital Controlled Drugs waste management procedure. After the KHP-CTO monitoring of IMP accountability is complete, destruction will occur following CI authorisation.

The King's Clinical Trials Unit (KCTU) clinical trials Pharmacist will track XR-Bup trial supplies at investigational sites and at Sharp Clinical Services, UK. The pharmacist will generate orders of IMP for delivery to sites and liaise with Indivior for the shipment of additional stock from the USA.

6.7.2 Met and Bup

Site staff will make a copy of the script record for the FP10 written for the trial and file in the relevant patients notes. Accountability records are not required for the active comparator arm (oral Met or Bup). Research teams will check medication compliance at clinic visits through questioning and clinical assessments. Adherence to oral medication – dispensed by community retail pharmacies – will be monitored as usual in the NHS by the retail pharmacy and the local clinic, such that if the patient does not attend to receive or collect three consecutive scheduled Met or Bup doses, this will trigger the pharmacy to inform the clinic. This event will be recorded in the patient's notes and should the patient present/contact the clinic requiring further Met or Bup, dosing will be re-started following the clinic's medication screening and induction protocol.

6.8 Supply, transport and storage of IMP

The Investigational Product Handling Manual gives detailed guidance on supply, transport and storage of IMP.

6.8.1 XR-Bup (Sublocade®)

XR-Bup must be stored in a locked fridge, maintaining a temperature between 2°C to 8°C. Appropriate storage conditions (for pharmacy and clinic fridges) must be ensured by completion of temperature monitoring logs.

Commercial USA licenced stock (Sublocade®) will be manufactured under contract to Indivior by Albany Molecular Research Inc. (AMRI), Burlington, MA. The stock will be imported into the UK. Labelling with an annex 13 compliant label, final QP release and distribution to UK sites has been contracted to Sharp Clinical Services, UK.

XR-Bup will be dispensed by the site pharmacy against a valid, sponsor approved clinical trial prescription. The dispensed XR-Bup will be transported to clinic, for the purpose of administration, using an appropriate transit method to maintain the cold-chain. The IMP transfer must be recorded on approved documentation to provide a full audit trail. Refer to section 6.6 of the protocol and the Investigational Product Handling Manual for further information.

On arrival at clinic, the dispensed XR-Bup will be checked and documented as received before being placed in a locked, temperature controlled and monitored pharmaceutical refrigerator.

Unused XR-Bup syringes and empty packaging will be returned to pharmacy for reconciliation prior to verification by the CRA. The sponsor must provide written permission for disposal prior to the product and empty packaging being destroyed at site. Participant compliance will be measured through medication dispensing records, attendance records and administration records.

After each participant’s last visit, patients will transition to Met/Bup as appropriate according to local practice.

6.8.2 Active Comparators (Bup/Met)

Bup (including Bup-NX and Esp) and Met will be stored at community pharmacies in accordance with their SmPC’s. Temperature monitoring records are not required for these products.

6.9 Concomitant Medication

Each participant's use of concomitant medications will be recorded continuously but reviewed at week 4, 12 and 24. The Investigator will record all medication used by the participant. This record will include the name of the medication, the dose, dates when drug was started and stopped.

7. Tailored Psychosocial Intervention

Convergent lines of epidemiologic and clinical research point to several behavioural factors which moderate Met/Bup effectiveness [10]. Addiction severity is moderator [11,12,13], and taking illicit drugs by injection correlates with higher levels of dependence and a likelihood of non-response [14]. Concurrent cocaine use and dependence is also common among the OUD population in the UK, and these patients tend to have poorer engagement with the clinic and outcome [15,16,17]. A significant minority of patients have co-existing chronic health and social problems which follow, precede, or are independent of the addictive disorder, and add complexity to clinical management [18,19,20]. The patient's family relationships and social networks may also support or hinder response [21]. These factors are screened early in treatment.

EXPO's tailored psychosocial intervention (PSI) is founded on the evidence that there are different reasons for non-response and that there will be no single best clinical intervention. The goal is to help the patient reduce the symptoms of heroin and cocaine addiction, to manage or attenuate concurrent health and social problems, to enhance engagement and to develop personal strengths and resources for recovery. The PSI has been successfully evaluated in a completed randomised controlled trial at the EXPO coordinating centre (ISRCTN number: 69313751) and further developed in a novel memory-focused cognitive therapy intervention (ISRCTN number: 164627831). We found the PSI to be well accepted and in the study. There was a relatively low level of loss to follow-up and all participants who withdrew from the study gave their consent for their data to be used in the analysis. There were no severe adverse events judged to be trial-related.

The PSI is guided by a cognitive case conceptualisation assessment to develop collaboratively a working hypothesis of how OUD is being maintained. A micro-formulation will be based on recent typical (and unusual) episodes of cocaine use and will include contexts, triggers, physical sensations, elaborated cognition (attention, memories, beliefs, appraisals [emotional 'hotspots']), motivation, coping strategies, actions, problematic affective and behavioural responses, post-opioid (and other drug use) evaluations and problems.

The EXPO PSI will be collaborative and flexible: trial psychologists will use a non-judgemental, collaborative counselling style (adapted from Motivational Interviewing [22]) and graphical representations and maps (adapted from node-link mapping to facilitate assessment, care planning, and progress review [23]. The PSI represents a point of departure from a traditional manual-guided psychological therapy in which there may be proscription of a sequence of specific techniques, or multi-modal therapies which combine two or more therapies. We will use a 'toolkit' approach with specific change methods from evidence-supported therapies are chosen collaboratively with the patient and tested for effectiveness in the form of a rolling set of behavioural experiments.
During development, national clinical guidelines [24] and the therapist manuals for the following psychological therapies:

- cognitive behavioural coping and skills training (CBT [25]);
- behavioural reinforcement ('contingency management' using a budget of £60 in value shop vouchers with clinic attendance and recovery activities in addition to the traditional drug abstinence operant reinforcer [26];

- behavioural psychotherapy for couples to promote relationship stability and abstinence reinforcement [27],
- Social Behaviour and Network Therapy to recruit family members and others to accompany the patient to PSI sessions and support their recovery [28,29];
- 12-Step Facilitation Therapy for self-help group attendance [30,31]; and
- CBT methods for depression to help raise awareness of automatic thoughts, depressive evaluations and increase activity [32].

Each PSI intervention will include two or more of these specific change techniques, with supporting participant informational and self-monitoring materials. The PSI intervention sessions will aim to take place on a weekly basis dependent on the participant and therapists availability for the duration of the trial. If the participant withdraws from the treatment, they will not be withdrawn from the PSI therapy sessions unless they wish to withdraw from therapy also. A random 5% sample of session recordings per therapist will be independently rated using the University College London scale for rating core and generic (psychological) therapeutic skills [33].

8. Selection and Withdrawal of Participants

A medically qualified chief, principal or sub-investigator will evaluate the following inclusion and exclusion criteria:

8.1 Inclusion criteria

Inclusion criteria

1. Aged ≥ 18 years (no upper age limit);
2. Current diagnosis of DSM-5 OUD via SCID-5-RV (moderate-severe at baseline for current episode);
3. Currently enrolled on Met (30mg/day or less) or sublingual Bup or Bup-NX (24mg/day or less) or Esp (18mg/day or less) and in the view of the clinician would be able to convert to XR-Bup within 7 days post randomisation;
4. Voluntarily seeking treatment and able to attend the clinic as required in the protocol;
5. Able to communicate in English to level required to accept standard care and psychosocial intervention;
6. Possession of a contactable personal mobile phone or landline telephone number and ability to nominate at least one locator individual with a verifiable address and a telephone number to assist with the arrangement of follow-up appointments;
7. Living circumstances judged to be of sufficient stability to be able to engage/adhere to the study protocol;
8. Is not pregnant (confirmed) or breast feeding and, if currently or intending to have potentially procreative intercourse, agrees to use a birth control method (either oral hormonal contraceptives, barrier [condom or diaphragm], or Nexplanon implant) for the duration of the study.

