BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-067194
Article Type:	Protocol
Date Submitted by the Author:	10-Aug-2022
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Keywords:	Substance misuse < PSYCHIATRY, QUALITATIVE RESEARCH, Clinical trials < THERAPEUTICS

Experience and response to a randomised controlled trial of extended-release buprenorphine and standard-of-care sublingual buprenorphine or oral methadone for opioid use disorder: protocol for a mixed-methods evaluation

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Words in abstract: 296
Words in text: 2843
Number of figures: 0
Number of tables: 1
Total pages: 15

Supplementary material

SPIRIT checklist: uploaded with manuscript

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ABSTRACT

Introduction Opioid use disorder (OUD) is a debilitating, persistent, but treatable condition. The standard-of-care (SOC) treatment for OUD is daily maintenance dosing – initially observed – with sublingual buprenorphine (BUP-SL) or oral methadone (MET). Not all patients adhere to these medications and attain desired reductions or abstinence from non-medical opioids. Monthly, extended-release, subcutaneous injectable buprenorphine (BUP-XR) has been developed to enhance treatment effectiveness. This protocol comprises three theory-based, qualitative-quantitative evaluations that will be embedded within a five-centre, open-label, superiority, randomised controlled trial of BUP-XR versus BUP-SL and MET. The aim of this study is to investigate: (A) the experiences of participants allocated to receive 6-months of BUP-XR; (B) the longer-term, quality of life among participants who have been enrolled in BUP-XR for a further 6-18months; and (C) the experiences of participants allocated to receive 6-months of BUP-XR or SOC medication with adjunctive personalised psychosocial intervention.

Methods and analysis Evaluation 1: a 4-centre, audio-recorded semi-structured qualitative interview with participants allocated to receive 6-months of BUP-XR treatment. The topic-guided interview is anchored on OUD-related dimensions of individual severity, complexity, and recovery. Evaluation 2: a 2-centre, audio-recorded, semi-structured interview with participants who experience longer-term BUP-XR maintenance up to 24-months. The topic-guided interview is anchored on OUD specific quality-of-life. Evaluation 3: a single-centre, audio-recorded, semi-structured interview with participants allocated to receive study medication and personalised psychosocial intervention. Qualitative data will be analysed via iterative categorisation, with descriptive use of specified clinical measures recorded by the trial, and each evaluation will be underpinned by theory, drawing on constructs from the behavioural model for health service use and health-related quality of life.

Ethics and dissemination The study protocol, consent forms and research questionnaires were approved by the London-Brighton and Sussex research ethics committee (reference: 19/LO/0483) and the Health Research Authority (IRAS project number: 255522).

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study will contribute to a better understanding of individual experiences while receiving extended-release buprenorphine treatment for opioid use disorder.
- This work will compare treatment outcomes and experiences of individuals receiving extended-release buprenorphine with personalised psychosocial intervention and individuals receiving oral opioid substitution treatment and personalised psychosocial intervention.
- This study will provide longer-term treatment outcomes for individuals receiving extended-release buprenorphine.
- This study will recruit from a population attending National health service centres, further research will be required in third sector addiction services across England and Scotland.

INTRODUCTION

Opioid use disorder (OUD) is a debilitating, persistent but treatable disorder characterised by continued use of non-medical opioids despite adverse physical and psychological harms (1). In the United Kingdom (UK) – and most countries with developed healthcare systems – sublingual (tablet) buprenorphine (BUP-SL) and oral (liquid) methadone (MET) is the standard-of-care (SOC) maintenance treatment (2). MET is a full μ opioid agonist, which poses potential risk of opioid poisoning if non-medical opioids are taken (3, 4). MET presents risk for respiratory depression, and interactions with other respiratory depressants – such as alcohol and benzodiazepines – may exacerbate this and cause severe respiratory depression (5). With a high affinity for the μ receptor but partial agonist action, BUP-SL can block the effects of any non-medical opioid use and gives a reduced risk of overdose (6).

In England, between April 2020 and March 2021, 140,863 individuals accessed National Health Service (NHS) and non-governmental community treatment clinics with OUD (7). In the UK, around 47% of patients complete episodes of MET and BUP-SL treatment (7). Several patient-level factors appear to moderate longer-term retention, including perceived stigma relating to observed dosing and the belief that prescribing is inflexible (8). Clinical research suggests that reduced retention is also associated with younger age, cocaine use, lower doses of MET, criminal activity and incarceration (9). These associations point to considerable heterogeneity in the OUD population (10). Many people with OUD also cycle through repeated periods of medication induction, stabilisation, and maintenance, but then early discontinuation and after a period out of treatment, re-admission. Clinical history and prevalent coexisting health and social problems – that are consequent or independent of OUD – add complexity to the planning and delivery of treatment for the patient (11).

There is a long challenging history of finding ways of improving treatment effectiveness for OUD (12), with a recent call for adaptive measurement-based care (13, 14). In a contribution to this effort, the pharmaceutical industry has developed long-acting injectable BUP (15). Using ARTIGEL (a proprietary polymer delivery technology), Indivior developed a monthly extended-release depot administered by subcutaneous injection (RBP-6000; licensed in the USA as Sublocade®; herein: BUP-XR) (16). The ***Ex***tended-release ***P***harmacotherapy for ***O***pioid use (EXPO) study is an ongoing, multi-centre, open-label, superiority, randomised controlled trial (RCT) in England and Scotland to determine the effectiveness and cost-effectiveness of 24-weeks of BUP-XR versus BUP-SL and MET (EU Clinical Trials Register number: 2018-00460-63).

The EXPO study will be done at five NHS community treatment centres in South London (Brixton), Solihull, Manchester, Newcastle and Dundee. At each centre, informed consenting adults (18 years and over) seeking ongoing treatment will be randomly allocated to receive BUP-XR (the

experimental condition) or BUP-SL or MET (the control condition) for 24 weeks (n=304). At the South London centre, there will be also an exploratory study in which patients are allocated to receive BUP-XR plus personalised psychosocial intervention (PSI) or MET or BUP-SL plus PSI for 24 weeks. With a 1-week grace period after randomisation, the primary outcome for EXPO is days of abstinence from all non-medical opioids to the 24-week endpoint combined with up to 12 urine drug screen (UDS) negative tests for opioids. Participants will be able to continue BUP-XR maintenance after the 24-week endpoint if they wish. Secondary outcome measures include time enrolled in treatment; days abstinent from cocaine and illicit/non-medical benzodiazepines; and craving for heroin and cocaine. The EXPO trial protocol has been published (17).

