BMJ Open

Trial protocol of an open-label pilot study of oral naltrexone–bupropion combination pharmacotherapy for the treatment of methamphetamine use disorder (the NABU trial)

Krista J Siefried ,[1,2,3,4] Liam Acheson ,[1,2,3,4] Brendan Clifford ,[1,2,3,4] Carl Moller,[1] Jonathan Brett,[5,6] Michael Christmass,[7] Adrian John Dunlop,[4,8,9] Paul S Haber,[4,10,11] Didier Jutras-Aswad,[12,13] Nicholas Lintzeris,[4,10,14] Kirsten Morley ,[10,11] Steven Shoptaw,[15] Madhukar H Trivedi,[16] Nadine Ezard [1,2,3,4]

To cite: Siefried KJ, Acheson L, Clifford B, *et al*. Trial protocol of an open-label pilot study of oral naltrexone–bupropion combination pharmacotherapy for the treatment of methamphetamine use disorder (the NABU trial). *BMJ Open* 2025;**15**:e092032. doi:10.1136/bmjopen-2024-092032

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-092032).

Received 05 August 2024
Accepted 17 January 2025

For numbered affiliations see end of article.

Correspondence to
Dr Krista J Siefried;
Krista.Siefried@svha.org.au

ABSTRACT

Introduction Methamphetamine use disorder is a global public health concern with no approved pharmacotherapies for its treatment. One recent randomised controlled trial conducted in the USA examined a combination of bupropion and naltrexone not readily available globally. Here, we report a trial protocol for an oral formulation of combined naltrexone and bupropion.

Methods and analysis This single-arm, open-label pilot study will assess the safety and feasibility of oral naltrexone and bupropion (40 mg/450 mg daily in divided doses) in adults with methamphetamine use disorder. Participants (n=20) will be outpatients of a stimulant treatment program at an inner-city hospital in Sydney, Australia. The primary endpoint is Day 84. Participants will attend weekly study visits from Baseline to Week 12 and a follow-up telephone visit at Week 16. All participants will receive treatment as usual, such as psychosocial therapy. Primary outcomes are safety (measured by treatment-emergent adverse events (AEs)/adverse reactions) and feasibility (measured by the time taken to recruit, the proportion of ineligible participants, retention in the study and study medication adherence). Secondary outcomes will assess methamphetamine use, craving and withdrawal; treatment goals and expectations; physical and psychological well-being; depression and anxiety; and treatment satisfaction. Qualitative interviews will assess the acceptability of the intervention and outcome measures.

Ethics and dissemination This study received ethics approval from the St Vincent's Hospital Human Research Ethics Committee (2023/ETH00549). Results will be submitted to peer-reviewed journals and scientific conferences, and a video abstract will be created to ensure that the findings are accessible to participants and people who use methamphetamines.

Trial registration number ANZCTR: ACTRN12623000866606 (protocol V.2.1 dated 08 April 2024).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study assesses a formulation of oral bupropion and naltrexone in combination in adults with methamphetamine use disorder.
⇒ The study methods incorporate quantitative analysis of safety and feasibility and qualitative analysis of participant experiences on the trial, to ensure consumer input to any further research.
⇒ This study is not powered to determine efficacy, and long-term outcomes will not be studied.

INTRODUCTION

Methamphetamine use disorder (MAUD) presents a significant public health concern globally,[1] impacting individuals, families and communities. The prevalence of MAUD in Australia is among the highest in the world.[1] MAUD is associated with increased mortality and morbidity, including cardiovascular events, risk of blood-borne infections, cognitive function and mental health complications such as psychosis and depression. Social issues associated with methamphetamine include difficulty maintaining employment and breakdown in families and relationships.[2–4]

Despite efforts to improve outcomes for people living with MAUD, interventions remain limited, primarily involving psychosocial therapies such as cognitive behavioural therapy (CBT). Evidence also supports contingency management, with scale-up occurring primarily in US government-sponsored health plans. A recent Cochrane review found that as compared with treatment as usual, psychosocial therapy does not increase

rates of abstinence, but it does demonstrate an effect on reducing early treatment discontinuation.[5] Pharmacotherapeutic interventions have likewise delivered limited treatment effects, with studies exploring pharmacotherapies that target the neurobiological mechanisms underlying MAUD.[6] Trials of pharmacotherapies are limited by low adherence rates.[6] Further, self-reported methamphetamine use, though subject to recall bias, correlates well with biological testing in clinical trials.[7] In draft guidance, the Food and Drug Administration supports daily reports of methamphetamine use.[8] However, an accepted self-report measure is the timeline follow-back method, validated for past 28 days[9] and past 7 days use.[8] Real-time data collection could enhance the accuracy of measures of adherence and methamphetamine use in clinical trials.

Bupropion hydrochloride is an atypical antidepressant and norepinephrine reuptake inhibitor with stimulant-like actions, effective in treating nicotine dependence.[12 13] Bupropion monotherapy has been investigated as a pharmacotherapy for the treatment of amphetamine-type stimulant use disorder. A systematic review and meta-analysis of eight randomised controlled trials (1239 participants) found that those randomised to bupropion were more likely to reduce their use of amphetamine type stimulants and less likely to report end-of-treatment stimulant cravings.[14] However, studies were rated to have low-quality evidence and required larger more diverse samples.[14] One proposed theoretical mechanism of action is that because bupropion acts as a selective inhibitor of neuronal reuptake of norepinephrine and dopamine,[15] it may potentially ameliorate symptoms of methamphetamine withdrawal.[16 17] Naltrexone, an opioid-receptor antagonist, is effective for the treatment of both opioid and alcohol use disorders.[18] Animal studies suggest the endogenous opioid system's involvement in methamphetamine-seeking behaviour,[19] and it is hypothesised that naltrexone may attenuate the reinforcing effects of methamphetamine or cue-induced craving.[20 21] However, naltrexone monotherapy has been examined for MAUD and demonstrated conflicting results.[6]