8.2 Exclusion criteria

1. Clinically significant medical condition or observed abnormalities on physical examination or laboratory investigation, including but not limited to:
(a) uncontrolled hypertension, significant heart disease (including angina and myocardial infarction in past 12 months), or any cardiovascular abnormality which is judged to be clinically significant;
(b) severe alcohol dependence/withdrawal syndrome which is judged to be clinically significant and may constitute a risk to the patient's safety;
(c) acute hepatitis taken as clinical jaundice on examination, or evidence of blood bilirubin level above the normal range for local reference criteria, or evidence of serum levels of aspartate aminotransferase, alanine aminotransferase levels that are more than three-times the upper limit of the normal range;
2. History of allergic or adverse reactions to Bup or the proprietary ATRIGEL delivery system for XR-Bup (Sublocade®)*;
3. Clinically significant or uncontrolled mental health problems (including but not limited to psychosis, bipolar disorder, schizoaffective disorder), or history or evidence of organic brain disease or dementia that may compromise safety or compliance with the study protocol;
4. Current (past 30 day) suicide plan or suicide attempt in past six months;
5. Current criminal justice involvement with legal proceedings, which in the opinion of a medically qualified investigator indicates a risk that the patient would fail to complete the study protocol due to re-incarceration or move away from the centre's catchment area.
6. Currently taking oral or depot naltrexone therapy or enrolment in any form of naltrexone therapy within 90 days prior to study screening;
7. Any contraindication to Bup*.

**Participant is ineligible if they have any allergic or adverse reactions or contraindication to Buprenorphine. If participant has any allergic or adverse reaction or contraindication to Met or naloxone, or excipients of Bup-NX or Esp they can be prescribed Bup within the trial.*

8.3 Selection of participants

All participants for EXPO will be recruited from specialist NHS addictions treatment programmes in community settings and already in receipt of opioid substitution therapy. Patients will consent prior to any screening procedures and will be randomised at a minimum of 24 hours post consent.

Post- randomisation treatment is summarised as follows:

Participants randomised to standard-of-care oral maintenance

Participants who are allocated to oral opioid pharmacotherapy will receive Bup/Met according to medical screening and informed by patient preference, following each site's usual screening, induction/stabilisation and maintenance dosing and medication dispensing procedure. There will be an additional requirement to attend the clinic after 2 weeks and then at least monthly to complete research measures and a urine drug screen procedure.

Met participants randomised to XR- Bup

Met participants will firstly be converted to Bup by following the sites local clinical procedure. Once stabilised on Bup, participants will require a period of at least 3 days on 8mg-24mg of Bup before they can receive the first dose of XR- Bup. The last dose of Bup is to be taken 1 day prior to the first dose of XR- Bup. Participants should receive their first injection of XR-Bup within 7 days of randomisation.

Bup participants randomised to XR- Bup

If the participant is prescribed less than 8mg of Bup there will be a minimum 3-day lead-in on 8mg Bup prior the first dose of XR-Bup. Participants who were previously prescribed 8mg or higher BUP can receive XR-Bup upon agreement of a suitable time with the participant and EXPO research team. The last dose of Bup is to be taken 1 day prior to the first dose of XR- Bup. Participants should receive their first injection of XR-Bup within 7 days of randomisation.

For all participants if during the transition period, the participant decides not to receive XR-Bup or clinical judgement deems it unsuitable to continue the participant will be withdrawn from the trial (ITT population).

8.4 Randomisation Procedure

The King's Clinical Trials Unit will oversee randomisation. This will be a secure password-protected, web-accessed system. The system will generate an email message on allocation.

Participants will be stratified by the following factors:

(a) Site (trust and city)
(b) Current (last 28 days) drug injecting status (yes/no)

Justification for these stratification factors is as follows: (a) site is required for the random-effects model; (b) it is expected that there will be relatively poorer outcome among participants who are drug injectors. The randomisation procedure will use stratified random blocks of varying size to ensure even allocation.

Only study site staff authorised by the trial manager will be given login details to the randomisation system. Authorised staff will be allocated a username and password for the randomization system. Prior to randomisation the site needs to ensure there is capacity for the XR-Bup or Bup/Met for each patient.

Once a patient has consented and it is confirmed that all potential medication is in place within the next 7 days, all baseline data collected and eligibility confirmed, the staff member will log into the randomization system (www.ctu.co.uk). The "help" section of the system has video demonstrations to aid new staff in using the system. Once randomized, the system automatically generates confirmation emails to key staff, with or without treatment allocation information, depending on their role in the study. EXPO is an open-label (unblinded) trial, so there is no emergency code break.

8.5 Withdrawal of participants

Participants have the right to withdraw from the study at any time for any reason. The investigator also has the right to withdraw patients from the study drug in the event of AE, SAE, SUSAR, or other reasons. Upon withdrawal from the study the patient will be asked to research measures (with a minimum to enable capture of the primary outcome measure [i.e. TLFB and UDS] and also craving measures). It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided. Participants who wish to withdraw from EXPO will be asked to confirm whether they are still willing to provide data. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible.

The Investigator will maintain a record of all patients who discontinue from the trial prior to completion; the reason(s) for trial discontinuation will be documented. If a patient chooses to withdraw from the trial, the Investigator should make a reasonable attempt to obtain and record the reason(s) for withdrawal, if possible, although the patient is not obligated to provide such a reason.

8.6 End of Trial Definition

The end of the trial will be deemed to occur after database lock (following completion of monitoring of the last patient last visit undergoing the EXPO trial).

9. Trial Procedures

9.1 By visit

The following standardised instruments will be administered during the study:

Urine drug screen (UDS; detection sensitivity: opiates: 2000ng/ml; cocaine and benzodiazepines: 300 ng/ml; window of detection: 72 hours; UDS procedure conducted each visit). A tamper-proof, instant result, immunoassay device (e.g. E-Z Split Key Cup; www.concateno.com) will screen for recent use of opioids, cocaine and benzodiazepines. The device uses a control line and a temperature sensor (required range: 92°-96 °F) to indicate that a valid test has been done. The UDS product for the study also includes measurement of Bup and Met (providing a proxy indicator of medication adherence) and also (meth)amphetamine and cannabis (for description and exploratory analysis).

*** Structured clinical interview for DSM-5 disorders – research version** (SCID-5-RV [34]). The SCID-5-RV contains a checklist of 11 symptoms (presence or absence) to diagnose the severity of current OUD (mild: 2–3 symptoms; moderate: 4–5; severe: ≥6). The American Psychiatric Association's definition for early OUD remission will be applied at 3-month follow-up (i.e. without substance use disorder criteria [except] craving, using the “on maintenance therapy” specifier as appropriate).

Alcohol - Quantity, Frequency and Maximum Consumption (ALC-QFM) This information will be recorded using an adapted version of the **Treatment Outcomes Profile** (TOP [54]). The TOP is the standard national instrument for monitoring the outcomes of public substance use disorder treatment services in England.

Time-Line Follow-Back (TLFB) interview for heroin, cocaine and benzodiazepine recorded for each day whether the participant reports using or not using these drugs. The TLFB, calendar-prompt interview will be adapted from the TOP.

Montreal Cognitive Assessment (MoCA; [35]. The MoCA is a brief screening instrument for mild cognitive impairment and assesses attention, concentration, working memory, visuo-constructional skills, and conceptual thinking. A score of ≥26 is considered to reflect normal range functioning. An alternate version of the MoCA will be used at follow-up to decrease the risk of learning effects. The MoCa will be completed on 2 visits: baseline (version 7.1) and study week 12 (version 7.2).

***Addiction Dimensions for Assessment and Personalised Treatment** (ADAPT [53]). The ADAPT is a clinician completed 14-item instrument used for drug addiction treatment planning and outcome evaluation with three-subscales: opioid addiction severity, coexisting health and social problems, and recovery strengths.

***Clinical Global Impression** (CGI-S and I; [36]). The CGI is a single item clinician assessment of disorder severity and improvement.

Craving Experience Questionnaire (CEQ-F [frequency] [56]). The CEQ-F will be completed for opioids (CEQ-F[H] and cocaine (CEQ-F[C]). This scale has a 14-day recall period and captures intensity, imagery, and intrusiveness aspects of drug craving.

Visual analogue scale of maximum need (VAS-N[H/C] and want (VAS-W[H/C]). These single item (0-100) rating scales have a recall period of the past 14 days.

Difficulties in Emotion Regulation Scale – Short Form (DERS-SF; [37]). The DERS The DERS is an 18 item self-report scale which records current emotional dysregulation in six subscales: non-acceptance, goals, impulse, aware, strategies and clarity.

QIDS-SR ([39]) The QIDS-SR is a brief scale which assesses the frequency of depressive symptoms during in past two weeks.

Work and Social Adjustment Scale (WSAS; [38]). The WSAS is a 5-item scale which records the extent of social functioning impairment perceived to be caused by OUD in the past two weeks.