There is limited qualitative and mixed-methods research into long-acting OUD treatments. To date, there has been a qualitative study conducted in Norway with patients intentionally discontinuing long-acting naltrexone treatment (18), and qualitative study conducted in Sweden (19), recruiting participants that were in the process of initiating or had recently initiated long-acting BUP treatment. Current literature has focused on specific time points within long-acting treatment, resulting a need for boarder and longer-term evaluations. The present proposed studies will further enhance the current body of literature around patients experiences whilst receiving BUP-XR.

The current research will also be enhanced by using, mixed-methods research, which is an emergent methodology to synergize qualitative and quantitative data. It is recommended for the analysis of complex interventions, particularly RCTs, where an in-depth exploration of participants' experiences can provide valuable insights additional to the primary and secondary outcome measures (20). Similar methodology has been applied to cocaine craving experience in a recent RCT (21) Accordingly, mixed-methods research will be embedded in the EXPO trial to investigate:

(A) the experiences of participants allocated to receive 6-months of BUP-XR (Evaluation 1);

(B) the longer-term, health-related quality of life among participants who have been enrolled in BUP-XR for a further 6-18 months of maintenance treatment beyond the trial endpoint (Evaluation 2); and

(C) the experiences of participants allocated to receive 6-months of BUP-XR or SOC medication with adjunctive personalised psychosocial intervention (Evaluation 3).

METHODS

Design

Theory driven research is important to enhances study rationale and allows comparison with and building upon existing literature (22). This mixed-methods research will be underpinned by theory, drawing on constructs from the behavioural model for health service use (23) and health-related quality of life (HRQoL)(24) . The behavioural model of health service use (23) aims to assess a populations consumption of medication and healthcare services and evaluated whether there is misuse, underuse or overuse of a treatment and service. The HRQoL (24) is a model used and accepted within research of many health conditions (25-27). Using this model will enable the evaluation of other healthcare needs within participants that are in OUD remission and whether not attaining OUD remission perpetuates negative overall quality of life. Qualitative data for the study will be obtained from in-depth, semi-structured (topic-guided), audio-recorded, personal interviews with trial participants, identifiable information will be anonymised to maintain confidentiality. Quantitative data for the study will be obtained from trial measures and additional questionnaires. Target sample sizes for our studies will fall within the recommended range for qualitative studies of this kind (i.e. 20–40 interviews) (28). In each study, participants will be offered a GBP20 prepaid card (https://www.b4bpayments.com) to offset their time taken to visit the centre for their interview.

To mitigate differences in interview style, all interviewers will receive training by N.L. and J.M. Each evaluation will have a target sample size; but this will also be pragmatic and will reflect data saturation. Saturation will be determined by discussing findings and themes that have emerged during the interviews and whether any new themes have recently emerged. Interviews will be transcribed verbatim. Participants will have the option to review their transcript and add any notes, comments, or corrections. The qualitative data analysis will follow iterative categorisation (IC)(22). All researchers and participants were unblind for each evaluation.

PATIENT AND PUBLIC INVOLVEMENT

The design of EXPO was conceived in collaboration with patient and public involvement representatives and were consulted throughout the trial in the design, conduct and upholding participant welfare. Patient public involvement representatives are members of the trial steering committee and the data management committee. Patients were not involvement in recruitment and conduct of the study. For each of the studies listed in this protocol, participants will have the option to review their transcript, make comments and corrects before analysis and they will be able to view and make any comments on preliminary results before publication to ensure research remains grounded in the patient's experience. Patient public involvement representative are thanked within the manuscript acknowledgements.

Data collection, analysis and reporting will adhere to the Consolidation Criteria for Reporting Qualitative Studies COREQ (29) and the Strengthening and Reporting of Observational Studies in Epidemiology (STROBE) (30) consensus guidelines.

Evaluation #1: Participants' experience of BUP-XR after 24-weeks

Procedure

This evaluation will be done at four trial centres (London, Newcastle, Solihull, and Dundee) with a target sample of 60 participants (15 per centre) to investigate participants' views of the delivery and effects of BUP-XR and will be theory-guided by the behavioural model for health service use. Consent can be obtained from December 2019 and recruitment is ongoing. On completion of the 24-week trial endpoint for participants allocated to BUP-XR, a member of the research team will approach the participant and describe the purpose of the evaluation, obtaining their written consent, and conducting a face-to-face, 30-45-minute interview. The topic guide will use the severity (OUD symptoms), complexity (individual and social functioning), and recovery strengths structure of the 14-item Addiction Dimensions for Assessment and Personalised Treatment (ADAPT) instrument developed for OUD measurement-based care (31).

The evaluation will utilise the following trial measures:
(1) BUP-XR status at interview (enrolled or discontinued);
(2) Number of BUP-XR injections received since enrolment;
(3) Self-reported opioid, cocaine and benzazepine use with UDS data for the past 3-months;
(4) OUD and cocaine use disorder (CUD) remission/status (DSM-5) (32).

Analysis

The IC analysis will be implemented in four steps. In the first *descriptive* step, each transcript will be deductively coded using ADAPT constructs, with residual data inductively coded. The codes will then be merged into headings and subheadings towards an emerging conceptual narrative. This narrative will be displayed in the form of a coding tree to ensure transparency. In the second *conceptualising* step, concepts from the descriptive analysis will be mapped onto the behavioural model for health service use (23). In the third *differentiating* step, similarities, and differences in participant experiences of BUP-XR will be investigated, highlighting any identified centre-level differences. To mitigate the risk of over-generalisation and to maintain nuance, concepts will be colour coded and mapped by centre. Quantitatively, the primary outcome and craving measures from the trial will be tabulated and reported alongside selected quotations from participants to

illustrate patterns of clinical response to BUP-XR. In the final *externalising* step, findings will be merged and evaluated in the context of the extent literature on OUD and health service evaluation.

