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Complete List of Authors:	Siefried, Krista J; University of New South Wales; St Vincent's Hospital Sydney Acheson, Liam; University of New South Wales; St Vincent's Hospital Sydney Clifford, Brendan; University of New South Wales; St Vincent's Hospital Sydney Moller, Carl; University of New South Wales Brett, Jonathan.; St Vincent's Hospital Sydney, Department of Clinical Pharmacology & Toxicology; University of New South Wales Christmass, Michael; Western Australia Mental Health Commission Dunlop, Adrian; Hunter New England Local Health District; New South Wales Ministry of Health Haber, Paul; University of Sydney - Camperdown and Darlington Campus; Royal Prince Alfred Hospital Jutras-Aswad , Didier; Centre Hospitalier de l'Université de Montréal; Université de Montréal, Department of Psychiatry and Addictology Lintzeris, Nicholas; New South Wales Ministry of Health; The University of Sydney Faculty of Medicine and Health Morley, Kirsten; The University of Sydney Faculty of Medicine and Health; Royal Prince Alfred Hospital Shoptaw, Steven; University of California Los Angeles, Family Medicine / Psychiatry and Biobehavioural Sciences Trivedi, Madhukar; The University of Texas Southwestern Medical Center Ezard, Nadine; University of New South Wales; St Vincent's Hospital Sydney
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Siefried et al - NABU

Title

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

Authors

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

1 The National Centre for Clinical Research on Emerging Drugs, c/o the University of New South Wales, Sydney, Australia

2 St Vincent's Hospital Alcohol and Drug Service, Sydney, Australia

3 The National Drug and Alcohol Research Centre, the University of New South Wales, Sydney, Australia

4 New South Wales Drug and Alcohol Clinical Research and Improvement Network, c/o the New South Wales Ministry of Health, Sydney, Australia

5 St Vincent's Hospital Clinical Pharmacology and Toxicology Unit and Psychiatric, Alcohol and Non-Prescription Drugs Assessment Unit, Sydney, Australia

7 Next Step Drug and Alcohol Services, Western Australia Mental Health Commission, Perth, Australia

8 Drug and Alcohol Clinical Services, Hunter New England Local Health District, Newcastle, Australia

9 School of Medicine and Public Health, the University of Newcastle, Newcastle, Australia

10 Faculty of Medicine and Health, Central Clinical School, Discipline of Addiction Medicine University of Sydney, Sydney, Australia

11 Edith Collins Centre for Translational Research, Drug Health Services, Royal Prince Alfred Hospital, Sydney, Australia

12 Research Centre, Centre Hospitalier de l'Université de Montréal (CRCHUM), Montréal, Canada

13 Department of Psychiatry and Addictology, Faculty of Medicine, Université de Montréal, Montréal, Canada

14 The Langton Centre, South East Sydney Local Health District, Sydney, Australia

15 Department of Family Medicine, The University of California Los Angeles, Los Angeles, USA

16 Peter O'Donnell Jr. Brain Institute, the University of Texas Southwestern Medical Center

Corresponding author:

Krista J Siefried

The National Centre for Clinical Research on Emerging Drugs (NCCRED)

c/o the University of New South Wales

Sydney, Australia

P: +61 410 360 102

E: krista.siefried@svha.org.au

Declarations / Conflicts of interest

KJS, LA, BC, CM, MC, AD, DJA, KM, SS, NE – none to declare.

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Abstract

Background: Methamphetamine use disorder is a public health concern globally, yet there are no approved pharmacotherapies for its treatment. One recent randomised controlled trial conducted in the United States examined a combination of bupropion and naltrexone in formulations that are not immediately translatable in all contexts. Here we report a trial protocol of a combination oral formulation of naltrexone bupropion.

Methods: A single-arm, open-label pilot study to examine the safety and feasibility of oral naltrexone and bupropion (40mg/450mg) 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 will be Day 84. Participants will attend weekly study visits (Baseline to Week 12) and a follow-up visit by telephone at Week 16. All participants will receive treatment as usual psychosocial therapy. Primary outcomes are safety (measured by treatment emergent adverse events / adverse reactions), and feasibility (measured by the time taken to recruit the sample, the proportion of ineligible participants, retention in study, and study medication adherence). Secondary outcomes will assess methamphetamine use, craving and withdrawal scores; treatment goals and expectations; changes in physical and psychological wellbeing; depression and anxiety; and treatment satisfaction. Qualitative interviews will assess the acceptability of the intervention and outcome measures.

Discussion: This study is the first to assess this formulation of oral bupropion and naltrexone in combination in adults with methamphetamine use disorder. If safe and feasible, this combination may provide a more scalable formulation to take to next-phase trials.

Strengths and Limitations of this study

- This protocol will examine a pharmacotherapy in a formulation not previously trialled in adults with methamphetamine use disorder

- If feasible and safe, would present a scalable treatment option to progress to larger trials

Trial Registration: ANZCTR: ACTRN12623000866606 (protocol version 2.1 dated 08 April 2024)

Keywords: methamphetamine; substance use disorder; naltrexone; bupropion; clinical trial

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Introduction

Methamphetamine use disorder (MAUD) presents a significant public health concern globally (1), characterised by its impact on individuals, families and communities. The prevalence of MAUD in Australia is amongst the highest in the world (1). MAUD is associated with increased mortality and morbidity (including from cardiovascular events), risk of blood borne infections, cognitive function and mental health complications (psychosis, depression), as well as social issues including difficulty maintaining employment and breakdown in families and relationships (2-4).

Despite concerted efforts to improve outcomes for people living with MAUD, interventions remain limited. These generally consist of psychosocial therapy, such as cognitive behavioural therapy (CBT). Evidence also supports contingency management, with scale-up occurring primarily in United States (US) government-sponsored health plans. A recent Cochrane review suggests that as compared to 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).

One promising study emerging from the US examined a combination of bupropion, a noradrenaline reuptake inhibitor with stimulant-like actions, and naltrexone, an opioid-receptor antagonist. 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 two weeks of treatment) than those randomised to placebo (7). Since that publication, the American Society of Addiction Medicine / American Academy of Addiction Psychiatry have released clinical practice guidelines for the management of stimulant use disorder (8). These include a recommendation to consider bupropion in combination with naltrexone for the management of amphetamine type stimulant use disorder, including methamphetamine used disorder (8).

Bupropion hydrochloride is an atypical antidepressant which is also well established as an effective treatment approach for nicotine dependence (9, 10). 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 RCTs (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 (11). However, studies were rated to have low quality evidence and required larger more diverse samples (11). One proposed theoretical mechanism of action is that because bupropion acts as a selective inhibitor of neuronal reuptake of norepinephrine and dopamine (12), it may potentially ameliorate symptoms of methamphetamine withdrawal (13, 14). Naltrexone is an opioid antagonist which is well established as an effective treatment for both opioid and alcohol use disorders (15). Animal studies suggest there is involvement of the endogenous opioid system in methamphetamine-seeking behaviour (16), and it is hypothesised that naltrexone may attenuate the reinforcing effects of methamphetamine or cue-induced craving (17, 18). Naltrexone monotherapy has been examined for MAUD and demonstrated conflicting results (6).