Service User Recovery Evaluation (SURE; [6]). The SURE is a patient-reported outcome measure and is a multi-dimensional measure of perceived recovery status.

Patient reported outcome measure - Status (PRO-S and I). The PRO-S is a single 7-point item assessment of the extent to which the participant perceives the severity of their opioid-related problems at baseline and at follow-up.

EQ-5D-5L ([39])The EQ-5D-5L is a brief generic scale which captures health status on five dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and with a 20cm vertical visual analogue scale. These responses generate health profiles from which health utilities can be
calculated for economic evaluations.

Alcohol and Drug Service Use Schedule (ADSUS). The ADSUS is a well-developed structured patient interview that records use of health, social, welfare and criminal justice services and crime. The ADSUS was successfully used in the ARC trial.

Keyworker Contact Form (KCF). The KCF records the clinical team's direct and indirect time working on EXPO.

The Opioid Substitution Treatment Quality of Life scale (OSTQOL; [40]). The OSTQOL is a 38-item instrument assessing quality of life specific to patients in opioid substitution therapy across 6 subscales; personal development, mental distress, social contacts, material well-being, opioid substitution treatment, and discrimination.

Patient Health Questionnaire- 15 (PHQ-15; [41]). The PHQ-15 is a self-administered somatic symptoms subscale which screens for 15 somatic symptoms that account for more than 90% of the physical complaints reported in the outpatient setting (exclusive of self-limited upper respiratory symptoms).

Patient Health Questionnaire- 4 (PHQ-4; [42]). The PHQ- 4 is a 4-item inventory, rated on a 4-point Likert-type scale. Its purpose is to allow for very brief and accurate measurement of depression and anxiety.

*** The CI/ PI is able to delegate the administration of these instruments to a suitably trained health care professional at all visits subsequent to the baseline/screening assessment.**

9.1.2 Optional Consents

Week 24 onwards. Participants randomised to XR-Bup can continue to receive monthly injections as detailed in section 6.3 until the date the last participant is randomised plus 9 months. The Trial Manager will inform study sites when this date is approaching. At week 24 complete all research measures as detailed in the week 24 summary. Prior to the 7th injection at week 24 the continuing XR-Bup consent form is to be completed and pregnancy test recorded as negative. Following week 24, LFT to be taken approximately every 6 months or as clinically indicated. Conmeds and Adverse Events to be recorded at each visit that XR-Bup is administered.

Exit Interview. To be conducted at the South London, Newcastle, West Midlands and Tayside sites with XR-Bup participants only. An additional consent will be taken from the participant to undertake a semi structured, topic guided interview detailing their drug use and experiences whilst being on the trial (based on the ADAPT). This interview can take place at the same time as the week 24 visit or scheduled for a time convenient to the participant and interviewer. Participants will be reimbursed an additional £20 for their time in taking part in the interview. Researchers are to follow the EXPO Exit Interview Schedule as a topic guide, but the interview is designed to be semi structured. Where possible, have the participant to do a face-to-face interview when they are coming in for their injection (week 28 etc) if they are continuing onto the extension phase or at a time convenient to them at a time after their week 24 visit. If a face-to-face interview is not possible interviews can be recorded over the telephone; with the call on speaker and recorded using the audio recorder. When starting the interview, the participant should be reminded that the interview will be recorded, the length of time it may last, arrangements for payment and that they can withdraw from the interview at any time. Audio recordings should be recorded on trust approved audio recorders, the interviewer who conducted the interview is responsible for transcribing the interviews verbatim, naming the document with the participant number for the trial. Original audio file recordings are to remain at the site, securely stored electronically as per local policy unless a Data Share Agreement is in place with the study sponsor. Transcripts with no personal identifiable information of the recordings will be sent to the study sponsor periodically upon request.

Bup/Met +PSI Interview. To be conducted at the South London site only with approx. 30 participants who are randomised to the Bup/Met +PSI arm. An additional consent will be taken from the participant to undertake a semi structured, topic guided interview detailing their drug use and experiences whilst being on the trial (based on the ADAPT). This interview can take place at the same time as the week 24 visit or scheduled for a time convenient to the participant and interviewer. Participants will be reimbursed an additional £20 for their time in taking part in the interview. Researchers are to follow the EXPO PSI Interview Schedule as a topic guide, but the interview is designed to be semi structured. If a face-to-face interview is not possible, interviews can be recorded over the telephone; with the call on speaker and recorded using the audio recorder. When starting the interview, the participant should be reminded that the interview will be recorded, the length of time it may last, arrangements for payment and that they can withdraw from the interview at any time. Audio recordings should be recorded on trust approved audio recorders, the interviewer who conducted the interview is responsible for transcribing the interviews verbatim, naming the document with the participant number for the trial. Original audio file recordings are to remain at the site, securely stored electronically as per local

policy unless a Data Share Agreement is in place with the study sponsor. Transcripts with no personal identifiable information of the recordings will be sent to the study sponsor periodically upon request.

Extension Phase Interview. To be conducted at the South London and Newcastle sites with approx. 60 XR-Bup participants who consented to continue treatment after week 24 between 12-24 months of them being randomised in the trial. An additional consent will be taken from the participant to undertake a semi structured; topic guided interview (based on the OSTQOL) and additional assessment measures as outlined in section 9.2 of this protocol. If a UDS is not provided at the time of the interview, the most recent UDS taken within routine clinical care, up to 90 days prior to the interview date, can be recorded for trial purposes (consent permitting).

This interview can take place at a time convenient to the participant and interviewer. Participants will be reimbursed an additional £20 for their time in taking part in the interview. For the semi structured, topic guided section of the interview, researchers are to follow the EXPO Extension Phase Interview Schedule as a topic guide, but the interview is designed to be semi structured. If a face-to-face interview is not possible interviews can be recorded over the telephone; with the call on speaker and recorded using the audio recorder. When starting the interview, the participant should be reminded that the interview will be recorded, the length of time it may last, arrangements for payment and that they can withdraw from the interview at any time. Audio recordings should be recorded on trust approved audio recorders, the interviewer who conducted the interview is responsible for transcribing the interviews verbatim, naming the document with the participant number for the trial. Original audio file recordings are to remain at the site, securely stored electronically as per local policy unless a Data Share Agreement is in place with the study sponsor. Transcripts with no personal identifiable information of the recordings will be sent to the study sponsor periodically upon request.

9.2 Assessments by Study Week and Study Timeline

Measure	Baseline	Randomisation	Ongoing	Week 1	Week 2~	Week 4	Week 6~	Week 8	Week 10~	Week 12	Week 14~	Week 16	Week 18~	Week 20	Week 22~	Week 24	Withdrawal	Week 24 onwards	Ext. Phase Interview +++
Consent §	X																	X	X
Screening	X																		
UDS					X	X	X	X	X	X	X	X	X	X	X	X	X		X
LFT *	X					X				X						X		X	
XR-Bup**				X		X		X		X		X		X				X	
Bup/Met **			X																
ALC-QFM (TOP)***	X															X			
SCID-5-RV	X									X						X			X
ADAPT	X					X				X						X			
CGI-S	X																		
CGI-I						X				X						X			
CEQ-F – H***	X					X		X		X		X		X		X	X		
CEQ-F – C***	X					X		X		X		X		X		X	X		
VAS-N (H/C)***	X					X		X		X		X		X		X	X		
VAS-W (H/C)***	X					X		X		X		X		X		X	X		
DERS-SF	X					X				X						X			X
WSAS	X					X				X						X			
EQ-5D-5L	X									X						X			
AD-SUS	X									X						X			
KCF***						X				X						X			
QIDS-SR	X					X				X						X			
SURE						X				X						X			
PRO-S	X																		
PRO-I						X				X						X			
MoCA***	X									X									
OSTQOL																			X
PHQ-4																			X
PHQ-15																			X
Exit Interview+																X			
Bup/Met + PSI Interview++																X			
TLFB	X		X																X
Con Meds****			X			X				X						X		X	
Adverse Events Log			X															X	
Research Payments *****	X 20			X 10	X 10	X 10	X 5	X 10	X 10	X 10	X 5	X 10	X 10	X 10	X 5	X 10			X 20

§ screening to include pregnancy test, demographics and medical history. Participants receiving XR- Bup reconsented once at week 24 to continue receiving monthly injections;
* LFT for all participants at screening; during treatment for XR-Bup participants only under protocol;
** refer to section 6 of the protocol for guidelines;
*** used for mediation model;
**** ConMeds to be recorded continuously and reviewed at week 4, 12 and 24;
***** research payments are time offset to attend the clinic to complete research measures and cover travel (either a £20, £10, or £5 value, as detailed per visit applicable; loaded onto a prepaid card).