Evaluation #2: Participants' experience of longer-term BUP-XR maintenance

Procedure

This evaluation will be done at two of the five centres (London and Newcastle) with a target sample of 30 participants (15 per centre) to investigate longer-term experience of BUP-XR. It will theory-guided by the HRQoL (24). Participants completing the trial endpoint who wish to receive continued BUP-XR maintenance (between 12–24 months from enrolment) will be eligible. On completion of the 24-week trial endpoint for participants allocated to BUP-XR who wish to receive further maintenance, a member of the research team will approach the participant and describe the purpose of the evaluation, obtaining their written consent for a face-to-face, ~30-minute interview at the centre. Consent was able to be obtained from June 2021 and recruitment is ongoing.
This evaluation will investigate clinical response using the trial outcomes and HRQoL (the latter the target outcome). The topic guide will follow the structure of the 39-item Opioid Substitution Treatment Quality of Life scale (OSTQOL) (33), which captures patients' views of their personal development, mental distress, social contacts, material wellbeing, treatment and experience of discrimination.

The following measures used in trial will also be collected:

(0) OSTQOL – structured questionnaire for the past month;
(2) BUP-XR status at interview (enrolled or discontinued);
(2) Number of BUP-XR injections received since enrolment;
(3) Self-reported opioid, cocaine and benzazepine use with UDS data for the past 3-months;
(4) OUD and CUD DSM-5 remission/status;
(5) Difficulties in Emotion Regulation – Short Form (DERS-SF) for the past 2-weeks (34);
(6) Patient Health Questionnaire (PHQ; 4-item) for the past 2-weeks (35);
(7) 15-item version of the PHQ assessing somatisation syndromes for the past 4-weeks (36).

Analysis

The IC analysis of the interview transcripts will proceed via descriptive, conceptualising, differentiating and externalising steps as followed in Evaluation 1. Initial deductive coding will use the concept structure of the OSTQOL (33) with mapping using the HRQoL model (24). For quantitative analyses, we will tabulate the 7 measures per centre and present bivariate correlations (alpha set at 5%). An exploratory mixed-effects multivariable linear regression will be done, with OSTQOL as the dependent variable and the seven clinical measures and personal demographic

characteristics (sex, age, and ethnicity) as covariables. Research centre will be included as a random intercept, and results will be presented with unadjusted and adjusted beta coefficients, with associated 95% confidence intervals. Covariables may be removed if there is evidence of multi-collinearity or other model fit problems that may be related to the small sample size.

Evaluation #3: Participants' experience of BUP-XR or SOC with PSI

Procedure

This is a single centre evaluation at the London centre with a target sample of 30 participants (15 allocated to BUP-XR and 15 allocated to BUP-SL or MET) to investigate the experience of trial medication plus adjunctive PSI over 24-weeks. It will theory-guided by the behavioural model for health service use. Participants completing the trial endpoint will be approached to consent for a face-to-face, ~30-minute interview at the centre. The interview topic guide will follow the structure of the ADAPT. This evaluation will utilise a repeated-measures set of clinical measures from the trial (**Table 1**).

The primary outcome measure will be reported every two weeks and at the baseline visit: Self-reported opioid, cocaine and benzodiazepine use will be validated with Urine Drug Screens (UDS). A PSI therapy session log will be recorded frequently throughout the trial, including type, format and duration of the therapy received. The number of days enrolled in study treatment and PSI engagement will be calculated when the participant reaches the study endpoint. Participants classified as 'engaged' will have attended at least one PSI appointment after the initial formulation. Recruitment for the quantitative aspect of the project ran from August 2019 to November 2021. Consent for the qualitative aspect could be obtained from December 2019 and is ongoing.

Table 1. Schedule of assessments for Evaluation 3

	Study week													
Measure	**B**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**
SCID-5-RV	X							X						X
BUP-XR		X		X		X		X		X		X		
SOC (BUP-SL or MET)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TLFB	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ALC-QFM	X													X
CEQ-F (H/C)	X			X		X		X		X		X		X
VAS-N (H/C)	X			X		X		X		X		X		X
VAS-W (H/C)	X			X		X		X		X		X		X
QIDS-SR	X			X				X						X
DERS-SF	X			X				X						X
WSAS	X			X				X						X
SURE				X				X						X
PRO-S	X													
PRO-I				X				X						X
ADAPT	X			X				X						X
CGI-S	X													
CGI-I				X				X						X
UDS			X	X	X	X	X	X	X	X	X	X	X	X
PSI – therapy log	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Note:

SCID-5-RV (Structured Clinical Interview for DSM-5 disorders – research version);

BUP-XR (extended-release buprenorphine);

SOC, standard-of-care, study comparator;

TLFB, time-line follow-back, calendar prompt interview;

ALC-QFM, alcohol quantity, frequency and maximum consumption;

CEQ-F (H/C), craving experience questionnaire, frequency for heroin and cocaine;

VAS-N (H/C), visual-analogue scale of perceived need for heroin and cocaine;

VAS-W (H/C), visual-analogue scale of perceived want for heroin and cocaine;

QIDS-SR, Quick Inventory of Depressive Symptomatology-Self-Report;

DERS-SF, Difficulties in Emotion Regulation Scale-Short Form;

WSAS, Work and Social Adjustment Scale;

SURE, Service User Recovery Evaluation;

PRO-S/I, patient reported outcome-severity and improvement;

ADAPT, Addiction Dimensions for Assessment and Personalised Treatment;

CGI-S/I, Clinical Global Impression – severity and improvement;

UDS, Urine Drug Screen;

PSI – therapy log

Analysis

The IC analysis of the interview transcripts will use the same four-step – descriptive, conceptualising, differentiating and externalising – approach in study one using the ADAPT (31). This will guide deductive coding and mapping into the behavioural model for health service use (23) instead of comparing centre-level groups and treatment groups will be compared along with 'engaged' and 'non-engaged' participants. For the quantitative analysis, measures will be tabulated by BUP-XR and SOC group (alpha set at 5%). An exploratory quantitative analysis of the primary and secondary outcome measures will be reported following the statistical analysis plan for the trial (17).

ETHICS AND DISSEMINATION

The EXPO trial started recruitment in 2019, therefore has been conducted in the context of the COVID-19 pandemic (37), which must be considered when assessing outcomes in treatment. The proposed projects include two health psychology models to aid analysis. The behavioural model of health service use (23) aims to assess how a population uses a health care system. If the healthcare utilization is appropriate, an individual's health is optimised and there is a lower burden on healthcare systems, meaning there are reduced levels of misuse, underuse and overuse of services. To achieve this, an investigation into the contextual and individual level influencing factors is crucial (39). The nature of qualitative research provides rich in-depth data and, therefore, is an appropriate methodology for assessing influencing factors that will map onto the behavioural model for health service use (23) and aid the evaluation of treatments for OUD.