The US study conducted by Trivedi et al. (7) thus represents a new combination that may deliver stronger outcomes than either medication can on its own. In other therapeutic indications, combination extended release naltrexone (32mg) / bupropion (360mg) led to significant weight loss in treatment of overweight/obesity (19), and is approved for this indication in the US, Canada, Europe and Australia. While the exact mechanism of action is not entirely understood, the theory is that this combination works synergistically in the hypothalamus and mesolimbic dopamine circuit (20).

The Trivedi study used an extended-release injectable formulation of naltrexone (380mg every three weeks) and an oral extended-release bupropion (450mg daily). However, the formulation of injectable naltrexone is not widely available outside the US, Europe, Russia, and the United Kingdom. Even within the US, it is estimated to cost $1,000-$1,700USD per dose (21), rendering its likely uptake inequitable. Similarly, access to

extended-release bupropion, is limited outside the US, with immediate or sustained release formulations more widely available. Therefore, jurisdictions outside the US need a readily accessible formulation to introduce bupropion / naltrexone combination 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 (22), 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 wellbeing, 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 (SURGE) questionnaire (23) 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 (SPIRIT) guidelines (24), a checklist for which is available in **Supplementary 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 from patients seeking treatment at the clinic, referrals from nearby services, and by 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, Adverse Events), 20 participants will ensure these will be identified (with 85% confidence) (25). This will allow for descriptive analysis and accounts for potential attrition (26). The study is not powered to determine efficacy, we will not conduct hypothesis testing, thus no power calculation was performed (27). Given larger studies exist (7, 11), 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 (27, 28).

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 (8mg/90mg) (29). A five-day dose escalation period will commence with one tablet on Day One, increasing to the investigational dose of five tablets (three morning, two evening) by Day Five (40mg/450mg). The dose escalation period allows a participant to adjust to the medication, and is slightly longer than the three day period examined by Trivedi et al (7), but less gradual than in weight loss studies (29). The primary

endpoint will be Day 84 (the last day at the highest dose of study drug). A five-day taper period will commence on Day 85, with medication 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: 32mg/360mg) (29), 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 management of stimulant use. Standard of care counselling involves evidence-based motivational interviewing and cognitive behavioural therapy (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 (7)), demonstrated systemic naltrexone exposure of approximately four times greater for the intramuscular versus oral route of administration (30). Conversely, systemic exposure to naltrexone's primary active metabolite (6β-naltrexol) is 3.4 times lower following intramuscular administration compared to oral dosing (30) 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 50mg naltrexone equivalency data.

In Australia, bupropion is approved for use in nicotine dependence to a maximum dose of 300mg 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 US, a maximum daily dose of 450 mg is recommended (31).

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 twice daily (32mg naltrexone and 360mg bupropion daily). This study will use a maximum dose of three tablets in the morning and two tablets in the afternoon (40mg naltrexone and 450mg bupropion daily). Study drug will be prepared by the St Vincent's Hospital Sydney clinical trials pharmacist in medication packs containing one weeks supply for the induction period, then for the remainder of the study two packs containing one weeks' 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 (32) 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 copmared with responses to weekly SMAQ adherence questionnaire (33) responses.

Stopping criteria

If a participant experiences a Grade 3 or Grade 4 Adverse Event (AE) (34) 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 adverse events / adverse reactions through to the final study visit. These will be described by seriousness, severity, causality and expectedness (35, 36). Participants will be asked to provide information about any treatment emergent AE's, and encouraged to provide any information spontaneously at weekly study visits. Feasibility will be assessed by: (i) the time taken to recruit the sample; (ii) the proportion of ineligible participants at pre-screening and screening; (iii) retention rate [in study]; and (iv) medication adherence (pill counts, app responses, weekly SMAQ questionnaire (33)).

Secondary outcomes are: Self-reported days of methamphetamine use from baseline to Day 84 (including mode, frequency and dose) (via smartphone ecological momentary assessment using the same app (32) as measures adherence); self-reported change in days of methamphetamine and other substance use over past 28-days from baseline to Days 28, 56 and 84 using the timeline follow-back method (37); proportion of methamphetamine-positive point of care urine drug screens (POC UDS) conducted at weekly study visits; treatment goals and expectations (by the Substance Use Recovery Goals and Expectations – 'SURGE' questionnaire (23)); change in physical and psychological wellbeing (Promis-29) (38) and depression and anxiety (DASS-21) (39) scores from baseline to Day 84; changes in methamphetamine craving by visual analogue scale (CVAS) (40) and withdrawal symptoms by the amphetamine withdrawal questionnaire (AWQ) (41) from baseline to Day 84; treatment satisfaction (TSQM-II) (42); and acceptability of the intervention and the feasibility and acceptability of smartphone app data collection, assessed via qualitative interviews.

Participant timeline

Potential participants who express interest in the study will be pre-screened (by phone) and 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 two weeks, however the following assessments must be completed within 24 hours of the first dose of study drug: urine for human chorionic gonadotropin (hCG); UDS POC (all drugs – must be negative for opioids); and timeline follow-back (37) for methamphetamines, opioids, alcohol, 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 (WURS) (43) to retrospectively evaluate the presence of childhood ADHD symptoms; and the ENRICHD Social Support Inventory (ESSI) (44) to assess social support. History of suicidal ideation or suicide attempts will be collected by the Columbia Suicide Severity Rating Scale (C-SSRS lifetime) (45). This will allow any adverse events relating to suicidal ideation to assessed in subsequent visits by the C-SSRS since last visit form (45). Participants will attend weekly clinic reviews, receive fortnightly medication packs, and any concomitant treatment (e.g. 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 **Table 3**.

Patient and public involvement

This study is in response to a national priority setting study for clinical research to address methamphetamine use (46). It involved people with lived and living experience, and

those that care about them, to drive the research agenda. One of the key priorities was a pharmacotherapy for methamphetamine use disorder (46). As this is a pilot study, we are undertaking qualitative interviews, to ensure that participant perspectives on the study design and conduct is 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 (47). Reimbursements of $40 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 $80. An additional $40 gift card will be provided upon completion of the (optional) qualitative interview. Thus, the maximum potential reimbursement is $680 of gift cards per person.

Data Collection and Reporting

This study will use electronic data capture in the form of REDCap (Research Electronic Data Capture) (48) 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 re-identifiable 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 no less than 15 years as per ICH-GCP guidelines (35). Data will be published in a peer-review 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 chi-square and relative risk. For the analysis of qualitative interview data, a thematic analysis approach will be undertaken (49).

Monitoring

Data Safety Monitoring Board (DSMB)

A 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 Adverse Events (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 (35) and the Australian National Statement on Ethical Conduct in Human Research (50).

Ethics

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 in the study.

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 (7). This meant designing a study that examined formulations accessible in other contexts. We designed this study to examine a more flexible and available formulation of the product outside of the US. 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. 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, whilst 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. 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 300mg (11), and whilst unsuccessful in primary analysis; post hoc analyses in one study found a statistically significant effect amongst 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 two week baseline period) (51). Similar effects were demonstrated in another study, where a planned sub-group 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 to 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 (11). Our eligibility threshold will be methamphetamine use disorder (52), 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 aims to be as closely representative of the underlying population as possible. Whilst 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 (22). Given the recent data on bupropion (11) and bupropion in combination with naltrexone (7), assessing 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 (53). 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 smart phone EMA app for adherence assessment and methamphetamine use. More frequent ongoing assessment of methamphetamine use may be more reliable than self-report 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 POC tests. Whilst 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 application, and we will therefore be assessing the feasibility of these measures overall.