+ Exit Interview conducted at South London, Newcastle, West Midlands and Tayside sites with XR-Bup participants only. Participants will be reimbursed an additional £20 for their time in taking part in the interview (loaded onto a prepaid card).

++ Bup/Met +PSI Interview conducted at South London with Bup/Met +PSI participants only. Participants will be reimbursed an additional £20 for their time in taking part in the interview (loaded onto a prepaid card).

+++ Extension Interview conducted at the South London and Newcastle sites with XR-Bup participants who consented to continue treatment after week 24 between 12-24 months of them being randomised in the trial.

~ Due to the Coronavirus 2019 (COVID-19) pandemic and to limit health care contacts, week 2, 6, 10, 14, 18 and 22 visits are permitted to be conducted via telephone if required. In this instance a UDS may not be obtained. Missed UDS due to visits being conducted by telephone are not considered a protocol deviation and do not have to be recorded on the deviations log however missed UDS for all other reasons should be recorded. All other visits are to be conducted in person at the study centre.

9.3 Laboratory Tests

Each site will determine all participants' liver function (as defined in the inclusion/exclusion criteria) after consent either by conducting an LFT (serum) blood-test following their local laboratory procedure, or accessing this information from the participant's hospital medical records if a prior LFT test result has been done and recorded within 12 weeks from the date of screening. During post-randomisation 6-month treatment phase, participants allocated to the XR-Bup arm will be asked to have further LFT testing at visits 4, 12 and 24, or more often as judged by the CI or PI. After the post-randomisation 6-month treatment phase, participants who consent to continue having XR-Bup injections will be asked to have further LFT testing approximately every 6 months or more often as judged by the CI or PI.

If the participant does not have their bloods taken post randomisation for any reason (i.e., including but not limited to, participant refusal , they do not attend the visit or if it is not possible to take bloods); they may continue in the trial at the discretion of the PI or Sub Investigator based on their clinical judgement. Participants randomised to BUP or Met in the study will have LFT testing according to their local standard of care.

10. Assessment of Efficacy

10.1 Primary efficacy parameter

With a 1-week measurement grace period from randomisation, the primary endpoint is the count of days abstinent from all non-medical opioids between days 8-168 (weeks 2-24; 161 days), combined with up to 12 urine samples for opioids providing biological verification of 36 of the 161 days in the outcome measure. If the UDS shows positive, the 3 days prior to the UDS will be reported as a positive and override what is reported on the timeline follow-back interview.

10.2 Secondary Efficacy Parameters

There will be 19 secondary within-study efficacy parameters:

(1) Clinical superiority of XR-Bup plus PSI versus Bup/Met plus PSI using the primary outcome measure;
(2) Safety measured by all adverse event reporting;

(3) Time (days) enrolled in study treatment (retention) to week 24;
(4) OUD and CUD remission status (severity) measured by SCID-5-RV for DSM5;
(5) Clinician rating of severity, complexity and recovery strengths (ADAPT);
(6) Clinician rating of global impression (CGI-I anchored on baseline severity [CGI-S]);
(7) Count of days abstinent from cocaine and illicit/non-medical benzodiazepines during weeks 2 to 24 (range: 0-161 days); combining self-report information from Time-Line Follow-Back interview adapted from the Treatment Outcomes Profile and incorporating data from 12 scheduled urine drug screens;
(8) Craving for opioids and cocaine (CEQ-F[H] and CEQ-F[C]);
(9) VAS-N and VAS-W craving need for heroin and cocaine;
(10) Difficulties in Emotion Regulation – Short Form (DERS-SF);
(11) QIDS-SR (depression rating);
(12) WSAS (work and social adjustment);
(13) Subjective recovery and improvement (SURE);
(14) Subjective rating of OUD improvement (PRO-I; on baseline severity [PRO-S);
(15) Cognitive impairment (MoCA);
(16) Alcohol: typical quantity and frequency (ALC-QFM)
(17) Time (days) enrolled in study treatment (retention) from week 24 to date last participant randomised plus 9 months;
(18) Semi structured, topic guided interviews after week 24 (XR-Bup, XR-Bup +PSI & Bup/Met +PSI treatment arms) and after 12 months of enrolment within the trial (XR-Bup treatment arm only);
(19) Among participants enrolled in longer term XR-Bup treatment: OUD and CUD remission status (SCID-5-RV); heroin, cocaine and illicit/non-medical benzodiazepine use in past 90 days (TLFB; UDS); somatic symptoms (PHQ-15), emotion regulation (DERS-SF), depression and anxiety symptoms (PHQ-4) and quality of life (OSTQOL).

Analysis of other research measures will be specified in the statistical analysis plan.

10.3 Procedures for assessing efficacy parameters

Endpoint data collection will be gathered during 13 clinic visits using the TOP (timeline follow-back [TLFB] interview) and will also include recording of cocaine and non-medical benzodiazepines. All participants will be asked to provide a urine sample during each visit. If the participant does not take a UDS then all tested drugs will be taken to be positive for the past 3 days.

10.a Assessment of Cost Effectiveness

10.1a Primary Economic Parameter

The primary economic endpoint will be the incremental cost per quality-adjusted life year (QALY) gained of injectable depot maintenance buprenorphine versus standard oral therapy, adopting a broad societal cost perspective. Incremental costs will be determined from responses to the ADSUS questionnaire and the EXPO keyworker contact form. QALYs will be calculated from EQ-5D-5L scores and by applying the EQ-5D-3L crosswalk value set. This has no implications for the sample size calculation.

10.2a Secondary Economic Parameters

There will be 2 secondary economic parameters:

(1) Health profiles (EQ-5D-5L);
(2) Quantities of resource use (ADSUS) and total costs disaggregated by broad categories;

10.3a Procedures for assessing cost-effectiveness parameters

The cost utility analysis will consider patient QALYs and costs from a broad societal perspective including NHS and personal social services, productivity losses (including time off work because of illness), and criminal activity. This will be based on an incremental analysis of the mean costs and QALYs for injectable depot maintenance buprenorphine versus standard oral therapy.

Trial participants' direct and indirect costs will be estimated from responses to the ADSUS questionnaire, which includes items related to use of primary care services (including out-of-hours services), Emergency Department and hospital care; in addition to services provided by local authorities, including accommodation, day care, and drop-in centres; and personal costs in terms of days off work, out-of-pocket expenses, time spent seeking healthcare, etc. Participants' use of secondary care services will also be measured directly using the study CRFs. This will ensure missing data on important cost drivers are reduced to a minimum. The keyworker contact form will be used to record the clinical team's direct and indirect time working as part of the trial. Unit costs will be obtained from routine hospital data (NHS reference costs) and other resources such as the British National Formulary for medicines, and the Personal Social Services Research Unit's unit costs of health, social care [43], and criminal justice [44]. Indirect costs will be valued using the human-capital method, based on the average annual earnings data by sex and age group obtained from the Office for National Statistics.

Trial participants will be asked to complete the EQ-5D-5L questionnaire at baseline, and weeks 12 and 24. Responses will be used to calculate 3L utilities, based on the crosswalk [45] which is the current recommendation by NICE. Should a EQ-5D-5L value set become available by the time of analysis, this will be used in a secondary analysis.

Longer-term data linkage after end of study

An analysis using data-registry indicators of mortality, convictions and health service utilisation (the later longer-term research aims). In preparation for this, we will ask participants for their consent.

Subject to patient consent and securing approval from Public Health England (PHE), Ministry of Justice and NHS Digital, public, EXPO data will be linked to the following external-study measures at 3 years: This review at 3 years will be a non-CTIMP data audit and does not form part of the current CTIMP trial.

(1) National Drug Treatment Monitoring System (total time in community and prison setting treatment, number of treatment journeys, treatment status at end of follow-up (in treatment; left successfully or unsuccessfully).

(2) NHS hospital episodes statistics: contact with inpatient and outpatient hospital services.

(3) Police National Computer (net change in number of convictions before and after the trial by offence type. PNC: for each member of the cohort: (a) lifetime convictions history to point of enter into the study and nature and number of convictions (severity); (b) count of convictions 2 years before and after index prison discharge. All recordable offence types will be included where an individual was charged, then subsequently proven guilty and either convicted, cautioned, reprimanded or warned. The two-year observation period will be used to allow time for police and court processing of offences committed before treatment.