The HRQoL (24) model is widely accepted across many health conditions (25-27). Using this model will enable patient comparison between treatment for OUD and other health-related conditions. This allows research, policymakers, and healthcare professions to assess areas of quality of life that are common across all health conditions and those that are OUD specific. The finding from these projects will be disseminated through peer-reviewed publications.

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AUTHORS' CONTRIBUTIONS

The design was conceived by NL (Research worker) and JM (Co-Clinical Lead). NL and JM drafted the initial and subsequent drafts of this manuscript. All authors contributed to the revision of the manuscript and consented to be authors. The views expressed in this article are the authors' and are not necessarily those of the funder. The funder will be invited to comment on research products, but will have no role in the analysis, interpretation, report writing, and the decision to submit reports for publication. NL took the final decision to submit the manuscript for publication.

ACKNOWLEDGEMENTS

This protocol paper represents independent, investigator-initiated research at King's College London and South London & Maudsley NHS Trust, Bangor University and collaborating NHS hospitals: Northumberland, Tyne & Wear NHS Foundation Trust; Birmingham & Solihull Mental Health NHS Foundation Trust; Greater Manchester Mental Health NHS Foundation Trust and Dundee Drug & Alcohol Recovery Service. The views expressed in this protocol paper are the authors' and are not necessarily those of the funder or sponsor. Kings College London and South London & Maudsley NHS Trust are the joint study sponsors and hold the indemnity insurance policy.

The authors wish to thank the members of the study oversight committees: TSC: Prof. Richard Holland, Head of Leicester Medical School and Professor of Public Health Medicine (Chair); Steve Taylor, Programme Manager; Public Health England ; Martin McCusker, PPI Representative; Jenny Bearn, Consultant Psychiatrist, Independent Advisor; Rory Gray, Senior Commissioning Officer Primary Care, Substance Misuse & Homeless Health; Lambeth Council and Christopher D'Souza, Lead Commissioner Substance Misuse, Primary Care and Homeless Health. DMC: Tim Millar, Professor of Substance Use and Addictions, University of Manchester (DMC Chair); Simon Skene, Professor of Medical Statistics, Director of Surrey Clinical Trials Unit and Clinical Research Facility (Independent Statistician); Dr John Dunn, Consultant in Addiction Psychiatry, Camden Specialist Drug Treatment Service (Independent Clinician); Paul Lennon (PPI Representative); April Wareham (PPI Representative).

FUNDING

The study was funded by Indivior (grant number: KCLEXPOINDV19). Kings College London and South London and Maudsley NHS Trust are the study sponsors and hold the indemnity insurance policy. The sponsor's representative will be Amy Holton, Quality Manager, King's Health Partners Clinical Trials Office, London.

COMPETING INTERESTS STATEMENT

M.K., J.M. and L.M. declare an unrestricted research grant at IoPPN and SLaM from Indivior via Action on Addiction for a randomised controlled trial of personalised psychosocial intervention in opioid agonist medication for OUD (published in 2019).

In the past three years, JM declares research grants from the National Institute for Health Research (NIHR; randomised controlled trial of depot naltrexone for OUD, and a randomised controlled trial of acamprosate for AUD), and the NIHR Biomedical Research Centre for Mental Health at South London and Maudsley NHS Mental Health Foundation Trust (SLaM; randomised controlled trial of novel cognitive therapy for cocaine use disorder). JM is a clinical academic consultant for the US National Institute on Drug Abuse, Centre for Clinical Trials Network. He declares an unrestricted research grant at IoPPN and SLaM from Indivior via Action on Addiction for a randomised controlled trial of personalised psychosocial intervention in opioid agonist medication for OUD (published in 2019). He has received honoraria and travel support from Reckitt-Benckiser (2016; treatment of OUD) and PCM Scientific and Martindale for the Improving Outcomes in Treatment of Opioid Dependence conference (2018 and 2021).

F.C. declares co-applicant status for the Scottish Drug Death Task Force Research Programme to the University of Stirling, exploring the utility and safety of benzodiazepine prescribing among people receiving opiate replacement therapy (BENZORT). Co-applicant for Chief Scientist Office Research Grant for u sing remote digital respiration monitoring for prevention of drug related deaths – evaluating the feasibility of establishing a virtual safe consumption facility. F.C. was also author for the Medical Research Scotland (VAC-1437-2019), Characteristics of non-fatal overdoses and associated risk factors in patients attending a specialist community-based substance misuse service.

All other authors have no interests to declare.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 4, 5
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	5
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	14
	5b	Name and contact information for the trial sponsor	14
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	6-10

Objectives	7	Specific objectives or hypotheses	6-10
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6-10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6, 7, 8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	5 (N/A)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	5 (N/A)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5 (N/A)
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6-10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6-10
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6-10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6-10

Methods: Assignment of interventions (for controlled trials)

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	5 (N/A)
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	5 (N/A)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5 (N/A)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6-10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	(N/A)
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	5 (N/A)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	6-10

	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	6-10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	5
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	5
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	5
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	5
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	5 (N/A)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	5
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	2
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Experience and response to a randomised controlled trial of extended-release injectable buprenorphine versus sublingual tablet buprenorphine and oral liquid methadone for opioid use disorder: protocol for a mixed-methods evaluation

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2022-067194.R1
Article Type:	Protocol
Date Submitted by the Author:	22-Sep-2022
Complete List of Authors:	Lowry, Natalie; King's College London Institute of Psychiatry Psychology and Neuroscience, Addictions Department; South London and Maudsley Mental Health NHS Trust Cowden, Fiona; Dundee Drug & Alcohol Recovery Service, Constitution House, Scotland, United Kingdom Day, Edward; Birmingham and Solihull Mental Health NHS Foundation Trust Gilvarry, Eilish; Northumberland Tyne & Wear NHS Foundation Trust Johnstone, Stacey; Dundee Drug & Alcohol Recovery Service Murray, Robbie; Northumberland Tyne & Wear NHS Foundation Trust Kelleher, Mike; King's College London Institute of Psychiatry Psychology and Neuroscience, Addictions Department; South London and Maudsley Mental Health NHS Trust Mitcheson, Luke; South London and Maudsley NHS Foundation Trust; King's College London Institute of Psychiatry Psychology and Neuroscience, Addiction Department Marsden, John; King's College London Institute of Psychiatry Psychology and Neuroscience, Addictions Department ; South London and Maudsley Mental Health NHS Trust
Primary Subject Heading:	Addiction
Secondary Subject Heading:	Pharmacology and therapeutics, Health services research, Patient-centred medicine, Qualitative research
Keywords:	Substance misuse < PSYCHIATRY, QUALITATIVE RESEARCH, Clinical trials < THERAPEUTICS