One promising study emerging from the USA examined a combination of bupropion and naltrexone. That study reported that participants randomised to treatment (at either a first stage or adapted, second randomisation) had greater treatment effect (characterised as three of four urines negative for methamphetamine in the last 2 weeks of treatment) than those randomised to placebo.[10] Following this, the American Society of Addiction Medicine/American Academy of Addiction Psychiatry released clinical practice guidelines for the management of stimulant use disorder[11] recommending bupropion in combination with naltrexone be considered for the management of amphetamine type stimulant use disorder.[11]

The US study conducted by Trivedi *et al*[10] thus represents a new combination that may deliver stronger outcomes than either medication can on its own. In other therapeutic indications, a combination of extended-release naltrexone (32 mg)/bupropion (360 mg) led to significant weight loss in treatment of overweight/obesity.[22] For this reason, it is approved for this indication in the USA, Canada, Europe and Australia.[23] In theory, this improves access to this formulation.

The Trivedi study used an extended-release injectable naltrexone (380 mg every 3 weeks) and oral extended-release bupropion (450 mg daily). However, injectable naltrexone is not widely available outside the USA, Europe, Russia and the UK. Even within the USA, it is estimated to cost US$1000–US$1700 per dose,[24] rendering its likely uptake inequitable. Similarly, access to extended-release bupropion is limited outside the USA, with immediate or sustained release formulations more widely available. Therefore, accessible formulations are needed for bupropion/naltrexone treatment. In addition, countries with access to the aforementioned formulations may benefit from cheaper alternatives. This study seeks to use formulations currently available in Australia. Repurposing existing medications leverages existing data and safety profiles in applying them in new contexts and may lead to faster pathways to registration,[25] and are within reach of investigator-initiated trials that lack industry sponsorship.

OBJECTIVES

This study aims to determine the safety and feasibility of orally administered combination naltrexone/bupropion pharmacotherapy over 84 days for people with MAUD, in an outpatient setting.

Secondary objectives are to explore changes in methamphetamine use, cravings and withdrawal, other drug use, treatment satisfaction, physical and psychological well-being, depression and anxiety, and study medication adherence over the intervention period. The study also aims to examine the feasibility and acceptability of measuring self-reported methamphetamine use and study medication adherence via a smartphone app, and the Substance Use Recovery Goals and Expectations questionnaire[26] for measuring motivation for treatment.

METHODS

Trial design

This study is an open-label, single-arm pilot clinical trial. This paper reports on the study protocol in line with the Standard Protocol Items: Recommendations for Interventional Trials guidelines,[27] a checklist for which is available in online supplemental table 1.

Study setting

The study will be conducted in an outpatient stimulant treatment clinic, located in the Alcohol and Drug Service at St Vincent's Hospital, Sydney, Australia. St Vincent's Hospital Sydney is the study sponsor and is an acute care public teaching hospital. Participants will be recruited

Table 1 Eligibility criteria

Inclusion criteria	Exclusion criteria
All participants must/must be:	All participants must not:
► ≥18 years of age	► Be currently pregnant, breastfeeding or planning on becoming pregnant during the course of the study
► Able to provide informed consent	► Have presence of any psychiatric or physical comorbidity that would interfere with study participation
► Meet DSM-5-TR diagnostic criteria for Stimulant Use Disorder – Amphetamine-Type Substance (methamphetamine), as determined by a specialist in addiction medicine or psychiatry	► Have coexisting dependence on or withdrawal from alcohol, non-prescribed benzodiazepines or GHB, or undergoing treatment for any other substance use disorder which in the opinion of the site principal investigator would interfere with study participation (with the exception of cannabis and nicotine)
► Opioid-free for at least 7 days by self-report	► Be currently receiving opioid analgesics, or: 1. Dependent on opioids, 2. In acute opioid withdrawal, or 3. Has an anticipated need for opioid-containing medications at any point during the study (eg, planned surgery)
► Provide a urine drug screen point of care test positive for methamphetamines (during screening) and negative for opioids (during screening, repeated on the first day of study drug)	► Likely or planned surgery, travel, incarceration or other engagement during the study period that may interfere with study participation
► Willing to avoid pregnancy for study duration if a person of childbearing potential	► Have a history of sensitivity to naltrexone, bupropion or any other components of investigational product
► Willing and able to comply with all study requirements, including the ability to store study medications securely	► Be currently treated with any other preparation containing bupropion or naltrexone
► Agree to use a smartphone to self-report daily adherence to the provided medication and daily methamphetamine use	► Have acute hepatitis, liver failure or liver impairment (aspartate aminotransferase or alanine transaminase >5 times upper limit of normal (ULN), total bilirubin>ULN)
	► Have a seizure disorder or any history of seizures
	► Have a known CNS tumour
	► Have a current or previous diagnosis of bulimia or anorexia nervosa
	► Be concomitantly prescribed MAOIs (at least 14 days should elapse between discontinuation of MAOIs and initiation of treatment with the investigational product)
	► Have hypertension uncontrolled by a single antihypertensive agent
	► Currently enrolled in another treatment trial of MAUD or clinical trial which would interfere in participation in this study as determined by the PI

CNS, Central Nervous System; DSM-5 TR, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision; GHB, gamma-hydroxybutyrate; MAOI, monoamine oxidase inhibitor; MAUD, methamphetamine use disorder; PI, principal investigator.

from patients seeking treatment at the clinic, referrals from nearby services and a social media campaign.