Our trial offers the opportunity to translate findings and contextualise them to increase their accessibility and reproducibility in other settings. 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. 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 (e.g. 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.

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Tables and Figures

Table 1 – Eligibility Criteria

Inclusion criteria	Exclusions criteria
All participants must / must be:	*All participants must not:*
▪ ≥18 years of age	▪ Be currently pregnant, breast feeding, 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 (54) (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: (i) dependent on opioids, (ii) in acute opioid withdrawal, or (iii) has an anticipated need for opioid-containing medications at any point during the study (e.g. planned surgery)
▪ Provide a urine drug screen (UDS) point of care (POC) test positive for methamphetamines (during screening) and negative for opioids (during screening, repeated on 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 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 [AST] or alanine transaminase [ALT] > 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 investigational product) ▪ Have hypertension uncontrolled by a single anti-hypertensive 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

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	8mg/90mg
2	1	1	16mg/180mg
3	2	1	24mg/270mg
4	2	2	32mg/360mg
5 – 84	3	2	40mg/450mg
85	2	2	32mg/360mg
86	2	1	24mg/270mg
87	1	1	16mg/180mg
88[a]	1	0	8mg/90mg
89	0	0	0mg

[a] Day 88 is final study drug dose

Table 3: Schedule of assessments

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Study day	0[a]	1[b]	7	14	21	28	35	42	49	56	63	70	77	84	112
Protocol window - days	-14	0	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3
Study Week	0	0	1	2	3	4	5	6	7	8	9	10	11	12	16
Assessments															
Pre-screening	•														
Informed consent	•														
Demographics, medical history	•														
Confirm eligibility	•	•													
Prior concomitant medication	•														
Medical review	•													•	
Weight		•	•	•	•	•	•	•	•	•	•	•	•	•	
Concomitant medication	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Concomitant psychosocial care	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Investigational Product															
Study medication dispensed		•	•		•		•		•		•		•		
Medication pack returned for pill count			•		•		•		•		•		•	•	
Safety															
Adverse events		•	•	•	•	•	•	•	•	•	•	•	•	•	•
Blood pressure, pulse, temperature	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
C-SSRS Lifetime/Recent		•													
C-SSRS Since Last Visit						•				•				•	•
Pathology															
hCG±	•					•				•				•	
UDS POC all substances	•														
UDS POC opioids		•[d]				•				•				•	
UDS POC MA		•	•	•	•	•	•	•	•	•	•	•	•	•	
Liver function tests	•														
Questionnaires															
TLFB (alcohol, MA, opioids, cigarettes/nicotine)	•	•[d]				•				•				•	•
SURGE	•	•				•				•				•	•
Daily methamphetamine use[c]		•	•	•	•	•	•	•	•	•	•	•	•	•	
Daily adherence[c]		•	•	•	•	•	•	•	•	•	•	•	•	•	
SMAQ			•	•	•	•	•	•	•	•	•	•	•	•	
WURS		•													
ESSI		•													
Promis-29		•												•	
DASS-21		•												•	
CVAS		•												•	
AWQ		•												•	
TSQM v. II														•	
Optional Interview															
Qualitative interview														◄	►

a	= screening	b	= baseline (Day 1, first dose of study investigational product)
•	= study activity	c	= daily smartphone EMA (self-report)
◄►	= study activity conducted any time on indicated days inclusive	±	= people of childbearing potential only
	= post-primary endpoint (taper-down and follow-up periods)	d	= TLFB, UDS POC (opioids) must be repeated on day of first dose if screening and baseline visits not combined
AWQ	Amphetamine Withdrawal Questionnaire	Promis-29	Patient-Reported Outcomes Measurement Information System-29
C-SSRS	Columbia Suicide Severity Rating Scale	SMAQ	Simplified Medication Adherence Questionnaire
CVAS	Craving Visual Analogue Scale	SURGE	Substance Use Recovery Goals and Expectations
DASS-21	Depression Anxiety Stress Scales	TLFB	Timeline Follow-Back
ESSI	ENRICHD Social Support Inventory	TSQM	Treatment Satisfaction Questionnaire for Medication
hCG	Human chorionic gonadotropin (urine)	UDS POC	Urine drug screen – point of care
		WURS	Wender Utah Rating Scale

SPIRIT-Outcomes 2022 Checklist (for combined completion of SPIRIT 2013 and SPIRIT-Outcomes 2022 items)[a]

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
Administrative information				
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	-	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	-	Page 4
	2b	All items from the World Health Organization Trial Registration Data Set	-	Page 4
Protocol version	3	Date and version identifier	-	Page 4
Funding	4	Sources and types of financial, material, and other support	-	Page 4
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	-	Page 1
	5b	Name and contact information for the trial sponsor	-	Page 8
	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	-	Page 4
	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)	-	Pages 8, 10, 13
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	-	Pages 5-7
	6b	Explanation for choice of comparators	-	NA
Objectives	7	Specific objectives or hypotheses	-	Page 7

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
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)	-	Page 7
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	-	Page 8
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)	-	Page 8, table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (for specific guidance see TIDieR checklist and guide)	-	Pages 8-10
	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)	-	Page 10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	-	Page 10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	-	Page 9
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	-	Pages 11-12

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
	12.1		Provide a rationale for the selection of the domain for the trial's primary outcome	Page 11
	12.2		If the analysis metric for the primary outcome represents within-participant change, define and justify the minimal important change in individuals	NA
	12.3		If the outcome data collected are continuous but will be analyzed as categorical (method of aggregation), specify the cutoff values to be used	NA
	12.4		If outcome assessments will be performed at several time points after randomization, state the time points that will be used for analysis	Table 1
	12.5		If a composite outcome is used, define all individual components of the composite outcome	Page 11
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)	-	Page 12
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	-	Page 8
	14.1		Define and justify the target difference between treatment groups (eg, the minimal important difference)	NA
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	-	NA
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	-	NA

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
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	-	NA
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	-	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	-	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-	NA
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	-	Page 12
	18a.1		Describe what is known about the responsiveness of the study instruments in a population similar to the study sample	Page 12
	18a.2		Describe who will assess the outcome (eg, nurse, parent)	NA
	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	-	Page 10

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
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	-	Page 13
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	-	Page 13
	20a.1		Describe any planned methods to account for multiplicity in the analysis or interpretation of the primary and secondary outcomes (eg, coprimary outcomes, same outcome assessed at multiple time points, or subgroup analyses of an outcome)	NA
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	-	NA
	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)	-	NA
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	-	Page 13
	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	-	Page 13
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	-	Page 11

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-	Page 13-14
Ethics and dissemination				
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	-	Page 14
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)	-	NA
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	-	Page 11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-	NA
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	-	Page 13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	-	Journal submission
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	-	Page 13
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	-	Page 9
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	-	Page 13
	31b	Authorship eligibility guidelines and any intended use of professional writers	-	Journal submission

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-	NA
Appendices				
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	-	On request
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	-	NA

[a]It is strongly recommended that this checklist be read in conjunction with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) Statement paper 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 and is reproduced with permission.

[b]Indicates page numbers and/or manuscript location: to be completed by authors.