(4) NHS Digital: NHS digital: mortality: (a) incident and date of mortality; (b) cause of mortality; (c) involvement of alcohol or drugs; (d) location of death. Following our previous work with the Office for National Statistics, case definitions will involve: 'Mental and behavioural disorders due to drug use' (ICD-10 codes: F11-F16, F18, F19) and an opioid was mentioned on the death certificate; or to any of the following: 'Accidental poisoning by drugs, medicaments and biological substances' (X40-X44); 'Intentional self-poisoning by drugs, medicaments and biological substances' (X60-X64); 'Assault by drugs, medicaments and biological substances' (X85); and 'Poisoning by drugs, medicaments and biological substances, undetermined intent' (Y10-Y14), where any controlled drug and an opioid was mentioned (and potentially referring to the same drug, such as heroin).

11. Assessment of Safety

11.1 Specification, timing and recording of safety parameters

For participants assigned to XR-Bup, LFT (blood sampling) will be done at screening (or recorded from the participants medical records if an LFT procedure was done no more than 12 weeks before consent), and at 4-weeks, 12-weeks and end of study (24-weeks). Participants who consent to receive XR-Bup treatment past 6 injections, a LFT will be taken every 6 months.

If a participant does not have their bloods taken for any reason post randomisation (i.e., including but not limited to, participant refusal, they do not attend the visit or if it is not possible to take bloods); they may continue in the trial at the discretion of the PI or Sub Investigator based on their clinical judgement. The CI or PI may judge that more frequent LFT monitoring is clinically indicated for these and other participants in the study.

11.2 Procedures for recording and reporting adverse events

The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 gives the following definitions:

Adverse Event (AE): Any untoward medical occurrence in a subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR): Any untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.

Unexpected Adverse Reaction (UAR): An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in the SmPC for that product (for products with a marketing authorisation), or The Investigator's Brochure (IB) relating to the trial in question (for any other investigational product).

Serious adverse Event (SAE), **Serious Adverse Reaction (SAR)** or **Suspected Unexpected Serious Adverse Reaction (SUSAR)**: Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that results in death; is life-threatening; required hospitalisation or prolongation of existing hospitalisation; results in persistent or significant disability or incapacity; consists of a congenital anomaly or birth defect.

As documented within the EXPO Trial Investigator Brochure all SARs in the XR-Bup IMP groups are unexpected and will be reported as SUSARS in the study.

Important Medical Events (IME) & Pregnancy Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious. Although not a serious adverse event, any unplanned pregnancy will be reported via the trial's SAE reporting system as stated below.

Reporting Responsibilities: King's College London & South London and Maudsley NHS Foundation Trust have delegated the delivery of the Co-sponsors' responsibility for Pharmacovigilance (as defined in Regulation 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004 to the King's Health Partners Clinical Trials Office (KHP-CTO).

All SAEs, SARs and SUSARs will be reported immediately (and certainly no later than 24 hours) by the Investigator to the KHP-CTO and the CI will review in accordance with the current Pharmacovigilance Policy. The adverse event log (AEL) will be reviewed at each trial assessment clinic visit and at all follow-ups and following any occurrences in between study visits and follow-ups.
All clinical investigators in the study will be provided with full details of possible adverse medical events that may result from the trial medication and/or procedure, as well as other possible occurrences that may not be caused by or related to that product or procedure. Any adverse events occurring during the trial will be recorded in the participant's source data worksheet and filed in their medical records at the end of the trial. They will also be transcribed on to the electronic Case Record Form (eCRF).

Clinicians will report, and the centre's PI will assess, each adverse event for seriousness, causality (definite, probable, possible, remote, none) and intensity (mild, moderate and severe). The Sponsor will make the expectedness assessment against the Reference Safety Information section of each Investigational Medicinal Product. If the Sponsor (CI)

does not agree with the investigator's causality assessment the opinion of both the investigator and the Sponsor will be provided with the report.

The KHP-CTO Clinical Research Associate (CRA) will review the SAE once it's received by email and follow up queries will be sent to the site team and CI. The original SAE form and documentation of event in source data will also be verified at monitoring visits. The information will be entered on the eCRF. The CI (or a doctor nominated by the CI) will review every event within one working day of the SAE form being received and determine whether the event was expected or unexpected. The CI may upgrade the causality of an event without the centre PI's agreement.

On a scheduled basis, the Data Management Committee (DMC) will review adverse event information. The KHP-CTO will report SUSARs to the Medicines and Healthcare Product Regulatory Agency (MHRA).

The reporting timelines are as follows:

- SUSARs, which are fatal, or life threatening must be reported no later than 7 days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the sponsor first becoming aware of the reaction.
- The Chief Investigator and KHP-CTO (on behalf of the co-sponsors), will submit a Development Safety Update Report (DSUR) relating to this trial IMP, to the MHRA and REC annually.

Any safety concern/ safety signal raised by the DMC will be communicated by SLaM & KCL to Indivior European Economic Area Qualified Person Responsible for Pharmacovigilance (INDV EEA QPPV) at EEAQPPV@indivior.com within 24 hours of awareness.

11.3 Treatment stopping rules

EXPO may be prematurely discontinued by the Co-sponsors or Regulatory Authority on the basis of new safety information or for other reasons given by the DMC and TSC regulatory authority or ethics committee concerned. The Competent Authority and Research Ethics Committee (REC) will be informed within 15 days of the early termination of the trial.

12. Statistics

12.1 Sample size

A target sample of 604 participants has been estimated for the study. The sample size calculation is strategic, ensuring that there is a reliable estimate of the XR-Bup versus Bup effect aimed to be conducted in q42020 (at the end of Phase I). The estimate of the main effect for XR-Bup + PSI versus Bup/Met + PSI (Phase II) has been assumed to be equivalent to the main effect or Phase I.

The required number of participants has been estimated using that required for a Poisson regression model taking a baseline rate of 0.6 and assuming a 23% target difference in the count of days of abstinence from heroin over the study period of 161 days. (ARC trial (ISRCTN69313751; 56.78% for the treatment-as-usual control i.e. assuming 17 abstinent days over a period of 28 days).

To obtain 90% power, for a Poisson regression, with alpha at 5% and with 15% inflation for attrition, EXPO has a target total of 304 participants for the statistical comparison of the primary outcome recorded for XR-Bup and Met/Bup and a target total of 300 participants for the statistical comparison of the primary outcome recorded for XR-Bup + PSI and Bup/Met + PSI. The statistical analysis plan will present a sensitivity check on this power calculation on the assumption of a greater response for the control groups.

At each of the 5 study sites, the plan is to enrol a maximum of 76 participants for this comparison. This will achieve a study that is well-powered to detect a main treatment effect of medication [7]. At the end of Phase II (at the co-ordinating centre) there will be a targeted recruitment of 150 to receive XR-Bup + PSI and 150 patients to Bup/Met + PSI [8]. After analysis of the Phase I and Phase II contrasts, there will be an exploratory meta-analysis, pooled data from all sites.

12.2 Statistical analysis

Assessment of Efficacy

The Statistical Analysis Plan (SAP) - approved by the trial committees - will be published on the Open Science Framework (www.osf.io) and summarised in the published trial protocol paper. After data lock in MACRO for each phase, the statistical analysis will be completed in Stata and R. Pooling data from all clinical treatment sites, a mixed-effects multivariable regression model for the primary analysis, with covariates (sex, age, drug injecting status, centre and baseline score on the outcome measure), and a site-varying random intercept. The medication preference factor will be explored for inclusion through interaction tests because it is expected that many participants have a medication preference given past or current exposure.

A maximum-likelihood multiple imputation approach will be used for the management of missing data with a sensitivity comparison to the complete case dataset. The cumulative distribution function of the primary endpoint will also be plotted for comparison purposes. Analyses of secondary outcomes will proceed using the same stratification and covariates as defined for the primary analysis model with linear (continuous outcomes) or logistic (binary or ordinal outcomes) regression framework. A causal mediation analysis (including craving, MoCa, and WSAS as mediators in separate models) will be implemented using a counterfactual framework to include a treatment/mediator interaction and covariates, based on univariable path screening, and with bias corrected bootstrapped estimates.

The clinical analysis will follow the intention-to-treat principle and include all patients in the group to which they are allocated. Alpha will be set at 5% for the primary and secondary outcomes (with associated 95% confidence intervals). The distributions of scale and count measures may be non-normal (skewed), so test statistics and effect sizes will be computed following appropriate transformation (e.g. natural log to obtain a geometric mean).