Sample size

The study aims to examine the feasibility and safety of the methods and will recruit 20 participants. Allowing for problems with a prevalence of 10% (screen failures, AEs), and 20 participants will ensure these will be identified (with 85% confidence).[28] This will allow for descriptive analysis and accounts for potential attrition.[29] The study is not powered to determine efficacy, and we will not conduct hypothesis testing, thus no power calculation was performed.[30] Given larger studies exist,[10 14] it is not intended that this pilot study will be used to inform the power calculation for a larger trial, due to the risk of skewed data in small samples.[30 31]

Eligibility criteria

Eligible participants will be adults with MAUD. They must satisfy the inclusion and exclusion criteria set out in table 1.

Intervention

Participants will receive oral extended-release combination naltrexone hydrochloride and bupropion hydrochloride (8 mg/90 mg).[32] A 5-day dose escalation period will commence with one tablet on Day 1, increasing to the investigational dose of five tablets (three in the morning and two in the evening) by Day 5, which commences the target maintenance dose of 40 mg/450 mg. The dose escalation period allows a participant to adjust to the medication and is slightly longer than the 3-day period examined by Trivedi *et al*,[10] but less gradual than in weight loss studies.[32] The primary endpoint will be Day 84 (the last day at the highest dose of the study drug). A 5-day taper period will commence on Day 85, with medication

Table 2 Study drug schedule

Study day	Morning dose (n tablets)	Evening dose (n tablets)	Total daily dose (mg naltrexone/ mg bupropion)
1	1	0	8/90
2	1	1	16/180
3	2	1	24/270
4	2	2	32/360
5–84	3	2	40/450
85	2	2	32/360
86	2	1	24/270
87	1	1	16/180
88*	1	0	8/90
89	0	0	0

*Day 88 is the final study drug dose.

ceasing by Day 89. While there was no evidence of a withdrawal syndrome following discontinuation of use in trials associated with weight loss (at a dose of bupropion/naltrexone: 32 mg/360 mg),[32] a conservative approach was taken to include a taper to allow participants to adjust to discontinuation. The study drug schedule is shown in table 2. The pharmacological intervention is delivered alongside standard-of-care counselling and case management provided to all patients attending the clinic for the management of stimulant use. Standard-of-care counselling involves evidence-based motivational interviewing and CBT,[5] delivered in person or via telehealth at weekly intervals. It is a publicly funded, person-centred service, and can continue as clinically indicated following completion of/withdrawal from the trial.

Study drug dose selection

Research comparing the pharmacokinetics of oral naltrexone (50 mg daily for 28 days) and intramuscular injectable long-acting naltrexone (380 mg once every 28 days) (such as that used in the Trivedi study[10]) demonstrated systemic naltrexone exposure of approximately four times greater for the intramuscular versus oral route of administration.[33] Conversely, systemic exposure to naltrexone's primary active metabolite (6β-naltrexol) is 3.4 times lower following intramuscular administration compared with oral dosing[33] as unlike orally administered naltrexone, intramuscular naltrexone does not undergo first-pass metabolism in the liver. We, therefore, selected a dose of naltrexone available in the fixed-dose oral formulation combination with bupropion closest to the 50 mg naltrexone equivalency data.

In Australia, bupropion is approved for use in nicotine dependence to a maximum dose of 300 mg daily but is used off-label for the treatment of depressive disorders.[12] In other markets where bupropion is licenced for use in depression, such as the USA, a maximum daily dose of 450 mg is recommended.[34]

In selecting a combined product, we sought to support adherence to both components including the non-psychoactive component (naltrexone). The combined product (Contrave 8/90) is registered in Australia for weight reduction in adults with obesity at a maximum dose of two tablets two times per day (32 mg naltrexone and 360 mg bupropion daily). This study will use a maximum dose of three tablets in the morning and two tablets in the afternoon (40 mg naltrexone and 450 mg bupropion daily). Study drug will be prepared by the St Vincent's Hospital Sydney clinical trials pharmacist in medication packs containing 1 week's supply for the induction period, then for the remainder of the study two packs containing 1 week's supply each per fortnight. These will be separated into morning and evening doses for each day. Packs will contain a maximum of 35 tablets each.

Adherence

At fortnightly study drug collection, prior medication packs will be collected by study staff to verify adherence by pill counts. In addition, a study smartphone ecological momentary assessment (EMA) application ('app') will be registered to each participant[35] to collect data daily. Participants will have an option to install the app on their personal mobile phone, or to be provided with a study mobile phone. The app will be registered to their study participant identification, and a push notification will be sent daily asking if the participant had taken their prescribed dose in the previous day, and if not how much was taken and why they did not take their prescribed dose. Responses to the app will be compared with responses to weekly Simplified Medication Adherence Questionnaire (SMAQ) adherence questionnaire[36] responses.

Stopping criteria

If a participant experiences a Grade 3 or Grade 4 AE[37] considered to be causally related to the study medication, no further study medication will be dispensed until the participant has been reviewed by the site principal investigator (PI). If the AE is resolved to the satisfaction of the PI, the dose can be recommenced and the participant will be reviewed the subsequent day. If the AE is not resolved or recurs after recommencing the study medication, the site PI will consider ceasing the medication and withdrawing the participant from the treatment component of the study. Unless they revoke their consent, all participants withdrawn from treatment will continue to be followed as intention to treat.