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)

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Primary Subject Heading:	Addiction
Secondary Subject Heading:	Pharmacology and therapeutics, Research methods, Public health, Mental health
Keywords:	Clinical Trial, MENTAL HEALTH, Substance misuse < PSYCHIATRY, PUBLIC HEALTH

Siefried et al - NABU

Title

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

Authors

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

1 The National Centre for Clinical Research on Emerging Drugs, c/o the University of New South Wales, Sydney, Australia

2 St Vincent's Hospital Alcohol and Drug Service, Sydney, Australia

3 The National Drug and Alcohol Research Centre, the University of New South Wales, Sydney, Australia

4 New South Wales Drug and Alcohol Clinical Research and Improvement Network, c/o the New South Wales Ministry of Health, Sydney, Australia

5 St Vincent's Hospital Clinical Pharmacology and Toxicology Unit and Psychiatric, Alcohol and Non-Prescription Drugs Assessment Unit, Sydney, Australia

7 Next Step Drug and Alcohol Services, Western Australia Mental Health Commission, Perth, Australia

8 Drug and Alcohol Clinical Services, Hunter New England Local Health District, Newcastle, Australia

9 School of Medicine and Public Health, the University of Newcastle, Newcastle, Australia

10 Faculty of Medicine and Health, Central Clinical School, Discipline of Addiction Medicine University of Sydney, Sydney, Australia

11 Edith Collins Centre for Translational Research, Drug Health Services, Royal Prince Alfred Hospital, Sydney, Australia

12 Research Centre, Centre Hospitalier de l'Université de Montréal (CRCHUM), Montréal, Canada

13 Department of Psychiatry and Addictology, Faculty of Medicine, Université de Montréal, Montréal, Canada

14 The Langton Centre, South East Sydney Local Health District, Sydney, Australia

15 Department of Family Medicine, The University of California Los Angeles, Los Angeles, USA

16 Peter O'Donnell Jr. Brain Institute, the University of Texas Southwestern Medical Center

Corresponding author:

Krista J Siefried

The National Centre for Clinical Research on Emerging Drugs (NCCRED)

c/o the University of New South Wales

Sydney, Australia

P: +61 410 360 102

E: krista.siefried@svha.org.au

Declarations / Conflicts of interest

KJS, LA, BC, CM, MC, AD, DJA, KM, SS, NE – none to declare.

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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 United States 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 (40mg/450mg 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 psychosocial therapy. Primary outcomes are safety (measured by treatment emergent adverse events / adverse reactions), and feasibility (measured by the time taken to recruit, the proportion of ineligible participants, retention in study, and study medication adherence). Secondary outcomes will assess methamphetamine use, craving, and withdrawal; treatment goals and expectations; physical and psychological wellbeing; 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 findings are accessible to participants and people who use methamphetamines.

Strengths and Limitations of this study

- This protocol will examine a pharmacotherapy in a formulation not previously trialled in adults with methamphetamine use disorder
- This study is the first to assess this 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

Trial Registration: ANZCTR: ACTRN12623000866606 (protocol version 2.1 dated 08 April 2024)

Keywords: methamphetamine; substance use disorder; naltrexone; bupropion; clinical trial

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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 amongst the highest in the world [1]. MAUD is associated with increased mortality and morbidity, including from 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 United States (US) government-sponsored health plans. A recent Cochrane review found that as compared to 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 FDA 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 accuracy of measures of adherence and methamphetamine use in clinical trials.

Bupropion hydrochloride is an atypical antidepressant and noradrenaline 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 RCTs (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 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 US 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 two 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, combination extended release naltrexone (32mg) / bupropion (360mg) led to significant weight loss in treatment of overweight/obesity [22]. For this reason, it is approved for this indication in the US, Canada, Europe and Australia. In theory, this improves access to this formulation.

The Trivedi study used an extended-release injectable naltrexone (380mg every three weeks) and oral extended-release bupropion (450mg daily). However, injectable

naltrexone is not widely available outside the US, Europe, Russia, and the United Kingdom. Even within the US, it is estimated to cost $1,000-$1,700USD per dose [24], rendering its likely uptake inequitable. Similarly, access to extended-release bupropion is limited outside the US, 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 wellbeing, 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 (SURGE) 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 (SPIRIT) guidelines [27], a checklist for which is available in **Supplementary 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 from patients seeking treatment at the clinic, referrals from nearby services, and by 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, Adverse Events), 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, 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 (8mg/90mg) [32]. A five-day dose escalation period will commence with one tablet on Day One, increasing to the investigational dose of five tablets (three morning, two evening) by Day Five, which commences the target maintenance dose of 40mg/450mg. The dose escalation period allows a participant to adjust to the medication,

and is slightly longer than the three 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 study drug). A five-day taper period will commence on Day 85, with medication 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: 32mg/360mg) [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 management of stimulant use. Standard of care counselling involves evidence-based motivational interviewing and cognitive behavioural therapy [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 to 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 50mg naltrexone equivalency data.

In Australia, bupropion is approved for use in nicotine dependence to a maximum dose of 300mg 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 US, 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 twice daily (32mg naltrexone and 360mg bupropion daily). This study will use a maximum dose of three tablets in the morning and two tablets in the afternoon (40mg naltrexone and 450mg bupropion daily). Study drug will be prepared by the St Vincent's Hospital Sydney clinical trials pharmacist in medication packs containing one weeks supply for the induction period, then for the remainder of the study two packs containing one weeks' 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 SMAQ adherence questionnaire [36] responses.

Stopping criteria

If a participant experiences a Grade 3 or Grade 4 Adverse Event (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 adverse events / 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 AE's, in addition to being encouraged to provide any information spontaneously at weekly study visits with study coordinators (Registered 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 pre-determined 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 known risks of the study medications, per the product label, and participant's past medical history/comorbidities. All AE's will receive final sign-off by the site PI.

Feasibility will be assessed by: (i) the time taken to recruit the sample; (ii) the proportion of ineligible participants at pre-screening and screening; (iii) retention rate in study; and (iv) 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 pre-screened 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 two weeks, however the following assessments must be completed within 24 hours of the first dose of study drug: urine for human chorionic gonadotropin (hCG); UDS POC (all drugs – must be negative for opioids); and timeline follow-back [9] for methamphetamines, opioids, alcohol, 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 (WURS) [50] to retrospectively evaluate the presence of childhood ADHD symptoms; and the ENRICHD Social Support Inventory (ESSI) [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 adverse events relating to suicidal ideation to 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 (e.g. 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 **Supplementary 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 that care about them, to drive the research agenda. One of the key priorities was a 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 is 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 $40 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 $80. An additional $40 gift card will be provided upon completion of the (optional) qualitative interview. Thus, the maximum potential reimbursement is $680 of gift cards per person.

Data Collection and Reporting

This study will use electronic data capture in the form of REDCap (Research Electronic Data Capture) [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 re-identifiable 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 no less than 15 years as per ICH-GCP guidelines [38]. Data will be published in a peer-review 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 chi-square and relative risk. For the analysis of qualitative interview data, a thematic analysis approach will be undertaken [55].

Monitoring

Data Safety Monitoring Board (DSMB)

A 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 Adverse Events (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 in the study. A copy of this is supplied in the **Supplementary text**. 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 US. 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, whilst 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. 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 300mg [14], and whilst unsuccessful in primary analysis; post hoc analyses in one study found a statistically significant effect amongst 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 two week baseline period) [57]. Similar effects were demonstrated in another study, where a planned sub-group 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 to 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 aims to be as closely representative of the underlying population as possible. Whilst 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 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 smart phone EMA app for adherence assessment and methamphetamine use. More frequent ongoing assessment of methamphetamine use may be more reliable than self-report 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 POC tests. Whilst 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 application, 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 (e.g. 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.