Assessment of Cost Effectiveness

The number of QALYs experienced by each participant will be calculated as the area under the curve, using the trapezoidal rule, and adjusted for baseline [46]. Total costs and QALYs will be used to calculate the incremental cost-effectiveness ratio of injectable depot maintenance buprenorphine versus standard oral therapy. Data that are assumed missing at random will be imputed using multiple imputation by chained equations as will be specified in the HEAP. Non-parametric bootstrapped 95% central ranges for items of resource use, costs and QALYs will be estimated (10,000 replicates).

A range of one-way sensitivity analyses will be conducted to test whether, and to what extent, the incremental cost-effectiveness ratio is sensitive to key assumptions in the analysis (e.g. unit prices). Multivariate sensitivity analyses will be applied where interaction effects are suspected, and the joint uncertainty in costs and benefits will be considered through application of bootstrapping and estimation of cost-effectiveness acceptability curves [47]. Alternative scenarios will be specified in the HEAP and will include consideration of a narrower cost perspective (NHS +/- personal social services) to enable comparison with the NICE threshold range of £20,000 to £30,000 per QALY.

A Health Economic Analysis Plan (HEAP) [48] (agreed prior to the analysis), will define the analytic steps to be undertaken. The economic findings will be reported according to the CHEERS guideline [49].

13. Trial Steering Committee

A TSC will operate independently from the Trial Management Group (TMG), the study funder (Indivior), and the Co-sponsors (King's College London and South London and Maudsley NHS Foundation Trust). The TSC's key purpose will be to ensure the overall integrity of the study. Committee membership will be documented in the first (joint) minutes of the TSC and DMC.

14. Data Monitoring Committee

The DMC's key purpose (as set out in DAMOCLES) will be defined in the DMC charter. Reports to the DMC will be prepared and presented by the Trial Statistician.

15.Trial Management Group

The TMG will be responsible for the trial's day-to-day running and management. Chaired by a Senior Investigator, the membership will include: The CI, Lead (clinical scientific) Investigator, Co-Lead (clinical scientific Investigator), EXPO Trial Manager (secretary to the TMG), EXPO Trial Pharmacist, EXPO Statisticians and EXPO Co-Applicants. The TMG will oversee the development and operation of the study, monitor and maintain recruitment rates, and devise any necessary workarounds that may arise in patient management or the conduct of the trial, ensure that all required financial, insurance and indemnity arrangements are instigated, organise site agreements between each clinical centre and the Study Office and, draw up the study publication policy and strategy.

16. Direct Access to Source Data and Documents

EXPO Investigators will permit trial-related monitoring, audits, REC review, and regulatory inspections by providing the Sponsors, Regulators and REC direct access to source data and other documents.

17. Ethics & Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments. The protocol and related documents will be submitted via IRAS application for review to a REC, and to the MHRA for Clinical Trial Authorisation. EXPO will comply with regulations, particularly specifying pharmacovigilance reporting. Subsequent protocol amendments will be submitted to the REC and the Regulatory Authorities for approval. Progress reports and a Final Study Report will be provided to the REC and the Regulatory Authorities.

The Senior Investigators will submit a final report at conclusion of the trial to the KHP-CTO (on behalf of the Cosponsor), the REC and the MHRA within the timelines defined in the regulations. In relation to the study's registration and adoption: an MHRA Clinical Trial Authorisation application will be made. The trial will be registered with an appropriate trials database (e.g. clinicaltrials.gov).

18. Quality Assurance

Monitoring of this trial will be to ensure compliance with Good Clinical Practice (GCP), and scientific integrity will be managed, and oversight retained, by the KHP-CTO Quality Team. The trial will incorporate a range of data management and quality assurance functions. As the data are entered online, the Trial Manager will log any queries generated and feed these back to the centre research workers in a timely manner. Any necessary alterations to entered data will be indicated clearly with an audit trail from the original point of data entry, to ensure that any such amendments, and the reasons for them, can be inspected and tracked. KHP-CTO will undertake, on behalf of the Sponsor, independent administrative audits of the trial master file and monitoring at all sites and pharmacies periodically during the trial to ensure compliance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and its subsequent amendments.

19. Data Handling

The Lead Investigator will act as custodian for the trial data under the General Data Protection Regulations. The following guidelines will be strictly adhered to: all patient data will be pseudo-anonymised and stored on a password protected computer; all trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the KHP-CTO Archiving SOP.

20. Data Management and Database Lock

All baseline and follow-up data will be entered on the online InferMed MACRO electronic data capture (EDC) system (infermed.com). This system is regulatory compliant (GCP, and the EC Clinical Trial Directive). An electronic case report form (eCRF) using the MACRO EDC will be programmed by the KCTU and hosted on a dedicated secure server. The eCRF system will have full audit trail, data discrepancy functionality, database lock functionality, and supports real time data cleaning and reporting. The Trial Manager will request usernames and passwords to any new researchers. Only those authorised by the Trial Manager will be able to use the system.

After written recording, each research worker will aim to transcribe data onto the eCRF within one working week of a participant assessment. After completion of all follow-ups and prompt entry of data, the Trial Manager will review the data and resolve queries with sites. At the end of the trial, each centre will be supplied with their eCRF data for storage. This will be filed locally for any future regulatory or internal audit.

Database lock for phase I will be undertaken within approximately 3 months of last patient, last visit and will be controlled by TMG of participants enrolled in groups 1 and 2. Database lock for phase II will be within approximately 3 months of last patient, last visit and will be controlled by TMG of participants enrolled in groups 3 and 4.

21. Publication Policy

A layered communication plan for the lifecycle of the trial will be developed to communicate material in the best format to our audiences (including service users; family members; policy makers; treatment commissioners; the general public; and scientific peers). The study will produce results and practice briefings for NHS Service and national stakeholder audiences. This collective activity will support the communication of results via high-impact general medical journals and addiction science journals.

22. Insurance & Indemnity

King's College London (KCL) will provide cover under its No Fault Compensation Insurance, which provides for payment of damages or compensation in respect of any claim made by a research subject for bodily injury arising out of participation in a clinical trial or healthy volunteer study (with certain restrictions). The co-sponsor, South London and Maudsley NHS Foundation Trust, takes responsibility for ensuring that appropriate standards, conduct and reporting are adhered to regarding its facilities and staff involved with the project

23. Financial Aspects

EXPO is funded by Indivior as research grant to King's College London (KCL; Lead [clinical scientific] investigator, Professor John Marsden; Addictions Department), listing Dr Mike Kelleher as Chief Investigator and Principal Investigator (at South London and Maudsley NHS Trust), with sub-contracts issued by KCL to South London and Maudsley NHS Trust and each clinical recruitment site. The lead sponsor, KCL, will take primary responsibility for ensuring that the design of the study meets appropriate standards and that arrangements are in place to ensure appropriate conduct and reporting.

24. Signatures

Dr. Mike Kelleher:

_____ _____
Chief Investigator Date

Dr. John Marsden:

_____ _____
Co- Lead Investigator Date

Dr. Zoë Hoare:

_____ _____
Statistician Date

Prof Dyfrig Hughes:

_____ _____
Health Economics Lead Date

Dr. Ed Day:

_____ _____
Principal Investigator Date

Dr. Jonathan Dewhurst:

_____ _____
Principal Investigator Date

Dr Eilish Gilvarry:

_____ _____
Principal Investigator Date

Dr Fiona Cowden:

_____ _____
Principal Investigator Date

25. Trial Protocol Version History Summary

Protocol Version Number	Issue Date	Summary of Significant Changes
1.2	13.06.2019	Clarification/expanding/amending minor instructions and details across the protocol. Section 2 Changes to central study team and removed Sponsor Representative contract details. Section 3 Added abbreviations. Section 4 Background information expanded. Section 5.2 Removal of study site and recalculation of targets. Senior Statistician to be blinded. Junior Statistician is unblinded to prepare reports. Section 6.1 Condensing of information regarding Imp and that the manufacturing and importing will be completed by Indivior. Section 6.2 Active Comparator arms will be dispensed by community pharmacies on receipt of a valid prescription, labelled with a normal dispensing label. Reference to SmPCs for oral Bup and Met. Section 6.3 Rescue dosing of Bup can be provided at any point after the first dose of XR-Bup. This will be recorded as concomitant medication. Schedule timing of minim 21 days added for XR Bup. Section 6.6 Guidelines on removal of XR Bup added. Section 6.7 Clarification on the accountability of XR Bup. Pharmacy team to manage accountability, Sponsor approval required for all destruction. EXPO Trial Pharmacist will manage IMP supply to sites. Section 6.7.2 Accountability records not required for comparator arms within the trial as they will be dispensed with local pharmacy. Site staff to check compliance with local pharmacies. Section 6.7- Supply, transport and storage of IMP. Repetition of numbering amended in protocol version 2.0. Reference to the Investigational Product Handling Manual for detailed information regarding storage guidelines. Temperature monitoring not required for comparator arms. Section 8.3 Clarification of induction procedure. Section 8.4 Removal of stratification factors. Section 9.1