Outcomes

The primary outcomes are safety and feasibility. Safety will be assessed by treatment-emergent AEs/adverse reactions through to the final study visit. These will be described by seriousness, severity, causality and expectedness.[38 39] Participants will be asked to provide information about any treatment-emergent AEs, in addition to being encouraged to provide any information spontaneously at weekly study visits with study coordinators (registered

Table 3 Secondary outcomes

Outcome	Measure	Time point
Self-reported days of methamphetamine use (including mode, frequency, dose)	Ecological momentary assessment by smartphone app[35]	Baseline to Day 84
Self-reported change in days of methamphetamine and other substance use	Timeline follow-back method[9]	Over the past 28 days from baseline to days 28, 56, 84
Proportion of methamphetamine-positive point-of-care urine drug screens	Point of care urine drug screens	Weekly
Treatment goals and expectations	Substance Use Recovery Goals and Expectations – 'SURGE' questionnaire[26]	Baseline, Days 28, 56, 84, 112
Change in physical and psychological well-being scores	Promis-29[45]	From baseline to Day 84
Change in depression and anxiety	DASS-21[46]	From baseline to Day 84
Changes in methamphetamine craving	Visual Analogue Scale (CVAS)[47]	From baseline to Day 84
Changes in withdrawal symptoms	Amphetamine Withdrawal Questionnaire[44]	From baseline to Day 84
Treatment satisfaction	TSQM-II[49]	Week 12
Acceptability of the intervention	Qualitative interviews	Week 12–16
Feasibility and acceptability of smartphone app data collection	Qualitative interviews	Week 12–16

CVAS, Craving Visual Analogue Scale; DASS-21, Depression Anxiety Stress Scales - 21 Items; Promis-29, Patient-Reported Outcomes Measurement Information System - 29; TSQM-II, Treatment Satisfaction Questionnaire for Medication II.

nurses) and study doctors. Following prompted or self-reported identification of AE's, the study coordinator or study doctor will record these into the study database.[40] Seriousness is predetermined by the National Health and Medical Research Council of Australia as any AE that results in death, is life-threatening, requires hospitalisation (not including planned hospitalisations for an unrelated procedure or underlying condition) or prolongation of hospitalisation, or results in persistent or significant disability or incapacity or is a congenital abnormality/birth defect.[39] Severity will be ranked from Grade 1 (mild event) through Grade 5 (death).[37] Causality and expectedness will be determined by the site PI. This assessment will take into consideration the known risks of the study medications, per the product label and the participant's medical history/comorbidities. All AE's will receive final sign-off by the site PI.

Feasibility will be assessed by (1) the time taken to recruit the sample; (2) the proportion of ineligible participants at pre-screening and screening; (3) retention rate in study; and (4) medication adherence measured by pill counts, app responses and weekly SMAQ questionnaire.[36]

We did not set safety and feasibility thresholds due to the inherent biases of an open-label pilot study.[41 42] Setting such thresholds prematurely could lead to incorrect assumptions about the study's success or failure.[43] Instead, we aim to present descriptive results to support decision-making for future larger studies.

Secondary outcomes are described in table 3. Importantly, data on participant experiences will be collected through qualitative interviews, which have been demonstrated as a rich resource for improving study design when moving from a pilot to a randomised trial.[44]

Participant timeline

Potential participants who express interest in the study will be prescreened by phone. Those who meet basic criteria will proceed to informed consent, after which they will be formally screened for eligibility. The screening period is permitted to last up to 2 weeks; however, the following assessments must be completed within 24 hours of the first dose of study drug: urine for human chorionic gonadotropin; urine drug screen point of care (all drugs—must be negative for opioids); and timeline follow-back[9] for methamphetamines, opioids, alcohol and cigarettes/nicotine in the past 28 days.

Eligible participants will be enrolled in the study. Baseline assessments to characterise the sample include the Wender Utah Rating Scale[50] to retrospectively evaluate the presence of childhood Attention-deficit/hyperactivity disorder (ADHD) symptoms and the ENRICHD Social Support Inventory[51] to assess social support. History of suicidal ideation or suicide attempts will be collected by the Columbia Suicide Severity Rating Scale (C-SSRS lifetime).[52] This will allow any AEs relating to suicidal ideation to be assessed in subsequent visits by the C-SSRS since last visit form.[52] Participants will attend weekly clinic reviews, receive fortnightly medication packs and any concomitant treatment (eg, psychosocial care) for the duration of the study. Semi-structured interviews will be conducted following the intervention, between Weeks 12–16. The interview guide includes themes of motivation to seek treatment for methamphetamine use and to join

a trial, experiences of being on the trial, perception of the trial medications (pill burden, side effects, frequency of dosing, satisfaction levels, etc) and the trial design (frequency of visits, study assessments). Experiences with the smartphone EMA app to collect adherence and methamphetamine use data will also be explored. The full participant schedule of assessments is outlined in online supplemental table 2.

Patient and public involvement

This study is in response to a national priority setting study for clinical research to address methamphetamine use.[53] It involved people with lived and living experience, and those who care about them, to drive the research agenda. One of the key priorities was pharmacotherapy for methamphetamine use disorder.[53] As this is a pilot study, we are undertaking qualitative interviews, to ensure that participant perspectives on the study design and conduct are incorporated in a larger, randomised controlled trial should this study demonstrate safety and feasibility.

Reimbursement

Participants will be reimbursed for participating, in accordance with Australian guidelines for appropriate and equitable payment of participants in research.[54] Reimbursements of $A40 gift cards will be made for attending weekly visits where all required assessments are completed, with the primary endpoint visit (Day 84) being reimbursed at $A80. An additional $A40 gift card will be provided on completion of the (optional) qualitative interview. Thus, the maximum potential reimbursement is $A680 of gift cards per person.

Data collection and reporting

This study will use electronic data capture in the form of Research Electronic Data Capture (REDCap).[40] REDCap is a secure, web-based software platform that includes audit trails. Access to study records will be limited to those approved by the site's governance approval. Data entered into REDCap will be reidentifiable by the local study staff to ensure it is verifiable to source documentation including hospital paper, electronic, pharmacy and pathology records. Following conclusion of the study, physical and digital records will be stored for a period of no less than 15 years as per International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines.[38] Data will be published in a peer-reviewed journal and participants will be notified of study findings by the investigator team.