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Tables and Figures

Table 1 – Eligibility Criteria

Inclusion criteria	Exclusions criteria
All participants must / must be:	*All participants must not:*
▪ ≥18 years of age	▪ Be currently pregnant, breast feeding, 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: (i) dependent on opioids, (ii) in acute opioid withdrawal, or (iii) has an anticipated need for opioid-containing medications at any point during the study (e.g. planned surgery)
▪ Provide a urine drug screen (UDS) point of care (POC) test positive for methamphetamines (during screening) and negative for opioids (during screening, repeated on 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 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 [AST] or alanine transaminase [ALT] > 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

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	▪ Be concomitantly prescribed MAOIs (at least 14 days should elapse between discontinuation of MAOIs and initiation of treatment with investigational product) ▪ Have hypertension uncontrolled by a single anti-hypertensive 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

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	8mg/90mg
2	1	1	16mg/180mg
3	2	1	24mg/270mg
4	2	2	32mg/360mg
5 – 84	3	2	40mg/450mg
85	2	2	32mg/360mg
86	2	1	24mg/270mg
87	1	1	16mg/180mg
88[a]	1	0	8mg/90mg
89	0	0	0mg

[a] Day 88 is final study drug dose

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 past 28-days from Baseline to Days 28, 56, 84
Proportion of methamphetamine-positive point of care urine drug screens (POC UDS)	Point of care urine drug screens (POC UDS)	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 wellbeing 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 (AWQ) (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

Participant Information Sheet/Consent Form

Interventional Study - *Adult providing own consent*

St Vincent's Hospital, Sydney

Title	An Open-Label Safety and Feasibility Pilot Trial of Oral Naltrexone-Bupropion Combination Pharmacotherapy for Methamphetamine Use
Short Title	Naltrexone-Bupropion for Methamphetamine Use (NABU)
Protocol Number	2023/ETH00549
Project Sponsor	St Vincent's Hospital, Sydney
Coordinating Principal Investigator/ Principal Investigator	Professor Nadine Ezard
Associate Investigator(s)	Dr Krista Siefried Dr Carl Moller Dr Brendan Clifford Liam Acheson
Location	St Vincent's Hospital, Sydney, Alcohol and Drug Service

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project. This is because you have indicated that you currently use methamphetamine and are interested in managing, reducing, or stopping your methamphetamine use. The research project is testing a new treatment for methamphetamine use disorder. The new treatment is called naltrexone-bupropion combination therapy.

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

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

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

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

- Understand what you have read

- Consent to take part in the research project
- Consent to have the tests and treatments that are described
- Consent to the use of your personal and health information as described.

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

2 What is the purpose of this research?

There are currently no approved medications in Australia to help treat methamphetamine dependence. This study aims to determine if it is safe and feasible for people who are using methamphetamine to be given two medications, called naltrexone and bupropion, combined together, to help manage, reduce, or stop their methamphetamine use.

Medications, drugs and devices have to be approved for use by the Australian Federal Government. A combination of naltrexone and bupropion (with the brand name Contrave® 8/90) is approved in Australia for weight reduction in obesity, however it is currently not approved to treat methamphetamine use disorder. Therefore, this is an experimental treatment for methamphetamine use disorder. This means that this medication must be tested to see if it is a safe and effective treatment for people with methamphetamine dependence.

This research has been initiated by the study doctor, Professor Nadine Ezard. This research is funded by the National Centre for Clinical Research on Emerging Drugs, University of New South Wales and a St Vincent's Clinic Foundation grant.

3 What does participation in this research involve?

If, after reading this information and discussing this research with your doctor, friends or family, you decide to take part, you will be asked to digitally sign the Consent Form confirming that you agree to participate. This study is designed to provide you with a combined formulation of naltrexone and bupropion, as well as your usual standard of care provided by St Vincent's Hospital, Sydney. This means that except for receiving the study medication, the medical care that you will receive will be the same whether you decide to take part in this research or not.

Screening and baseline assessments

Before you take part in the study, the researchers need to make sure it is safe and appropriate for you to do so. This will involve some screening procedures, including questionnaires, medical assessments, blood tests, and urine tests. These procedures are as follows:

- Review of your medical history including previous instances of substance use treatment, hepatitis C (HCV) history, and any medications you are taking currently.
- Routine medical screening, including blood pressure, pulse, temperature, and weight. All of these measures are non-invasive.
- Routine blood and urine tests, including:
    - Liver function tests (LFT) – these are blood tests that provide information about how your liver is working. These tests will require less than 5mL of blood.

- A dip-stick urine drug test for methamphetamine and opioids. This will require approximately 2-3 tablespoons (50mL) of urine.
- A pregnancy blood test will also be conducted if you are of childbearing potential.

- A series of baseline questionnaires to assess your:
  - Use of substances (including methamphetamine, opioids, alcohol, cigarettes, etc.) over the past 4 weeks (Timeline Follow Back (TLFB) method)
  - Craving for methamphetamine
  - Withdrawal from methamphetamine
  - Thoughts of suicide and acts of suicidal behaviour
  - Feelings of depression and anxiety
  - Quality of life
  - Social support
  - Care received outside St Vincent's Hospital
  - Physical health symptoms

These screening and baseline procedures are expected to take between one and two hours. These procedures can be completed over more than one clinic visit if necessary, but all procedures must be completed with 14 days of consenting to participate in the study.

Medication

This study involves a commercially available medication (branded as Contrave® 8/90) which contains naltrexone hydrochloride and bupropion hydrochloride. The medication is in tablet form and is taken orally (swallowed). You will be required to take this medication daily for 88 days (just under 13 weeks). The maximum number of tablets to be taken is 5 per day. The medication will be provided to you once a week for the first week, then every two weeks for the remainder of the study. The medication will be provided in a pack containing one weeks' supply for the first week, then two weeks' supply from then on, of the medications, separated into daily doses. Each pack will contain a maximum of 70 tablets of the medication, separated into morning and afternoon doses for each day. When you pick up your study medication you will be asked to return the previous pack, with any unused medication to study staff.

The dose of medication will start low and will be increased gradually each day over the first five days of the study, as follows:

- Day 1: 1 tablet morning (1 tablet per day)
- Day 2: 1 tablet morning & 1 tablet evening (2 tablets per day)
- Day 3: 2 tablets morning & 1 tablet evening (3 tablets per day)
- Day 4: 2 tablets morning & 2 tablets evening (4 tablets per day)
- Day 5: 3 tablets morning & 2 tablets evening (5 tablets per day)

From day 5 onwards the medication dose will remain at 5 tablets per day until the end of Week 12 (up to day 84 inclusive). Then the dose will be gradually decreased in Week 13, as follows:

- Day 85: 2 tablets morning & 2 tablets evening (4 tablets per day)
- Day 86: 2 tablets morning & 1 tablets evening (3 tablets per day)
- Day 87: 1 tablet morning & 1 tablet evening (2 tablets per day)
- Day 88: 1 tablet morning FINAL DOSE (1 tablet per day)

Daily medication reporting

Every day during the medication period (88 days) you will asked to report whether you have taken the daily medication dose by responding yes/no to a message sent to your mobile phone.

Daily methamphetamine reporting

Every day during the medication period (88 days) you will be asked to report whether you have consumed methamphetamine within the last 24 hours by responding to a message sent to your mobile phone.