		Amendment to research measures utilised and the timepoints of collection. Section 10.1 and 10.2 Clarification and additional primary and secondary efficacy parameters set. Section 11.2 All SARs in the XR-Bup IMP groups are unexpected and will be reported as SUSARS in the study. Amendment to sample size and statistical analysis to be conducted. Section 25 Signatures added for Co-Lead Investigator and Trial Statistician.
2.0	08.01.2020	Clarification/expanding/amending minor instructions and details across the protocol. Section2 Addition of PI contact details. Section 5.2 Addition of new recruiting site. Section 6.2 Removal of Buprenorphine Naloxone- Bup-NX (Suboxone) as an active comparator. Section 6.3 Dosing guidance for participants who consent to receive more than 6 doses of XR-Bup. Section 6.4 Amendment of the numbering of injection sites to be consistent across guidance given, PIL, database. Cold press is authorised upon injection. Section 6.6 Removal of XR Bup to be recorded as an Important Medical Event (IME). Section 6.8.1 Removal of instruction that IMP can be stored at room temperature for up to 7 days prior to administration. Section 7.0 Clarity and addition information on timetable of sessions and information regarding withdrawals. Section 8.1 Reducing Met from 50mg to 30mg/day or less for inclusion into the trial. Significant change of wording of inclusion criterions 7 and 8. Clarity of other inclusion/exclusion criterions. Section 8.3 Removing the induction process for participants new to treatment as all participants are to be already in receipt of opioid substitution therapy. Clarification of the induction process for all participants randomised to XR-Bup. Section 9.1 Detailing optional consent for an Exit Interview with participants randomised to XR-Bup at South London recruiting centre. Section 9.2 Adding timeline for procedures to be conducted with XR-Bup participants who consent to additional treatment. Adding timeline for Exit Interview. Change in payments to include payments at all visits. Section 9.3

		Change of procedure of collection of LFT blood test as only required for XR-Bup participants. Use of past blood results if available at screening. Section 10.2 Additional secondary efficacy parameters added to trial outcomes measures. Section 10.3 Error in number of trail visits from 10 to correct number of 13. Removal of alcohol consumption collected as endpoint data collection. Section 11.1 Clarity of procedure as per section 9.3. Section 12.2 Clarify of analysis. Section 15. Change of membership of TMG to remove site staff. Section 24 Signatures added for all PI's to confirm review and approval of protocol. Section 25 Addition of summary table of changes between protocols.
2.1	09.07.2020	Section 7 Removing instruction that the PI and lead therapist will meet weekly to discuss case management of non-PSI participants. Section 9.1.2 Amendment of sub-section heading Exit Interview to be conducted at Newcastle, West Midlands and Tayside in addition to South London. Section 9.2 Details of Exit Interview. Section 12.1 Correction of Typographical error from 4 to 5 sites. Section 24 Signature space for Dr Cowden PI at Tayside study centre.
3.0	22.07.2020	Section 6.2 Addition of Buprenorphine Naloxone [Bup-NX (Suboxone)] as an active comparator as this is routinely prescribed at the Tayside Site as standard of care medication for OUD. Section 9.2 Additional details of Exit Interview.
4.0	30.09.2020	Section 6.2 Addition of Espranor® (Esp) as an active comparator as this is routinely prescribed at the Tayside Site as standard of care medication for OUD. Clarity that participants randomised to group 2 and group 4 are permitted to change between the active comparator drugs whilst enrolled in the trial by following the prescribing guidelines as detailed in the SmPC and if there are no known allergic, adverse reactions or contraindications to the drug. Section 6.3 Esp usual daily dose separated from Bup as max daily is 18mg. Section 6.8.2 Addition of Bup-NX and Esp.

		Section 8.1 and 8.2 Updated Inclusion and Exclusion Eligibility criteria to include Bup NX and Esp. Clarity that participant is ineligible if they have any allergic or adverse reactions or contraindication to Buprenorphine. If participant has any allergic or adverse reaction or contraindication to Met or naloxone, or excipients of Bup-NX or Esp they can be prescribed Bup within the trial. Section 11.2 Updated reference dates for the Trial Specific Addendum to the Reference Safety Information for The Investigator's Brochure (IB; RBP-6000; Indivior 06 March 2020; pages 144-153).
5.0	01.06.2021	Section 2 Updated clinic name at Tayside study site. Section 3 Updated abbreviations for new terms introduced within the protocol. Section 5.2 Caveat to document new recruitment phase timelines. Section 5.3 Caveat to document amendment to study analysis timelines. Section 6.5 Removal of reference to EXPO Trial Specific Addendum to Reference Safety Information as the Investigator Brochure has been updated to incorporate this information. Therefore, no requirement for the Addendum. Section 9.1 Correction of Typo from clinician version to research version (SCID-5-RV) Addition of measurements OSTQOL; PHQ-15 and PHQ4. Confirmation that where document as clinician administered measure this can be delegated to a health care worker after the baseline/screening assessment. Exit Interview qualitative interview based on ADAPT measurement. Details what the Bup/Met +PSI and Extension Phase Interview comprise of Section 9.2 Addition of timepoints for Bup/Met + PSI Interview and Extension Phase Interview. Due to the Coronavirus 2019 (COVID-19) pandemic and to limit health care contacts, week 2, 6, 10, 14, 18 and 22 visits are permitted to be conducted via telephone if required. In this instance a UDS may not be obtained. Missed UDS due to visits being conducted by telephone are not considered a protocol deviation and do not have to be recorded on the deviations log however missed UDS for all other reasons should be recorded. All other visits are to be conducted in person at the study centre. Section 9.3 Clarification that participants can continue in the trial if LFT bloods are not taken post randomisation based on PI/Sub Investigator clinical judgement. Section 10.2 CUD remission status added as an efficacy parameter (previously omitted due to error but already approved as a measure). Addition of 2 secondary efficacy parameters for the measures/outcomes being collected within the Exit Interview, Bup/Met + PSI Interview and Extension Phase Interview. Section 11.1 Clarification that participants can continue in the trial if LFT bloods are not taken post randomisation based on PI/Sub Investigator clinical judgement.

		Section 11.2 Removal of reference to EXPO Trial Specific Addendum to Reference Safety Information as the Investigator Brochure has been updated to incorporate this information. Therefore, no requirement for the Addendum. Section 26 Addition of references for OSTQOL; PHQ-15 and PHQ4 and correction of reference 37.
5.1	06.10.2021	Section 2 Contact details for Health Economics Lead. Section 9.1 EQ-5D-5L amendment to the description of the scale as used for economic evaluation. Section 10.a Addition of section to detail Assessment of Cost Effectiveness. Section 10.1a Addition of section to detail Primary Economic Parameter. Section 10.2a Addition of section to detail Secondary Economic Parameters. Section 10.3a Addition of section to detail Procedures for assessing Cost-Effectiveness Parameters. Section 12.2 Additional details for assessment of cost effectiveness. Section 24 Signature for Health Economics Lead added. Section 26 References updated.

26. References

1. Peacock A et al. Global statistics on alcohol, tobacco and illicit drug use: 2017 status report. Addiction. 2018 May 10. doi: 10.1111/add.14234.

2. Mills H, Skodbo S, Blyth P. Understanding organised crime: Research Report 73. UK Home Office. 2013

3. Martins SS et al. Worldwide prevalence and trends in unintentional drug overdose: a systematic review of the literature. Am J Public Health. 2015; 105: e29-49.

4. Mattick RP et al. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database of Systematic Reviews. 2009; CD002209.

5. Mattick RP et al. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database of Systematic Reviews. 2014; CD002207.

6. Gossop M et al. The National Treatment Outcome Research Study (NTORS): 4-5 year follow-up results. Addiction. 2003; 98: 291-303.

7. Pierce M et al. Impact of treatment for opioid dependence on fatal drug-related poisoning: a national cohort study in England. Addiction. 2016; 111: 298-308.