Statistical methods

Study data will be presented as descriptive. Continuous measures such as mean changes in continuous measure scores from baseline across each assessment time point will be analysed using appropriate parametric approaches, such as paired-sample t-tests. For categorical measures such as the presence of AEs, rates will be analysed using appropriate non-parametric approaches, such as χ^2 and relative risk. For the analysis of qualitative interview data, a thematic analysis approach will be undertaken.[55]

MONITORING

Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be established prior to study recruitment, and the DSMB membership will include an addiction medicine specialist, a psychologist, and a pharmacologist (all not otherwise involved with the study). All serious AEs (SAEs) and suspected unexpected serious adverse reactions (SUSARs) will be reviewed by the DSMB quarterly. Following each meeting, the DSMB will advise one of four options: continue study as per protocol, continue study with protocol amendments, suspend study or discontinue study. The DSMB will agree to a Charter that outlines the aforementioned details and elect a Chair. The Charter and meeting agendas and outcomes will be filed in the Trial Master File and Investigator Site File.

Data monitoring

The study data will be monitored by a sponsor staff member not otherwise involved in the study, for accuracy, primary endpoint data and compliance with ICH-GCP[38] and the Australian National Statement on Ethical Conduct in Human Research.[56]

ETHICS AND DISSEMINATION

This study has been approved by the St Vincent's Hospital Human Research Ethics Committee, reference 2023/ETH00549. All participants will provide written, informed consent prior to commencing the study. A copy of this is supplied in the online supplemental text. The results will be submitted to peer-reviewed journals and scientific conferences, and a video abstract will be created to ensure findings are accessible to participants and people who use methamphetamines.

DISCUSSION

This study will examine the safety and feasibility of a combination pharmacotherapy for the treatment of methamphetamine use disorder over 84 days in adults in an outpatient setting.

A pragmatic study design was undertaken in replicating findings from a US study conducted by Trivedi *et al*.[10] This meant designing a study that examined formulations accessible in other contexts. The most recent knowledge we have on this combination therapy uses an expensive formulation that limits the use of this medication to reduce suffering in the majority of countries affected by MAUD. We designed this study to examine a more flexible and available formulation of the product outside of the USA. Furthermore, while this is an exploratory study examining feasibility and safety, the secondary outcomes are designed to consider outcomes for a larger-scale

study, and those that are adaptable to client-centred goals. For example, while some participants may aim to achieve abstinence from methamphetamine, we recognise the value of changes in methamphetamine use and improvements in physical and mental health, for those whose goal is not abstinence. In selecting outcomes, the study team considered outcomes most frequently assessed in clinical trials for interventions for MAUD.[6] However, there is discourse and variability in the literature. Furthermore, the present study is an open-label pilot, with participants on treatment to Day 84, whereas participants in Trivedi *et al*'s study were randomised in two stages (with re-randomisation occurring at Week 6, ahead of the second stage).

Both the Trivedi study and the present study examine higher doses of bupropion than have previously been examined for MAUD. Prior studies have investigated 300 mg,[14] and while unsuccessful in primary analysis, post hoc analyses in one study found a statistically significant effect among participants who consumed less methamphetamine at enrolment than those who consumed more (defined as 0–2 or 3–6 methamphetamine positive urine tests in a 2-week baseline period).[57] Similar effects were demonstrated in another study, where a planned subgroup analysis of participants who consumed≤18 days of the 30 days prior to baseline had an increase in weekly periods of abstinence from methamphetamine as compared with placebo. Meta-analysis of all trials of bupropion in amphetamine-type stimulant use disorder found that relative to placebo; bupropion was associated with reduced amphetamine-type stimulant use, end-of-treatment cravings and adherence.[14] Our eligibility threshold will be methamphetamine use disorder,[58] without a cut-point based on days of use at baseline. This reflects the breadth of patients seeking treatment and responds to prior studies of bupropion at lower doses and without naltrexone.

Designed to be pragmatic, the eligibility criteria for this study aim to be as closely representative of the underlying population as possible. While we recognise the need for sanitised clinical trial results, we also recognise the tension in providing findings that are generalisable to real-world populations. Where possible, we aim not to exclude participants with comorbid conditions and have attempted to keep our exclusion criteria closely aligned with the product label of the study drug.

Our study will repurpose a combination product that is already marketed for other purposes. This approach may provide a cheaper more accessible product that can be more readily scaled to a variety of contexts.[25] Given the recent data on bupropion[14] and bupropion in combination with naltrexone,[10] assessing the feasibility of this oral combination is imperative. A pilot study allows us to explore the feasibility of this formulation, and whether these methods may be feasible for a larger trial.[59] Crucially, the inclusion of qualitative interviews allows us to explore participant experiences and incorporate their feedback moving forward.

Our study will assess the suitability of a smartphone EMA app for adherence assessment and methamphetamine use. More frequent ongoing assessment of methamphetamine use may be more reliable than self-reporting at 28-day intervals. We will compare results collected within the app to those in the monthly self-reported methamphetamine use questionnaire and the weekly urine point of care tests. While our study will not be powered to detect differences in responses, we will also have the opportunity in qualitative interviews to explore participant experience of the app, including whether the app was supportive of positive reinforcement or produced a cue for craving by eliciting these reflections. Additionally, we will assess adherence to the study drug with the app, which provides daily notifications to complete questionnaires. This in itself may perhaps be an intervention motivating participants towards adherence rather than monitoring adherence, another theme we will explore qualitatively. Moreover, we recognise this population may be reticent to provide information of this sort on a smartphone app, and we will therefore be assessing the feasibility of these measures overall.