Weekly clinic visits

After enrolling in the study and completing all the screening and baseline measures, you will be required to attend St Vincent's Hospital, Sydney, Alcohol and Drug Service once a week for 13 weeks, plus a visit at Week 16. The purpose of these visits is to provide you with the study medication for each week (provided fortnightly),to monitor you for any medication related side effects, and to test your urine for methamphetamine. Each visit will take approximately one hour.

Each week, you will be asked about care received outside St Vincent's Hospital, other medications you are taking, and physical health symptoms. Your blood pressure, pulse, temperature, and weight will be recorded at each weekly visit. You will provide a urine sample for a point of care methamphetamine screen, and every four weeks for opioid screening and for pregnancy if you are of childbearing potential. In addition, every four weeks you will be asked about your drug consumption (methamphetamine, opioids, alcohol, and cigarettes/nicotine). At the study visit on Day 84, you will also be asked to complete many of the same questionnaires that you completed at the start of the study (baseline), assessing feelings of suicide, depression and anxiety, quality of life, social support, craving,

Optional Psychological Therapy

You will be offered psychological therapy as part of this study as per routine care at St Vincent's Alcohol and Drug Service. This psychological therapy is optional and it is up to you whether you would like to take part. Whether you decide to take part in the psychological therapy or not will not affect the care you receive or your participation in the study.

Optional Interview

We would also like to interview you about your experiences related to taking part in the study. This interview is optional, and you can participate in the main study without participating in the interview. At the Week 13 clinic visit you will be asked if you would like to take part in the interview. Your decision will not affect the care you receive in any way, or your participation in the rest of the study.

Interviews will be semi-structured, meaning that the interviewer will have questions to ask you, but some questions may be changed or skipped depending on what you wish to talk about.

Interviews will conducted one-on-one with a trained research staff member. The interview will take approximately 30 minutes. The interview will focus on your goals around managing your methamphetamine use, your expectations around taking the study medication, your experiences of taking the study medication, any concerns relating to the study medication, and your experience of taking part in the study in general.

Interviews will be conducted in a private treatment or interview room at St Vincent's Hospital, Sydney. Interviews will be conducted between Days 84 and 112 (Weeks 13 and 16) of the study. Interviews will be audio recorded and then transcribed (written down) in full.

Reimbursement

Participation in this study requires attending St Vincent's Hospital, Sydney, Alcohol and Drug Service every week for 13 weeks, in addition to taking the study medication daily, and one visit four weeks later. Each weekly visit will take approximately one hour. Given the time burden imposed by participation in this study, you will be reimbursed for your time and associated expenses. Reimbursements are a fixed amount and will be made after each weekly visit that you attend. If you consent to take part in the study and complete all the screening and baseline assessments within 14 days of consenting, you will receive a $40 gift card. If you attend your Week 1 clinic visit and complete the required assessments, you will receive an additional $40 gift card. Reimbursements of $40 gift cards will be made for each subsequent weekly visit where all required assessments are completed. An additional $40 gift card will be provided upon completion of the (optional) qualitative interview. Thus, the maximum potential amount of reimbursement over the entire duration of the study is $680 of gift cards per person.

Day	Screen	0	7	14	21	28	35	42	49	56	63	70	77	84	112	Interview
Amount	$40	$40	$40	$40	$40	$40	$40	$40	$40	$40	$40	$40	$40	$80	$40	$40*

* Optional qualitative interview

4 What do I have to do?

There are no lifestyle restrictions or dietary restrictions associated with this project. You may continue to do everything that you normally would. There are some medication restrictions, which means that certain medications should not be taken while you are taking the study medications. These include medications commonly taken for depression and other mental health conditions, and medications or other substances containing opioids. During the screening process, the study doctor will ask you about the medications that you are currently taking. It is important that you tell the study doctor what medications you are taking to ensure that it is safe for you to participate in the study. We also ask that you inform the study doctor if there are any changes to your medications or substance use at any point during the study.

If you take part in this study, you are asked to commit to taking the medication provided as instructed, in accordance with the requirements of the study. It is your responsibility to ensure the provided medications are stored safely and to not allow any other person access to the provided medications.

It is desirable that your local doctor (i.e. your GP) be advised of your decision to participate in this research project. If you have a local doctor, we strongly recommend that you inform them of your participation in this research project.

5 Other relevant information about the research project

You will be participating in a single group pilot study. In this study, all participants receive the same treatment. There will be a maximum of 20 participants taking part in this study.

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

There are no additional costs associated with participating in this research project. All medication, tests and medical care required as part of the research project will be provided to you free of charge.

This research involves collaboration with researchers from St Vincent's Hospital Sydney and the University of New South Wales.

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

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be asked to sign this Participant Information and Consent Form electronically and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with St Vincent's Hospital, Sydney.

7 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at St Vincent's Hospital. Other options are available; these include psychological therapies such as cognitive behavioural therapy and motivational interviewing. Your study doctor will discuss these options with you before you decide whether or not to take part in this research project. You can also discuss these options with your local doctor.

This research study differs from standard care for methamphetamine use, as there are currently no medications approved for the treatment of methamphetamine use in Australia.

8 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research; however, possible benefits may include reducing or stopping your methamphetamine use. Participation in this research may help to develop effective, evidence-based medication treatment options for people who use methamphetamine.

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

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

Although the side effects associated with naltrexone and bupropion at the doses provided in this study are well understood, there may be side effects that the researchers do not expect or do not know about, which may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get at any point during the study.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your study doctor may need to stop your treatment. Your study doctor will discuss the best way of managing any side effects with you.

The most commonly reported side effects associated with Contrave® 8/90 (combined naltrexone hydrochloride and bupropion hydrochloride) are nausea, constipation, vomiting (≥1/10 people), dizziness, dry mouth, and headache (≥1/100 to <1/10 people). Gastrointestinal symptoms are generally self-limited and self-resolving within 4 weeks. Contrave® can cause an increase in blood pressure as well as an increase in resting heart rate.

Side effects associated with naltrexone alone are typically mild and transient, meaning that they do not last long. Serious side effects are uncommon, however liver damage is possible at very high doses (4 to 6 times the weekly dose of this study). The following side effects have been reported among people taking naltrexone for alcohol dependence, however these may be caused by alcohol withdrawal itself, rather than the direct effects of naltrexone:

- Nausea (10 out of 100 people)
- Headache (7 out of 100 people)
- Dizziness (4 out of 100 people)
- Nervousness (4 out of 100 people)
- Fatigue (4 out of 100 people)
- Insomnia (3 out of 100 people)
- Vomiting (3 out of 100 people)
- Anxiety (2 out of 100 people)
- Sleepiness (2 out of 100 people)

The following common side effects have been reported among people taking bupropion for smoking cessation, for which a possible causal relationship with bupropion has been established. It is possible that some of these side effects may be caused by nicotine withdrawal itself, rather than the direct effects of bupropion:

Very common (at least 10 out of 100 people)

- Insomnia
- Headache
- Dry mouth
- Nausea and vomiting

Common (1-10 out of 100 people)

- Fever
- Asthenia (physical weakness or lack of strength)
- Dizziness
- Agitation
- Anxiety
- Tremor
- Concentration disturbance
- Depression
- Loss of appetite
- Abdominal pain and constipation
- Hypersensitivity reactions such as urticaria (hives), rash, pruritus (itchiness), sweating
- Visual disturbance (e.g. blurred vision, double vision), etc.), taste disorders

Bupropion is associated with an increased risk of seizures. This risk is dose dependent, meaning that the risk increases as the dose increases. At a daily dose of 450 mg, there is an approximately 4 in 1,000 chance (0.4% chance) of experiencing a seizure. If you have a pre-existing increased risk of seizure, including history of epilepsy or seizure disorder, or an acute eating disorder, or are currently undergoing acute alcohol withdrawal, you will not be able to participate in this study.

