



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

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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 UK. 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 medications for opioid use disorder-specific quality-of-life topic guide conducted among participants after 12–24 months. 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

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, although it does aim to investigate discontinuation after study allocation and over 12–24 months.

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 2018-004460-63.

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 UK—and most countries with developed healthcare systems—sublingual buprenorphine (BUP-SL; tablet, 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 (RCTs) and observational studies for the effectiveness of these medications for opioid use disorder (MOUDs).

MOUD adherence is expected to help patients reduce or abstain from non-medical opioid use and improve 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 1000 person years for BUP-SL, and 2.6 and 12.7 per 1000 person years in and out of MET, respectively.⁵

In England, between April 2020 and March 2021, 140863 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 (eg, 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 readmission. 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 (extended-release, subcutaneous injectable buprenorphine (BUP-XR) herein).¹⁵ The Extended-release Pharmacotherapy for Opioid use (EXPO) study is an ongoing, multicentre, 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 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 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 emergent qualitative literature on extended-release MOUD. Published evaluations include a qualitative study from Norway with 13 patients that have received one to four doses of extended-release naltrexone (an opioid antagonist) explored reasons for discontinuing treatment.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 buprenorphine 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 the 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 used to synergise 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 care²⁴; Andersen's behavioural model for health service use²⁵ 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 (1) the experiences of study participants who have been offered BUP-XR for 24 weeks (evaluation 1); (2) 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

(3) 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 multicentre RCT. All researchers and participants will be unblind.

Qualitative data for each evaluation will be obtained from in-depth, semistructured (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 NL and JM). 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 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 (ie, 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 follow iterative categorisation methodology.²²

Data collection, analysis and reporting will adhere to the Consolidation Criteria for Reporting Qualitative Studies³² and the Strengthening and Reporting of Observational Studies in Epidemiology³³ 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, South 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 min 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 use the following EXPO measures: (1) BUP-XR status at interview (ie, 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](#).

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 overgeneralisation and to maintain nuance, concepts will be colour coded and mapped by EXPO centre. Quantitatively, the primary

Table 1 Schedule of assessments for the three evaluations

| Measure | Evaluation number | B | R | Study week | | | | | | | | | | | | E | |
|-------------|-------------------|---|---|------------|---|---|---|---|----|----|----|----|----|----|----|---|----|
| | | | | 1 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | | 24 |
| SCID-5-RV | 1, 2 and 3 | X | | | | | | | | | X | | | | | X | X |
| BUP-XR | 1, 2 and 3 | X | | X | | X | | X | | X | | X | | X | | X | X |
| TLFB | 1, 2 and 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 | X |
| VAS-W (H/C) | 3 | X | | | | X | | X | | X | | X | | X | | X | X |
| CEQ-F (H/C) | 3 | X | | | | X | | X | | X | | X | | X | | X | X |
| QIDS-SR | 3 | | | | | | | | | | | | | | | | |
| DERS-SF | 2 and 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 and 3 | | | | X | X | X | X | X | X | X | X | X | X | X | X | X |

ADAPT, Addiction Dimensions for Assessment and Personalised Treatment; ALC-QFM, alcohol quantity, frequency and maximum consumption; B, baseline; BUP-XR, extended-release, subcutaneous injectable buprenorphine; CEQ-F (H/C), Craving Experiences Questionnaire for Heroin and Cocaine; CGI-I, Clinical Global Impression-Improvement; CGI-S, Clinical Global Impression-Severity; DERS-SF, Difficulties in Emotion Regulation Scale-Short Form; E, extended BUP-XR study treatment for 12–24 months; OSTQOL, Opioid Substitution Treatment Quality of Life Scale; PHQ-4, 4-Item Patient Health Questionnaire; PHQ-15, 15-Item Patient Health Questionnaire; PRO-I, patient reported outcome-improvement; PRO-S, patient reported outcome-severity; QIDS-SR, Quick Inventory of Depressive Symptomatology-Self-Report; R, randomisation; SCID-5-RV, Structured Clinical Interview for DSM-5 Disorders-Research Version; SURE, Service User Recovery Evaluation; TLFB, time-line follow-back, calendar prompt interview; UDS, urine drug screen; VAS-N/W (H/C), Visual Analogue Scale of Perceived Need/Want for Heroin and Cocaine; WSAS, Work and Social Adjustment Scale.

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 (South 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 min 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 well-being, treatment and experience of discrimination. The evaluation will use the following measures: (1) OSTQOL—structured questionnaire for the past month; (2) BUP-XR status at interview (enrolled or discontinued); (3) number of BUP-XR injections received since enrolment; (4) self-reported opioid, cocaine and benzodiazepine use with UDS data for the past 3 months; (5) OUD and CUD remission/status; (6) Difficulties in Emotion Regulation Scale-Short Form for the past 2 weeks³⁵ (7) 4-Item Patient Health Questionnaire for the past 2 weeks³⁶; and (8) the 15-Item Patient Health Questionnaire 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 multicollinearity 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 South 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 min interview at the centre. The interview topic guide will follow the structure of the ADAPT. This evaluation will use a repeated measures set of clinical measures from the trial (table 1).

The primary outcome measure will be reported every 2 weeks and at the baseline visit using a Timeline Followback interview: self-reported opioid, cocaine and benzodiazepine use will be validated with a UDS. A Psychosocial intervention 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 psychosocial intervention engagement will be calculated when the participant reaches the study endpoint. Participants classified as 'engaged' will have attended at least one psychosocial intervention appointment after the initial formulation.

Analysis

The analysis of the interview transcripts will follow the same four-step procedure—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 the principal or appointed subinvestigator. The finding will be disseminated through publications in peer-reviewed scientific journals.

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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.

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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 (RCT) of personalised psychosocial intervention in opioid agonist medication for OUD (published in 2019). In the past 3 years, JM declared research grants from the National Institute for Health Research (NIHR; RCT of depot naltrexone for OUD and an RCT of acamprosate for AUD), and the NIHR Biomedical Research Centre for Mental Health at South London and Maudsley NHS Mental Health Foundation Trust (RCT 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 coapplicant 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. Coapplicant 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.

Patient and public involvement Patients and/or the public were involved in the design, conduct, reporting or dissemination plans of this research. Refer to the Methods and analysis section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by London-Brighton and Sussex research ethics committee reference number/ID:19/LO/0483Health Research Authority (IRAS project number: 255522). Participants gave informed consent to participate in the study before taking part.

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