Limitations and future implications

Our trial offers the opportunity to translate findings and contextualise them to increase their accessibility and reproducibility in other settings. However, it also has limitations. This trial will not enhance our understanding of other important questions related to the treatment of methamphetamine use disorder, such as whether a 12-week duration of a pharmacotherapy will be as effective as longer treatment periods, whether dose reduction over the taper-down period is comparatively better than an alternative taper regimen or post-trial longer-term outcomes. The study will be conducted at a single site in inner-city Sydney, Australia. This, and the pilot sample size, will mean that results will be limited in their generalisability outside of this context. The results will inform a larger study of participants in Australia, and contextual factors such as regional or rural/remote sites will need to be considered for nuances in participants and recruitment. Finally, this study examines a pharmacotherapy as an adjunct to treatment as usual. The benefit of combinations of psychosocial therapies, social interventions and pharmacotherapies over the spectrum of a substance use disorder and at various time points (eg, withdrawal, longer term, when relapsed to use after an abstinent period) remain to be elucidated. Continued investment and resources to conduct clinical research in this population are warranted.

Author affiliations
[1]The National Centre for Clinical Research on Emerging Drugs (NCCRED), The University of New South Wales, Sydney, New South Wales, Australia
[2]Alcohol and Drug Service, St Vincent's Hospital Sydney, Darlinghurst, New South Wales, Australia
[3]The National Drug and Alcohol Research Centre (NDARC), The University of New South Wales, Randwick, New South Wales, Australia

[4]New South Wales Drug and Alcohol Clinical Research and Improvement Network (DACRIN), c/o The Ministry of Health New South Wales, St Leonards, New South Wales, Australia
[5]Department of Clinical Pharmacology and Toxicology; and Psychiatric, Alcohol and Non-Prescription Drug Assessment Unit, St Vincent's Hospital Sydney, Darlinghurst, New South Wales, Australia
[6]St Vincent's Clinical School, The University of New South Wales, Sydney, New South Wales, Australia
[7]Next Step Drug and Alcohol Services, East Metropolitan Health Service, Perth, Western Australia, Australia
[8]Drug and Alcohol Clinical Services, Hunter New England Local Health District, Newcastle, New South Wales, Australia
[9]School of Medicine and Public Health, The University of Newcastle, Newcastle, New South Wales, Australia
[10]Faculty of Medicine and Health, Central Clinical School, Discipline of Addiction Medicine, University of Sydney, Sydney, New South Wales, Australia
[11]Edith Collins Centre for Translational Research, Drug Health Services, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia
[12]Research Centre, Centre Hospitalier de l'Université de Montréal (CRCHUM), Montreal, Quebec, Canada
[13]Department of Psychiatry and Addictology, Faculty of Medicine, Université de Montréal, Montreal, Quebec, Canada
[14]The Langton Centre, South Eastern Sydney Local Health District, Sydney, New South Wales, Australia
[15]Department of Family Medicine, University of California Los Angeles, Los Angeles, California, USA
[16]Peter O'Donnell Jr. Brain Institute, The University of Texas Southwestern Medical Center, Dallas, Texas, USA

Acknowledgements We would like to thank site staff Teodora Zanesheva-Karamanlieva, Clare Smylie, Lucy Flood and Arabella McMahon for their support in study set-up and implementation.

Contributors KJS prepared the first draft of this manuscript. All authors contributed to the conception and design of the study, provided feedback on the manuscript, provided final approval of the manuscript and agree to be accountable for the work. KJS is the guarantor.

Funding This study is funded by the National Centre for Clinical Research on Emerging Drugs (NCCRED). NCCRED receives funding from the Australian Department of Health and Aged Care. Neither the study funders nor sponsor had any role in the design of the study.

Competing interests KJS, LA, BC, CM, MC, AJD, DJ-A, KM, SS, NE—none to declare. JB is supported by the National Health and Medical Research Council (NHMRC) Centre of Research Excellence in Medications Intelligence (ID: 1196900) and an NHMRC Investigator Grant (ID: 1196560), PSH has received research funding from Invidior, NL has received grants from the Australian NHMRC, Camurus and Indivior for unrelated work, MHT has provided consulting services to Acadia Pharmaceuticals, Alkermes Inc., Alto Neuroscience Inc, Axsome Therapeutics, BasePoint Health management LLC, Biogen MA Inc, Cerebral Inc., Circular Genomics Inc., Compass Pathfinder Limited, Daiichi Sankyo Inc., GH Research, GreenLight VitalSign6 Inc, Heading Health, Janssen Pharmaceutical, Legion Health, Merck Sharp & Dohme Corp., Mind Medicine Inc., Myriad Neuroscience, Naki Health Ltd, Neurocrine Biosciences Inc., Noema Pharma AG, Orexo US Inc., Otsuka America Pharmaceutical Inc., Otsuka Europe LTD, Otsuka Pharmaceutical Development & Commercialization Inc., Praxis Precision Medicines Inc, PureTech LYT Inc, Relmada Therapeutics Inc., SAGE Therapeutics, Signant Health, Sparian Biosciences, Titan Pharmaceuticals, Takeda Pharmaceuticals Inc, WebMD. He has received grant/research funding from NIMH, NIDA, NCATS, American Foundation for Suicide Prevention, Patient-Centered Outcomes Research Institute (PCORI), Blue Cross Blue Shield of Texas, SAMHSA and the DoD and has received editorial compensation from Elsevier and Oxford University Press.