The use of bupropion has been associated with an increased risk of suicidal thinking and behaviour. If you experience thoughts of suicide, or are worried about them, talk with your study doctor. In the weekly clinic visits, your study doctor will also ask you about suicidal thoughts and behaviours.

The effects of naltrexone hydrocholoride and bupropion hydrochloride on the unborn child and on the newborn baby are not known. Because of this, it is important that research project participants are not pregnant or breast-feeding and do not become pregnant during the course of the research project. You must not participate in the research if you are pregnant or trying to become pregnant, or breast-feeding. If child-bearing is a possibility for you, you will be required to undergo a pregnancy test prior to commencing the research project. If you can make someone pregnant, you should not make someone pregnant or donate sperm for at least one month after the last dose of study medication.

All participants must avoid pregnancy during the course of the research and for a period of one month after completion of the research project. You should discuss effective methods of avoiding pregnancy with your study doctor.

If you do become pregnant whilst participating in the research project, you should advise your study doctor immediately. Your study doctor will withdraw you from the research project and advise on further medical attention should this be necessary. You must not continue in the research if you become pregnant.

You should advise your study doctor if you have made someone pregnant while participating in the research project. Your study doctor will advise on medical attention for your partner should this be necessary.

If you become upset or distressed as a result of your participation in the research, the study doctor will be able to arrange for counselling or other appropriate support. Any counselling or support will be provided by qualified staff who are not members of the research project team. This counselling will be provided free of charge.

This research project involves the collection of information about your use of drugs. Participation in the research project includes urine analysis to determine the presence of methamphetamine and opioids. That information will be stored in a re-identifiable (or coded) format. In the event that SVHS is required to disclose that information, it may be used against you in legal proceedings or otherwise. These legal obligations apply whether you are involved in a research study or not. That is, participation in this study will not change the legal obligations that SVHS has in relation to information collected from you.

Having a blood sample taken may cause some mild discomfort, bruising, minor infection or bleeding. If this happens, it can be easily treated.

10 What will happen to my test samples?

This study includes the collection of both blood and urine. These collections are a mandatory component of the research. The samples collected from you are part of routine care and will be used to help determine if it is safe for you to participate in this study. All samples collected for routine care will be individually identifiable, meaning your name will be on the sample. This is standard procedure in the hospital, and your privacy will be maintained as per hospital procedures. All physical samples will be destroyed immediately upon analysis and will not be stored for any future use.

11 What if new information arises during this research project?

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

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

12 Can I have other treatments during this research project?

Whilst you are participating in this research project, you may not be able to take some or all of the medications or treatments you have been taking for your condition or for other reasons. It is

important to tell your study doctor and the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the research project. Your study doctor should also explain to you which treatments or medications need to be stopped for the time you are involved in the research project.

13 What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by St Vincent's Hospital up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

14 Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:

- Unacceptable side effects
- The medications being shown not to be effective
- The medications being shown to work and not need further testing
- Decisions made by local regulatory/health authorities

15 What happens when the research project ends?

Should you require treatment for methamphetamine dependence in the future, you will be offered the clinic's usual care of counselling and psychosocial support and follow-up. The study drugs naltrexone and bupropion are currently not licensed for use outside of clinical trials for the treatment of methamphetamine use in Australia. When the study is finished, you should speak to your Doctor about the treatment options available to you.

If you would like to find out about the results of the research, please advise your study coordinator who will be able to email you a one-page summary of the findings after the analysis is completed.

Part 2 How is the research project being conducted?

16 What will happen to information about me?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. All information that is collected about you for the purposes of this study will be recorded with a code number instead of your name. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

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

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified.

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

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

After the study has been completed, all study-related documents will be stored securely for 15 years in line with national research guidelines, and then securely destroyed.

17 Complaints and compensation

If you suffer any injuries or complications as a result of this study, you should contact the study team as soon as possible and you will be assisted in arranging appropriate medical treatment. In the event of loss or injury, the parties involved in this research project have agreed that you may be entitled to seek compensation for any injuries or complications resulting from the study if your injury or complication is sufficiently serious and is caused by unsafe Investigational Product or by the negligence of one of the parties involved in the study (for example, the researcher, the hospital, or the treating doctor). You may wish to seek legal advice to explore your options. You do not give up any legal rights to compensation by participating in this study.

If you receive compensation that includes an amount for medical expenses, you will be required to pay for any medical treatment required for your injury or complication from those compensation monies. If you are not eligible for compensation for your injury or complication under the law, but are eligible for Medicare, then you can seek medical treatment required for your injury or complication free of charge as a public patient in any Australian public hospital. If you are not eligible for Medicare you may be able to claim compensation back via your private health insurance.

18 Who is organising and funding the research?

This research project is being conducted by St. Vincent's Hospital, Sydney and is being funded by the National Centre for Clinical Research on Emerging Drugs (NCCRED), the University of New South Wales. NCCRED is funded by the Australian Government Department of Health and Aged Care. Funding has also been obtained by a St Vincent's Clinic Foundation grant.

St. Vincent's Hospital, Sydney, may benefit financially from this research project if, for example, the project assists St. Vincent's Hospital, Sydney to obtain approval for a new drug.

You will not benefit financially from your involvement in this research project even if, for example, your samples (or knowledge acquired from analysis of your samples) prove to be of commercial value to St. Vincent's Hospital, Sydney.

In addition, if knowledge acquired through this research leads to discoveries that are of commercial value to St. Vincent's Hospital, Sydney, the study doctors or their institutions, there will be no financial benefit to you or your family from these discoveries.

St. Vincent's Hospital, Sydney will receive a payment from the University of New South Wales, National Centre for Clinical Research on Emerging Drugs for undertaking this research project.

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

19 Who has reviewed the research project?

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

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007-updated 2023)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

20 Further information and who to contact

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

If you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor (clinical contact person) as follows:

Clinical contact person

Name	Nadine Ezard
Position	Principal Investigator
Telephone	02 8382 1111
Email	Nadine.Ezard@svha.org.au

If you have any general enquiries about the study or want any further information concerning this study, you can contact the general enquiries contact person as follows:

General enquiries contact person

Name	Clare Smylie
Position	Research Officer
Telephone	02 8382 1233
Email	clare.smylie@svha.org.au

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

Complaints contact person

Name	Research Office Manager
Position	Research Office Manager
Telephone	02 8382 4960
Email	svhs.research@svha.org.au

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

Reviewing HREC approving this research and HREC Research Officer details

Reviewing HREC name	St Vincent's Hospital, Sydney HREC
Position	Research Officer
Telephone	02 8382 4960
Email	svhs.research@svha.org.au

Local HREC Office contact (Single Site -Research Governance Officer)

Name	Research Governance Officer
Position	Research Governance Officer
Telephone	02 8382 4960
Email	svhs.research@svha.org.au