Experience and response to a randomised controlled trial of extended-release injectable buprenorphine versus sublingual tablet buprenorphine and oral liquid methadone for opioid use disorder: protocol for a mixed-methods evaluation

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ABSTRACT

Introduction: Opioid use disorder (OUD) is a debilitating and persistent disorder. The standard-of-care treatment is daily maintenance dosing of sublingual buprenorphine (BUP-SL) or oral methadone (MET). Monthly, extended-release, subcutaneous injectable buprenorphine (BUP-XR) has been developed to enhance treatment effectiveness. This study aims to investigate: the experiences of participants who have been offered BUP-XR (Evaluation 1); health-related quality-of-life among participants who have opted to receive BUP-XR longer-term (Evaluation 2); and the experiences of participants allocated to receive BUP-XR or BUP-SL or MET with the offer of adjunctive personalised psychosocial intervention (Evaluation 3).

Methods and analysis: Three qualitative-quantitative (mixed-methods) evaluations embedded in a five-centre, head-to-head, randomised controlled trial of BUP-XR versus BUP-SL and MET in the United Kingdom. Evaluation 1 is a four-centre interview anchored on an OUD-related topic guide and conducted after the 24-week trial endpoint. Evaluation 2 is a two-centre interview anchored on MOUD-specific quality-of-life topic guide conducted among participants after 12–24 weeks. Evaluation 3: single-centre interview after the 24-week trial endpoint. All evaluations include selected trial clinical measures, with Evaluation 2 incorporating additional questionnaires. Target participant recruitment for Evaluations 1 and 2 is 15 participants per centre (n=60 and n=30, respectively). Recruitment for Evaluation 3 is 15 participants per treatment arm (n=30). Each evaluation will be underpinned by theory, drawing on constructs from the behavioural model for health service use or the health-related quality-of-life model. Qualitative data analysis will be by iterative categorisation.

Ethics and dissemination: Study protocol, consent materials and questionnaires were approved by the London-Brighton and Sussex research ethics committee (reference: 19/LO/0483) and the Health Research Authority (IRAS project number: 255522). Participants will be provided with information sheets and informed written consent will be obtained for each evaluation. Study findings will be disseminated through peer-reviewed scientific journals.

Trial registration number: EU Clinical Trials Register, 2018-004460-63.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This is a qualitative-quantitative (mixed-methods) study, embedded within a randomised controlled trial, to investigate patient experience of extended-release injectable buprenorphine treatment to provide the patient perspective additional to trial outcome measures.
- The study will investigate patients' experience and response to extended-release injectable buprenorphine up to 24 months.
- This study does not recruit from a population attending third sector addiction services across England and Scotland.
- This research does not report experiences of people that declined to receive extended-release buprenorphine treatment before the 24-week EXPO trial endpoint, although it does aim to investigate discontinuation after study allocation and over 12–24 months.

INTRODUCTION

Opioid use disorder (OUD) is a debilitating and persistent disorder, characterised by continued use of non-medical opioids despite adverse physical and psychological harms (1). In the United Kingdom (UK) – and most countries with developed healthcare systems – sublingual (tablet) buprenorphine (BUP-SL; a partial μ opioid agonist) and oral (liquid) methadone (MET; a full μ opioid agonist) are the standard-of-care daily maintenance treatments (2). There is a long-established evidence-base from randomised controlled trials (RCT) and observational studies for the effectiveness of these medications for OUD (MOUD).

MOUD adherence is expected to help patients reduce or abstain from non-medical opioid use and improvement their health and social functioning (3). Retention in treatment is associated with a substantial reduction – but not a complete elimination – in the risk of unintentional fatal opioid poisoning (overdose) (4). Rates of overdose mortality among people in and out of MOUD are 1.4 and 4.6 per 1,000 person years for BUP-SL, and 2.6 and 12.7 per 1,000 person years in and out of MET, respectively (5).

In England, between April 2020 and March 2021, 140,863 individuals accessed National Health Service (NHS) and non-governmental community treatment clinics with OUD (6). Meta-analysis has shown that around 47% of patients complete episodes of MOUD treatment (6). Several patient-level factors appear to moderate retention. This includes negative attitudes (e.g. perceived stigma) towards supervised dosing of MOUD, and regard prescribing arrangements as inflexible to their needs (7). Some patients cycle through repeated periods of MOUD admission, discontinuation, and re-admission. Younger age, cocaine use, lower doses of MOUD, and criminal involvement have been shown to be associated with discontinuation from treatment (8). These associations reflect heterogeneity in the characteristics of the OUD treatment seeking population (9). Coexisting health and social problems – consequently or independent of OUD – add complexity to the planning and delivery of treatment and supporting medical and social services (10).

There is a long history of efforts to improve treatment effectiveness for OUD (11), with a recent call for adaptive measurement-based care (12, 13). In a contribution to this effort, the pharmaceutical industry has developed long-acting injectable BUP (14). Using ARTIGEL® (a polymer delivery technology), Indivior developed a monthly extended-release depot administered by subcutaneous injection (RBP-6000/Sublocade®) now licensed in Australia, North America and several European countries (BUP-XR herein) (15). The ***Ex***tended-release ***P***harmacotherapy for ***O***pioid use (EXPO) study is an ongoing, multi-centre, open-label, superiority RCT in England and Scotland to determine the effectiveness and cost-effectiveness of 24-weeks of BUP-XR versus BUP-SL and

MET (EU Clinical Trials Register, 2018-004460-63). EXPO is conducted in five NHS community addiction treatment centres in South London (Brixton), Solihull (West Midlands), Manchester, Newcastle, and Dundee. Participants are informed consenting adults (18 years and over) seeking maintenance MOUD. They will be randomly allocated to receive BUP-XR (the experimental condition) or BUP-SL or MET (the control condition) for 24 weeks (target sample is n=304). At the South London centre, there will be also an exploratory study in which patients are randomly allocated to receive BUP-XR and personalised psychosocial intervention or MET or BUP-SL and psychosocial intervention for 24 weeks.