8. Amato L et al. Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence. Cochrane Database Syst Rev. 2011 Oct 5;(10):CD004147.

9. Marsden J et al. Development of the Addiction Dimensions for Assessment and Personalised Treatment (ADAPT). Drug Alcohol Depend. 2014; 139: 121-31.

10. Grella, C.E., Lovinger, K. Thirty-year trajectories of heroin and other drug use among men and women sampled from methadone treatment in California, Drug and Alcohol Dependence 118 (2011) 251-258.

11. Sayre S.L., Schmitz J.M., Stotts A.L., Averil P.M., Rhoades H.M., Grabowski J.J. Determining predictors of attrition in an outpatient substance abuse program, American Journal of Drug and Alcohol Abuse 28 (2002) 55-72.

12. Morral A.R., Iguchi M.Y., Belding M.A., Lamb R.J. Natural classes of treatment response, Journal of Consulting and Clinical Psychology. 65 (1997) 673-685.

13. McLellan A.T., Alterman A.I., Metzger D.S., Grissom G.R., Woody G.E., Luborsky L., O'Brien C.P. Similarity of outcome predictors across opiate cocaine and alcohol treatments: role of treatment services, Journal of Consulting and Clinical Psychology 62 (1997) 1141-1158.

14. Marsden J., Eastwood B., Jones H., Bradbury C., Hickman M., Knight J., Randhawa K., White M. Risk adjustment of heroin treatment outcomes for comparative performance assessment in England, *Addiction* 107 (2012) 2161-2172.

15. Bux D.A., Lamb R.J., Iguchi M.Y. Cocaine use and HIV risk behavior in methadone maintenance patients, Drug Alcohol Dependence 29 (1992) 263-268.

16. Williamson A., Darke S., Ross J., Teesson M. The effect of persistence of cocaine use on 12-month outcomes for the treatment of heroin dependence, Drug Alcohol Dependence 81 (2006) 293-300.

17. Marsden, J. Eastwood B., Bradbury C., Dale-Perera A, Farrell M, Hammond P, Knight J., Randhawa, K., Wright C. Effectiveness of community treatments for heroin and crack cocaine addiction in England: a prospective, in-treatment cohort study, Lancet 374 (2008) 1262-1270.

18. Broome K.M., Flynn P.M., Simpson D.D. Psychiatric comorbidity measures as predictors of retention in drug abuse treatment programs, Health Services Research 34 (1999) 791-806.

19. O'Toole T.P., Pollini R.A., Ford D., Bigelow G. Physical health as a motivator for substance abuse treatment among medically ill adults: Is it enough to keep them in treatment? Journal of Substance Abuse Treatment 31 (2006) 143-150.

20. Kleber, H.D., Weiss, R.D., Anton, R.F., Rounsaville, B.J., George, T.P., Strain, E.C., Greenfield, S.F., Ziedonis, D.M., Kosten, T.R. et al. Treatment of patients with substance use disorders, American Journal of Psychiatry 163 (2006) (Supplement 8) 5-82.

21. Litt M.D., Kadden R.M., Kabela-Cormier E., Petry N.M. Changing network support for drinking: network support project 2-year follow-up, Journal of Consulting and Clinical Psychology 77 (2009) 229-242.

22. Miller W.R., Rollnick S. Motivational Interviewing: Helping People Change (Applications of Motivational Interviewing). The Guilford Press. 2012.

23. Dansereau D.F., Simpson D.D. A picture is worth a thousand words: the case for graphic representations, Professional Psychology: Research and Practice 40 (2009) 104-110.

24. National Institute for Health and Clinical Excellence. Psychosocial interventions. National Clinical Practice Guideline Number 51. 2008. NICE (CG51).

25. Mitcheson L., Maslin J., Meynen T., Morrison T., Hill R., Wanigaratne S. Applied Cognitive and Behavioural Approaches to the Treatment of Addiction: A Practical Treatment Guide. Chichester: Wiley-Blackwell. 2010.

26. Higgins S.T., Silberman, S.H., Heil S.H. Contingency management in substance abuse treatment. New York, Guilford Press.

27. Fals-Stewart W., O'Farrell T.J., Birchler G.R. Behavioral Couples Therapy for Substance Abuse: Rationale, Methods, and Findings, Sci Pract Perspect. 2 (2004) 30–41.

28. Copello A, Orford J, Hodgson R, Tober G, Barrett C: Social behaviour and network therapy - basic principles and early experiences. Addictive Behaviours 27 (2002) 345–366

29. Copello A, Williamson E, Orford J, Day E: Implementing and evaluating social behaviour and network therapy in drug treatment practice in the UK: a feasibility study, Addictive Behaviours 31 (2006) 802–810.

30. Nowinski J., Baker S., Carroll K. Twelve step facilitation therapy manual. A clinical research guide for therapists treating individuals with alcohol abuse and dependence. National Institute on Alcohol Abuse and Alcoholism Project MATCH Monograph Series Volume 1. 1999. National Institute on Alcohol Abuse and Alcoholism.

31. Donovan D.M., and Wells E.A. "Tweaking 12-step": The potential role of 12-Step self-help group involvement in methamphetamine recovery. Addiction 102(Suppl. 1):121-129, 2007.

32. Gilbert P. Overcoming depression. A self-help guide using cognitive behavioural techniques. London: Robinson. 2009.

33. UCL scale for rating core and generic therapeutic skills (accessed: www.ucl.ac.uk/CORE/).

34. First MB et al., Structured Clinical Interview for DSM-5 Disorders – Research Version (SCID-5-RV), American Psychiatric Association, 2015.

35. Nasreddine Z.S., Phillips N.A., Bédirian V., Charbonneau S., Whitehead V., Collin I., Cummings JL, Chertkow H. The Montreal Cognitive Assessment (MoCA): A Brief Screening Tool for Mild Cognitive Impairment, Journal of the American Geriatrics Society. 53 (2005) 695-699.

39. Rush, A.J., Carmody, T. and Reimitz, P.E. The Inventory of Depressive Symptomatology (IDS): Clinician (IDS-C) and self-report (IDS-SR) ratings of depressive symptoms. International Journal of Methods in Psychiatric Research, 9:45-59, 2000.

36. Busner J et al. The Clinical Global Impressions Scale Applying a Research Tool in Clinical Practice.

37. Kaufman, Xia, Fosco, Yaptangco, Skidmore, & Crowell (2016). The Difficulties in Emotion Regulation Scale Short Form (DERS-SF): Validation and replication in adolescent and adult samples. Journal of Psychopathology and Behavioral Assessment, 38(3), 443–455.

38. Mundt J.C, Marks I.M. Shear M.K, Greist J.M. The Work and Social Adjustment Scale: a simple measure of impairment in functioning, The British Journal of Psychiatry. 180 (2002) 461-464.

39. Brooks R. EuroQol: the current state of play. Health Policy, 37(1996) 53-72.

40. Strada L, Franke GH, Schulte B, Reimer J, Verthein U. Development of OSTQOL: A Measure of Quality of Life for Patients in Opioid Substitution Treatment. Eur Addict Res. (2017);23(5):238-248.

41. Kroenke K, Spitzer RL, Williams JB: The PHQ-15: validity of a new measure for evaluating the severity of somatic symptoms. Psychosom Med. (2002) 64: 258-66.

42. Kroenke, K., Spitzer, R. L., Williams, J. B. W., Löwe, B. An ultra-brief screening scale for anxiety and depression: the PHQ-4 Psychosomatics. (2009) 50, 613-621.

43. https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2020/

44. https://www.pssru.ac.uk/publications/pub-4459/

45. Van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, Lloyd A, Scalone L, Kind P, Pickard AS. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012 Jul-Aug;15(5):708-15.

46. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. Health Econ. 2005 May;14(5):487-96.

47. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. Health Econ. 2001 Dec;10(8):779-87.

48. Thorn JC, Davies CF, Brookes ST, Noble SM, Dritsaki M, Gray E, Hughes DA, Mihaylova B, Petrou S, Ridyard C, Sach T, Wilson ECF, Wordsworth S, Hollingworth W. Content of Health Economics Analysis Plans (HEAPs) for Trial-Based Economic Evaluations: Expert Delphi Consensus Survey. Value Health. 2021 Apr;24(4):539-547.

49. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, Augustovski F, Briggs AH, Mauskopf J, Loder E; CHEERS Task Force. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. BMJ. 2013 Mar 25;346:f1049.