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

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Krista J Siefried http://orcid.org/0000-0002-6534-3325
Liam Acheson http://orcid.org/0000-0002-2343-5504
Brendan Clifford http://orcid.org/0000-0002-9178-9013
Kirsten Morley http://orcid.org/0000-0002-0868-9928
Nadine Ezard http://orcid.org/0000-0002-7495-8305

REFERENCES

1 Farrell M, Martin NK, Stockings E, *et al*. Responding to global stimulant use: challenges and opportunities. *Lancet* 2019;394:1652–67.
2 Richards JR, Harms BN, Kelly A, *et al*. Methamphetamine use and heart failure: Prevalence, risk factors, and predictors. *Am J Emerg Med* 2018;36:1423–8.
3 Degenhardt L, Baxter AJ, Lee YY, *et al*. The global epidemiology and burden of psychostimulant dependence: findings from the Global Burden of Disease Study 2010. *Drug Alcohol Depend* 2014;137:36–47.
4 Potvin S, Pelletier J, Grot S, *et al*. Cognitive deficits in individuals with methamphetamine use disorder: A meta-analysis. *Addict Behav* 2018;80:154–60.
5 Minozzi S, Saulle R, Amato L, *et al*. Psychosocial interventions for stimulant use disorder. *Cochrane Database Syst Rev* 2024;2024:Cd011866.
6 Siefried KJ, Acheson LS, Lintzeris N, *et al*. Pharmacological Treatment of Methamphetamine/Amphetamine Dependence: A Systematic Review. *CNS Drugs* 2020;34:337–65.
7 Bharat C, Webb P, Wilkinson Z, *et al*. Agreement between self-reported illicit drug use and biological samples: a systematic review and meta-analysis. *Addiction* 2023;118:1624–48.
8 US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Stimulant use disorders: developing drugs for treatment, guidance for industry: draft guidance. 2023.
9 Robinson SM, Sobell LC, Sobell MB, *et al*. Reliability of the Timeline Followback for cocaine, cannabis, and cigarette use. *Psychol Addict Behav* 2014;28:154–62.
10 Trivedi MH, Walker R, Ling W, *et al*. Bupropion and Naltrexone in Methamphetamine Use Disorder. *N Engl J Med* 2021;384:140–53.
11 Clinical Guideline Committee (CGC) Members, ASAM Team, AAAP Team, *et al*. The ASAM/AAAP Clinical Practice Guideline on the Management of Stimulant Use Disorder. *J Addict Med* 2024;18:1–56.
12 Shoaib M, Buhidma Y. Why are Antidepressant Drugs Effective Smoking Cessation Aids? *Curr Neuropharmacol* 2018;16:426–37.
13 Patel K, Allen S, Haque MN, *et al*. Bupropion: a systematic review and meta-analysis of effectiveness as an antidepressant. *Ther Adv Psychopharmacol* 2016;6:99–144.
14 Bakouni H, Sharafi H, Bahremand A, *et al*. Bupropion for treatment of amphetamine-type stimulant use disorder: A systematic review and meta-analysis of placebo-controlled randomized clinical trials. *Drug Alcohol Depend* 2023;253:111018.
15 Aspen Pharmacare Australia. Australian product information - Zyban SR (bupropion hydrochloride) sustained release tablets. 2022.
16 Newton TF, Roache JD, De La Garza R II, *et al*. Bupropion Reduces Methamphetamine-Induced Subjective Effects and Cue-Induced Craving. *Neuropsychopharmacol* 2006;31:1537–44.
17 Reichel CM, Murray JE, Grant KM, *et al*. Bupropion attenuates methamphetamine self-administration in adult male rats. *Drug Alcohol Depend* 2009;100:54–62.
18 Center for Substance Abuse Treatment. Incorporating alcohol pharmacotherapies into medical practice. In: *Treatment improvement protocol (TIP) series 49. HHS publication no. (SMA) 09-4380*.