With a one-week grace period after randomisation, the primary outcome for EXPO is days of abstinence from all non-medical opioids to the 24-week endpoint combined with up to 12 urine drug screen (UDS) negative tests for opioids. Participants will have the option to continue BUP-XR maintenance after the 24-week endpoint for up to 24 months. Secondary outcome measures include time enrolled in treatment; days abstinent from cocaine and illicit/non-medical benzodiazepines; and craving for heroin and cocaine. The EXPO trial protocol has been published (16).

There is an emergent qualitative literature on extended-release MOUD. Published evaluations include a qualitative study from Norway with 32 patients enrolled in extended-release naltrexone (an opioid antagonist) in which more than half of the sample (n=19) intentionally discontinued treatment before 12 weeks (17). Reported reasons for discontinuation included feeling 'unfulfilled' by the treatment, with disappointment expressed around not achieving abstinence recovery goals, and discovery that treatment did not eliminate opioid cravings.

In contrast, a qualitative study in Sweden with 32 patients enrolled in extended-release BUP reported high treatment satisfaction (18). Patients described a sense of increased freedom in their everyday life, an ability to travel, a sense of normality, reduced stigma, and a shift in their identity. There were also negative appraisals including medication side effects, shorter than anticipated medication effects, opioid withdrawal symptoms and cravings which motivated some to leave treatment.

In Australia, 30 patients who were enrolled in extended-release buprenorphine treatment, expressed having more freedom and the ability to accomplish study, work and caring roles (19). However, some study participants found it hard to control their use of other psychoactive substances, and some reported that the inability to divert or sell oral medication increased financial strain. In Scotland and Wales, 11 homeless individuals with experience of extended-release buprenorphine treatment described that they were able to avoid people that would risk drug use, and felt a sense of freedom and openness to new opportunities (20).

The present study will extend this literature with capture of a wider range of measures, and with longer follow-up. A mixed-methods design will be utilised to synergize qualitative and quantitative data. Mixed-methods studies have been recommended for the analysis of complex interventions, particularly RCTs, where an in-depth exploration of participants' experiences can provide valuable insights additional to the primary and secondary outcome measures (21).

An approach underpinned by theory is also important because this provides structure to the comparison of populations and different health related domains, and in this context will help to integrate findings within the wider literature on OUD treatment and health service evaluation (22). A theory-driven, mixed-methods approach was successfully applied to the analysis of cocaine craving in a recent RCT (23).

The present study will draw on theoretical constructs from the 14-item Addiction Dimensions for Assessment and Personalised Treatment (ADAPT) instrument developed for OUD measurement-based care (24); Andersen's behavioural model for health service use (25) with a focus on how patients regard the utility of MOUD and other health services; and the health-related quality-of-life model (HRQoL) (26), which has been applied to the study of many health conditions (27-29).

Study aims are to investigate: (A) The experiences of study participants who have been offered BUP-XR for 24 weeks (Evaluation #1); (B) The experiences and health-related quality of life of study participants who have opted to receive BUP-XR for 12–24 months (Evaluation #2); and (C) The experiences of study participants who have been offered BUP-XR or BUP-SL or MET with adjunctive personalised psychosocial intervention over 24 weeks (Evaluation #3).

METHODS AND ANALYSIS

Study design

This is a three-evaluation, qualitative-quantitative (mixed-methods) study embedded in a multi-centre RCT. All researchers and participants will be unblind.

Qualitative data for each evaluation will be obtained from in-depth, semi-structured (topic-guided), audio-recorded, personal interviews with trial participants. Identifiable information will be anonymised to maintain confidentiality. To mitigate differences in interview style, all interviewers will receive training by N.L. and J.M. All interviews will be transcribed verbatim.

Quantitative data for the study will be taken from trial measures – including MOUD enrolment status; BUP-XR injections received; self-reported opioid, cocaine and benzodiazepine use and urine drug screen (UDS) data; and OUD and cocaine use disorder (CUD) remission status (DSM-

5) (30) – as well as several standardised questionnaires included to address study aims. EXPO primary and secondary outcome measures will be tabulated and reported alongside selected quotations from participants to illustrate their responses to interventions.

Each evaluation will have a target sample size that will fall within the recommended range for qualitative studies of this kind (i.e. 15–30 interviews) (31); but recruitment may be capped if there is evidence of data saturation. Data saturation will be determined through investigator discussion of findings and themes that emerge during the interviews and whether no new themes have been identified. In each study, participants will be offered a GBP20 prepaid card (https://www.b4bpayments.com) to offset their time taken to visit the centre for their interview. Analysis of qualitative data will be done thematically and inductively by iterative categorisation (22).

Data collection, analysis and reporting will adhere to the Consolidation Criteria for Reporting Qualitative Studies COREQ (32) and the Strengthening and Reporting of Observational Studies in Epidemiology (STROBE) (33) consensus guidelines.

Patient and public involvement

Patient and public involvement representatives will be consulted throughout the EXPO trial on research design, procedures, and reporting of findings. They will be members of the trial steering committee and the data management committee. In this study, participants will have the option to review their interview transcript, make comments and request corrections before the analysis. They will also be able to make comments on results before publication to ensure this research is grounded in their experience.

Evaluation #1: The experiences of study participants who have been offered BUP-XR for 24 weeks

Procedure and measures

This evaluation will be done at four EXPO centres (Dundee, London, Newcastle, and Solihull) with a target sample of 15 participants per centre (n=60), to investigate participants' views of receiving BUP-XR and their experience and evaluation of its effects. On completion of EXPO's 24-week endpoint, trial participants will be approached by a member of the research team who will describe the purpose of the qualitative study, obtain their written consent, and conduct a face-to-face ~45-minute interview. The interview topic guide will use the OUD addiction severity, complexity (individual and social functioning), and recovery strengths constructs from the ADAPT. This evaluation will utilise the following EXPO measures: (1) BUP-XR status at interview (i.e. enrolled in ongoing maintenance or discontinued); (2) the number of BUP-XR injections received; (3) self-reported opioid, cocaine and benzodiazepine use with UDS data for the past 3-months (which will

provide the trial's primary opioid abstinence outcome and drug use secondary outcomes); and (4) OUD and CUD remission status. Measures are summarised in **Table 1**.

Table 1. Schedule of assessments for the three evaluations

				Study week													
Measure	**Evaluation #**	**B**	**R**	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**E**
SCID-5-RV	1,2,3	X								X						X	X
BUP-XR	1,2,3	X		X		X		X		X		X		X		X	X
TLFB	1,2,3	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
ALC-QFM	3	X														X	
VAS-N (H/C)	3	X				X		X		X		X		X		X	
VAS-W (H/C)	3	X				X		X		X		X		X		X	
CEQ-F (H/C)	3	X				X		X		X		X		X		X	
QUIDS-SR	3																
DERS-SF	2,3	X				X				X						X	
WSAS	3	X				X				X						X	
PHQ-15	2																X
PHQ-4	2																X
OSTQOL	2																X
SURE	3					X				X						X	
PRO-S	3	X															
PRO-I	3					X				X						X	
ADAPT	3	X				X				X						X	
CGI-S	3	X															
CGI-I	3					X				X						X	
UDS	2,3				X	X	X	X	X	X	X	X	X	X	X	X	X

B, baseline; **R**, randomisation; **E**, Extended BUP-XR study treatment for 12–24 months; **SCID-5-RV** (Structured Clinical Interview for DSM-5 disorders – research version); **BUP-XR**, extended-release buprenorphine (injections received and enrolment status); **TLFB**, time-line follow-back, calendar prompt interview; **ALC-QFM**, alcohol quantity, frequency and maximum consumption; **VAS-N (H/C)**, visual-analogue scale of perceived need for heroin and cocaine; **VAS-W (H/C)**, visual-analogue scale of perceived want for heroin and cocaine; **CEQ-F (H/C)**, Craving Experiences Questionnaire for heroin and cocaine; **QIDS-SR**, Quick Inventory of Depressive Symptomatology-Self-Report; **DERS-SF**, Difficulties in Emotion Regulation Scale-Short Form; **WSAS**, Work and Social Adjustment Scale; **PHQ-15/4**; Patient Health Questionnaire (15 item and 4 item); **OSTQOL**, Opioid Substitution Treatment Quality of Life scale; **SURE**, Service User Recovery Evaluation; PRO-S/I, patient reported outcome-severity and improvement; **ADAPT**, Addiction Dimensions for Assessment and Personalised Treatment; **CGI-S/I**, Clinical Global Impression – severity and improvement; UDS, Urine Drug Screen.

Analysis

The analysis will be implemented in four steps. In the first *descriptive* step, each transcript will be deductively coded using ADAPT constructs, with residual data inductively coded. The codes will then be merged into headings and subheadings working towards an emerging conceptual narrative. This narrative will be displayed in the form of a coding tree to ensure transparency. In the

second *conceptualising* step, concepts from the descriptive analysis will be mapped onto the behavioural model for health service use. In the third *differentiating* step, similarities, and differences in participant experiences of BUP-XR will be investigated, highlighting any identified centre-level differences. To mitigate the risk of over-generalisation and to maintain nuance, concepts will be colour coded and mapped by EXPO centre. Quantitatively, the primary outcome and craving measures from the trial will be tabulated and reported alongside selected quotations from participants to illustrate response to BUP-XR. In the final *externalising* step, findings will be merged and evaluated in the context of the extant literature.

Evaluation #2: The experiences and health-related quality of life of study participants who have opted to receive BUP-XR for 12–24 months

Procedure and measures

This evaluation will be conducted at two centres (London and Newcastle) with a target sample of 15 participants per centre (n=30), to investigate longer-term experience of BUP-XR. Participants completing the 24-week trial endpoint who wish to receive continued BUP-XR maintenance will be eligible. After 12–24 months from original enrolment in EXPO, participants will be approached, irrespective of whether they are still receiving BUP-XR treatment. At the centre, a member of the research team will approach the participant and describe the purpose of the evaluation, obtain their written consent, and conduct a face-to-face, ~30-minute interview. The interview topic guide will follow the structure of the 39-item Opioid Substitution Treatment Quality of Life scale (OSTQOL) (34), which captures patients' views of their personal development, mental distress, social contacts, material wellbeing, treatment and experience of discrimination. The evaluation will utilise the following measures: (1) OSTQOL – structured questionnaire for the past month; (2) BUP-XR status at interview (enrolled or discontinued); (2) Number of BUP-XR injections received since enrolment; (3) Self-reported opioid, cocaine and benzodiazepine use with UDS data for the past 3-months; (4) OUD and CUD remission/status; (5) Difficulties in Emotion Regulation – Short Form (DERS-SF) for the past 2-weeks (35); (6) 4-item Patient Health Questionnaire (PHQ-4) for the past 2-weeks (36); and (7) The 15-item version of the PHQ (PHQ-15) assessing somatisation syndromes for the past 4-weeks (37). Measures are summarised in **Table 1**.

Analysis

Analysis of the interview transcripts will proceed via descriptive, conceptualising, differentiating and externalising steps (as followed in Evaluation 1). Initial deductive coding will use the concept structure of the OSTQOL. The HRQoL model will be used in the conceptualising stage to map headings and subheadings onto the constructs of this model. For the quantitative analysis, each of the measures will be tabulated by centre with differences assessed using a conventional 5% criterion for statistical significance. An exploratory mixed-effects multivariable linear regression will be done, with OSTQOL as the dependent variable with personal demographic characteristics (sex,

age, and ethnicity) and selected clinical measures as covariables. Study centre will be included as a random intercept, and results will be presented with unadjusted and adjusted beta coefficients, with associated 95% confidence intervals. Covariables may be removed if there is evidence of multi-collinearity or other model fit problems that are anticipated with small sample size.

Evaluation #3: The experiences of participants who have been randomly allocated to receive BUP-XR or BUP-SL or MET with adjunctive personalised psychosocial intervention over 24 weeks

Procedure and measures

This is a single centre evaluation at the London centre, with a target sample of 15 participants for each allocation (BUP-XR or BUP-SL or MET) to investigate the experience of trial medication and adjunctive personalised psychosocial intervention over 24-weeks. Participants completing the trial endpoint will be approached to consent for a face-to-face, ~30-minute interview at the centre. The interview topic guide will follow the structure of the ADAPT. This evaluation will utilise a repeated measures set of clinical measures from the trial (**Table 1**).