Rockville (MD): Substance Abuse and Mental Health Services Administration, 2009.
19 Chiu CT, Ma T, Ho IK. Attenuation of methamphetamine-induced behavioral sensitization in mice by systemic administration of naltrexone. *Brain Res Bull* 2005;67:100–9.
20 Ray LA, Bujarski S, Courtney KE, *et al*. The Effects of Naltrexone on Subjective Response to Methamphetamine in a Clinical Sample: a Double-Blind, Placebo-Controlled Laboratory Study. *Neuropsychopharmacol* 2015;40:2347–56.
21 Roche DJO, Worley MJ, Courtney KE, *et al*. Naltrexone moderates the relationship between cue-induced craving and subjective response to methamphetamine in individuals with methamphetamine use disorder. *Psychopharmacology (Berl)* 2017;234:1997–2007.
22 le Roux CW, Fils-Aimé N, Camacho F, *et al*. The relationship between early weight loss and weight loss maintenance with naltrexone-bupropion therapy. EClinicalMed 2022;49:101436.
23 Sherman MM, Ungureanu S, Rey JA. Naltrexone/bupropion ER (contrave): newly approved treatment option for chronic weight management in obese adults. *Pharmacy Therapeu* 2016;41:164–72.
24 Vivitrol price guide. Available: https://www.drugs.com/price-guide/vivitrol [Accessed 4 Feb 2025].
25 Brett J, Bahceci D, Lipworth W, *et al*. Can old drugs learn new tricks? Achieving registration and public subsidy listing for off-patent medicines with novel therapeutic applications. *Intern Med J* 2023;53:1284–7.
26 Sahid A, Lintzeris N. Substance use recovery goals and expectations (SURGE) questionnaire. 2024.
27 Chan A-W, Tetzlaff JM, Altman DG, *et al*. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200–7.
28 Viechtbauer W, Smits L, Kotz D, *et al*. A simple formula for the calculation of sample size in pilot studies. *J Clin Epidemiol* 2015;68:1375–9.
29 Hertzog MA. Considerations in determining sample size for pilot studies. *Res Nurs Health* 2008;31:180–91.
30 Kunselman AR. A brief overview of pilot studies and their sample size justification. *Fertil Steril* 2024;121:899–901.
31 Kraemer HC, Mintz J, Noda A, *et al*. Caution regarding the use of pilot studies to guide power calculations for study proposals. *Arch Gen Psychiatry* 2006;63:484–9.
32 iNova Pharmaceuticals. Australian product information – contrave 8/90 (naltrexone hydrochloride and bupropion hydrochloride) extended-release tablets. 2023.
33 Dunbar JL, Turncliff RZ, Dong Q, *et al*. Single- and multiple-dose pharmacokinetics of long-acting injectable naltrexone. *Alcohol Clin Exp Res* 2006;30:480–90.
34 US Food Drug Administration. WELLBUTRIN XL (bupropion hydrochloride extended-release tablets). Silver Spring, MD US Food and Drug Administration; 2011.
35 O'Brien ST, Dozo N, Hinton JDX, *et al*. SEMA3: a free smartphone platform for daily life surveys. 2023. Available: https://doi.org/10.31234/osf.io/cnar8
36 Ortega Suárez FJ, Sánchez Plumed J, Pérez Valentín MA, *et al*. Validation on the simplified medication adherence questionnaire (SMAQ) in renal transplant patients on tacrolimus. *Nefrologia* 2011;31:690–6.
37 U.S. Department of Health and Human Services. Division of AIDS (DAIDS), table for grading the severity of adult and pediatric adverse events, corrected version 2.1. National Institute of Allergy and Infectious Diseases; 2017.
38 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Annotated with TGA Comments. Integrated addendum to ICH E6(R1): guideline for good clinical practice ICH E6(R2). 2016. Available: https://admin.ich.org/sites/default/files/inline-files/E6_R2__Addendum_Step2.pdf?utm_medium=email&utm_source=transaction
39 National Health and Medical Research Council. *Guidance: safety monitoring and reporting in clinical trials involving therapeutic goods*. Canberra, 2016.
40 Harris PA, Taylor R, Thielke R, *et al*. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377–81.
41 Eldridge SM, Costelloe CE, Kahan BC, *et al*. How big should the pilot study for my cluster randomised trial be? *Stat Methods Med Res* 2016;25:1039–56.
42 Lancaster GA, Thabane L. Guidelines for reporting non-randomised pilot and feasibility studies. *Pilot Feasibility Stud* 2019;5:114.
43 Leon AC, Davis LL, Kraemer HC. The role and interpretation of pilot studies in clinical research. *J Psychiatr Res* 2011;45:626–9.
44 O'Cathain A, Hoddinott P, Lewin S, *et al*. Maximising the impact of qualitative research in feasibility studies for randomised controlled trials: guidance for researchers. *Pilot Feasibility Stud* 2015;1:32.
45 Hays RD, Spritzer KL, Schalet BD, *et al*. PROMIS®-29 v2.0 profile physical and mental health summary scores. *Qual Life Res* 2018;27:1885–91.
46 Sinclair SJ, Siefert CJ, Slavin-Mulford JM, *et al*. Psychometric Evaluation and Normative Data for the Depression, Anxiety, and Stress Scales-21 (DASS-21) in a Nonclinical Sample of U.S. Adults. *Eval Health Prof* 2012;35:259–79.
47 Lee JW, Brown ES, Perantie DC, *et al*. A Comparison of Single-Item Visual Analog Scales With a Multiitem Likert-Type Scale for Assessment of Cocaine Craving in Persons With Bipolar Disorder. *Addict Disord Their Treat* 2002;1:140–2.
48 Srisurapanont M, Jarusuraisin N, Jittiwutikan J. Amphetamine Withdrawal: I. Reliability, Validity and Factor Structure of a Measure. *Aust N Z J Psychiatry* 1999;33:89–93.
49 Atkinson MJ, Sinha A, Hass SL, *et al*. Validation of a general measure of treatment satisfaction, the treatment satisfaction questionnaire for medication (TSQM), using a national panel study of chronic disease. *Heal Qual Life Outcomes* 2004;2:12.
50 Ward MF, Wender PH, Reimherr FW. The Wender Utah Rating Scale: an aid in the retrospective diagnosis of childhood attention deficit hyperactivity disorder. *Am J Psychiatry* 1993;150:885–90.
51 Timmerman IGH, Emanuels-Zuurveen ES, Emmelkamp PMG. The social support inventory (SSI): a brief scale to assess perceived adequacy of social support. *Clin Psychol Psychother* 2000;7:401–10.
52 Posner K, Brown GK, Stanley B, *et al*. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry* 2011;168:1266–77.
53 Siefried KJ, Ezard N, Christmass M, *et al*. A clinical research priority setting study for issues related to the use of methamphetamine and emerging drugs of concern in Australia. *Drug Alcohol Rev* 2022;41:309–19.
54 National Health and Medical Research Council. *Payment of participants in research: information for researchers, HRECs and other ethics review bodies*. Commonwealth of Australia, Canberra: Australian Research Council and Universities Australia, 2019.
55 Ritchie J, Spencer L, O'Connor W. *Qualitative research practice: a guide for social science students and researchers*. 2003.
56 Australian Research Council and the Australian Vice-Chancellors' Committee. *National statement on ethical conduct in human research 2007*. Commonwealth of Australia, Canberra: National Health and Medical Research Council, 2015.
57 Shoptaw S, Heinzerling KG, Rotheram-Fuller E, *et al*. Randomized, placebo-controlled trial of bupropion for the treatment of methamphetamine dependence. *Drug Alcohol Depend* 2008;96:222–32.
58 American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 5th edn. 2016.
59 Thabane L, Ma J, Chu R, *et al*. A tutorial on pilot studies: the what, why and how. *BMC Med Res Methodol* 2010;10:1.