The primary outcome measure will be reported every two weeks and at the baseline visit using a Timeline Followback interview: Self-reported opioid, cocaine and benzodiazepine use will be validated with Urine Drug Screens (UDS). A PSI therapy session log will be recorded frequently throughout the trial, including type, format and duration of the therapy received. The number of days enrolled in study treatment and PSI engagement will be calculated when the participant reaches the study endpoint. Participants classified as 'engaged' will have attended at least one PSI appointment after the initial formulation.

Analysis

The analysis of the interview transcripts will follow the same four-step – descriptive, conceptualising, differentiating, and externalising – procedure as in evaluations 1 and 2. The ADAPT will guide deductive coding. Difference between treatment groups and groups of 'engaged' and 'non-engaged' participants will be mapped onto constructs of the behavioural model for health service use model, during the conceptualisation stage. For the quantitative analysis, measures will be tabulated by BUP-XR and BUP-SL and MET with differences evaluated using a 5% criterion for statistical significance. An exploratory quantitative analysis of the primary and secondary outcome measures will be reported following the statistical analysis plan for EXPO.

Study status

This research is ongoing at the time of protocol submission. Recruitment of participants for Evaluation #1 has been open since December 2019 and is expected to be completed in December 2022. Data analysis is scheduled to commence in December 2022. Recruitment of participants for

Evaluation #2 has been open since June 2021 and is expected to be completed in December 2022. Data analysis is planned to commence in early 2023. Recruitment of participants for Evaluation #3 has been open since December 2019 and is expected to be completed in December 2022. Data analysis is planned to commence in early 2023.

ETHICS AND DISSEMINATION

The EXPO study protocol, consent forms and research questionnaires were approved by the London-Brighton and Sussex research ethics committee (reference: 19/LO/0483) and the Health Research Authority (IRAS project number: 255522). The EXPO trial is registered (EudraCT, 2018-004460-63). Prior to consenting, participants will be provided with a participant information sheet; informed written consent will be obtained for each evaluation in this research and signed by principal or appointed sub-investigator. The finding will be disseminated through publications in peer-reviewed scientific journals.

Contributors

The design was conceived by NL and JM. NL drafted the initial and subsequent drafts of this manuscript. NL, FC, ED, EG, SJ, RM, MK, LM, and JM. contributed to the revision of the manuscript and consented to be authors. The views expressed in this article are the authors' and are not necessarily those of the funder and sponsor. The funder will be invited to comment on research products, but will have no role in the analysis, interpretation, report writing, and the decision to submit reports for publication. NL took the final decision to submit the manuscript for publication.

Acknowledgements

This protocol paper represents independent, investigator-initiated research at King's College London and South London & Maudsley NHS Trust, Bangor University and collaborating NHS hospitals: Cumbria, Northumberland, Tyne & Wear NHS Foundation Trust; Birmingham & Solihull Mental Health NHS Foundation Trust; Greater Manchester Mental Health NHS Foundation Trust and Dundee Drug & Alcohol Recovery Service. Kings College London and South London & Maudsley NHS Trust are the joint study sponsors and hold the indemnity insurance policy.

The authors wish to thank the members of the study oversight committees: TSC: Prof. Richard Holland, Head of Leicester Medical School and Professor of Public Health Medicine (Chair); Steve Taylor, Programme Manager; Public Health England ; Martin McCusker, PPI Representative; Jenny Bearn, Consultant Psychiatrist, Independent Advisor; Rory Gray, Senior Commissioning Officer Primary Care, Substance Misuse & Homeless Health; Lambeth Council and Christopher D'Souza, lead Commissioner Substance Misuse, Primary Care and Homeless Health. DMC: Tim

Millar, Professor of Substance Use and Addictions, University of Manchester (DMC Chair); Simon Skene, Professor of Medical Statistics, Director of Surrey Clinical Trials Unit and Clinical Research Facility (Independent Statistician); Dr John Dunn, Consultant in Addiction Psychiatry, Camden Specialist Drug Treatment Service (Independent Clinician); Paul Lennon (PPI Representative); April Wareham (PPI Representative).

Competing interests

MK, JM and LM declare an unrestricted research grant at Institute of Psychiatry, Psychology & Neuroscience, King's College London and South London and Maudsley NHS trust from Indivior via Action on Addiction for a randomised controlled trial of personalised psychosocial intervention in opioid agonist medication for OUD (published in 2019).

In the past three years, JM declares research grants from the National Institute for Health Research (NIHR; randomised controlled trial of depot naltrexone for OUD, and a randomised controlled trial of acamprosate for AUD), and the NIHR Biomedical Research Centre for Mental Health at South London and Maudsley NHS Mental Health Foundation Trust (SlaM; randomised controlled trial of novel cognitive therapy for cocaine use disorder). JM is a clinical academic consultant for the US National Institute on Drug Abuse, Centre for Clinical Trials Network. He has received honoraria and travel support from Reckitt-Benckiser (2016; treatment of OUD) and PCM Scientific and Martindale for the Improving Outcomes in Treatment of Opioid Dependence conference (2018 and 2021).

FC declares co-applicant status for the Scottish Drug Death Task Force Research Programme to the University of Stirling, exploring the utility and safety of benzodiazepine prescribing among people receiving opiate replacement therapy (BENZORT). Co-applicant for Chief Scientist Office Research Grant for using remote digital respiration monitoring for prevention of drug related deaths – evaluating the feasibility of establishing a virtual safe consumption facility. FC was also author for the Medical Research Scotland (VAC-1437-2019), Characteristics of non-fatal overdoses and associated risk factors in patients attending a specialist community-based substance misuse service.

NL, ED, EG, SJ and RM have no interests to declare.

FUNDING

The study was funded by Indivior (grant number: KCLEXPOINDV19). Kings College London and South London and Maudsley NHS Trust are the study sponsors and hold the indemnity insurance policy. The sponsor's representative will be Amy Holton, Quality Manager, King's Health Partners Clinical Trials Office, London.

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SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 5
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 10
	5b	Name and contact information for the trial sponsor	11, 12
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	11, 12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-10
	6b	Explanation for choice of comparators	6-10

Objectives	7	Specific objectives or hypotheses	6-10
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6-10
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6-10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	6-10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	(N/A)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	(N/A)
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	6-10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6-10
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6-10, 15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6-10

Methods: Assignment of interventions (for controlled trials)

Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6-10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	(N/A)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	(N/A)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6-10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6-10
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6-10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	6-10

	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	6-10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	4
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	2
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6-10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	5 (N/A)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	6-10
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	5
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.