ST VINCENT'S HOSPITAL SYDNEY
A FACILITY OF ST VINCENT'S HEALTH AUSTRALIA

Consent Form - *Adult providing own consent*

Title	An Open-Label Safety and Feasibility Pilot Trial Oral Naltrexone-Bupropion Combination Pharmacotherapy for Methamphetamine Use Disorder
Short Title	Naltrexone-Bupropion for Methamphetamine Use (NABU)
Protocol Number	2023/ETH00549
Project Sponsor	St Vincent's Hospital, Sydney
Coordinating Principal Investigator/ Principal Investigator	Professor Nadine Ezard
Associate Investigator(s)	Dr Krista Siefried Dr Carl Moller Dr Brendan Clifford Liam Acheson
Location	St Vincent's Hospital, Sydney, Alcohol and Drug Service

Declaration by Participant

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

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

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to St Vincent's Hospital, Sydney concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

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

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

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

Name of Participant (please print) _____

Signature _____ Date _____

Declaration by Study Doctor/Senior Researcher†

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

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

Signature _____ Date _____

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

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

Form for Withdrawal of Participation - *Adult providing own consent*

Title	An Open-Label Safety and Feasibility Pilot Trial Oral Naltrexone-Bupropion Combination Pharmacotherapy for Methamphetamine Use
Short Title	Naltrexone-Bupropion for Methamphetamine Use (NABU)
Protocol Number	2023/ETH00549
Project Sponsor	St Vincent's Hospital, Sydney
Coordinating Principal Investigator/ Principal Investigator	Professor Nadine Ezard
Associate Investigator(s)	Dr Krista Siefried Dr Carl Moller Dr Brendan Clifford Liam Acheson
Location	St Vincent's Hospital, Sydney, Alcohol and Drug Service

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with St Vincent's Hospital, Sydney.

Name of Participant (please print) _____

Signature _____ Date _____

Declaration by Study Doctor/Senior Researcher†

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

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

Signature _____ Date _____

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

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

SPIRIT-Outcomes 2022 Checklist (for combined completion of SPIRIT 2013 and SPIRIT-Outcomes 2022 items)[a]

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
Administrative information				
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	-	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	-	Page 4
	2b	All items from the World Health Organization Trial Registration Data Set	-	Page 4
Protocol version	3	Date and version identifier	-	Page 4
Funding	4	Sources and types of financial, material, and other support	-	Page 4
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	-	Page 1
	5b	Name and contact information for the trial sponsor	-	Page 8
	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	-	Page 4
	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)	-	Pages 8, 10, 13
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	-	Pages 5-7
	6b	Explanation for choice of comparators	-	NA
Objectives	7	Specific objectives or hypotheses	-	Page 7

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
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)	-	Page 7
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	-	Page 8
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)	-	Page 8, table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (for specific guidance see TIDieR checklist and guide)	-	Pages 8-10
	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)	-	Page 10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	-	Page 10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	-	Page 9
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	-	Pages 11-12

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
	12.1		Provide a rationale for the selection of the domain for the trial's primary outcome	Page 11
	12.2		If the analysis metric for the primary outcome represents within-participant change, define and justify the minimal important change in individuals	NA
	12.3		If the outcome data collected are continuous but will be analyzed as categorical (method of aggregation), specify the cutoff values to be used	NA
	12.4		If outcome assessments will be performed at several time points after randomization, state the time points that will be used for analysis	Table 1
	12.5		If a composite outcome is used, define all individual components of the composite outcome	Page 11
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)	-	Page 12
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	-	Page 8
	14.1		Define and justify the target difference between treatment groups (eg, the minimal important difference)	NA
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	-	NA
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	-	NA

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
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	-	NA
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	-	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	-	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-	NA
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	-	Page 12
	18a.1		Describe what is known about the responsiveness of the study instruments in a population similar to the study sample	Page 12
	18a.2		Describe who will assess the outcome (eg, nurse, parent)	NA
	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	-	Page 10

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
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	-	Page 13
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	-	Page 13
	20a.1		Describe any planned methods to account for multiplicity in the analysis or interpretation of the primary and secondary outcomes (eg, coprimary outcomes, same outcome assessed at multiple time points, or subgroup analyses of an outcome)	NA
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	-	NA
	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)	-	NA
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	-	Page 13
	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	-	Page 13
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	-	Page 11

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-	Page 13-14
Ethics and dissemination				
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	-	Page 14
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)	-	NA
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	-	Page 11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-	NA
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	-	Page 13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	-	Journal submission
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	-	Page 13
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	-	Page 9
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	-	Page 13
	31b	Authorship eligibility guidelines and any intended use of professional writers	-	Journal submission

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-	NA
Appendices				
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	-	On request
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	-	NA

[a]It is strongly recommended that this checklist be read in conjunction with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) Statement paper 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 and is reproduced with permission.

[b]Indicates page numbers and/or manuscript location: to be completed by authors.

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Supplementary Table 2 - Schedule of Assessments

Study day	0[a]	1[b]	7	14	21	28	35	42	49	56	63	70	77	84	112
Protocol window - days	-14	0	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3
Study Week	0	0	1	2	3	4	5	6	7	8	9	10	11	12	16
Assessments															
Pre-screening	•														
Informed consent	•														
Demographics, medical history	•														
Confirm eligibility	•	•													
Prior concomitant medication	•														
Medical review	•													•	
Weight		•	•	•	•	•	•	•	•	•	•	•	•	•	
Concomitant medication	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Concomitant psychosocial care	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Investigational Product															
Study medication dispensed		•	•		•		•		•		•		•		
Medication pack returned for pill count			•		•		•		•		•		•	•	
Safety															
Adverse events		•	•	•	•	•	•	•	•	•	•	•	•	•	•
Blood pressure, pulse, temperature	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
C-SSRS Lifetime/Recent		•													
C-SSRS Since Last Visit						•				•				•	•
Pathology															
hCG±	•					•				•				•	
UDS POC all substances	•														
UDS POC opioids		•[d]				•				•				•	
UDS POC MA		•	•	•	•	•	•	•	•	•	•	•	•	•	
Liver function tests	•														
Questionnaires															
TLFB (alcohol, MA, opioids, cigarettes/nicotine)	•	•[d]				•				•				•	•
SURGE	•	•				•				•				•	•
Daily methamphetamine use[c]		•	•	•	•	•	•	•	•	•	•	•	•	•	
Daily adherence[c]		•	•	•	•	•	•	•	•	•	•	•	•	•	
SMAQ			•	•	•	•	•	•	•	•	•	•	•	•	
WURS		•													
ESSI		•													
Promis-29		•												•	
DASS-21		•												•	
CVAS		•												•	
AWQ		•												•	
TSQM v. II														•	
Optional Interview															
Qualitative interview														◄—►	

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Supplementary Table 2 - Schedule of Assessments

a	= screening	b	= baseline (Day 1, first dose of study investigational product)
•	= study activity	c	= daily smartphone EMA (self-report)
↔	= study activity conducted any time on indicated days inclusive	±	= people of childbearing potential only
	= post-primary endpoint (taper-down and follow-up periods)	d	= TLFB, UDS POC (opioids) must be repeated on day of first dose if screening and baseline visits not combined
AWQ	Amphetamine Withdrawal Questionnaire	Promis-29	Patient-Reported Outcomes Measurement Information System-29
C-SSRS	Columbia Suicide Severity Rating Scale	SMAQ	Simplified Medication Adherence Questionnaire
CVAS	Craving Visual Analogue Scale	SURGE	Substance Use Recovery Goals and Expectations
DASS-21	Depression Anxiety Stress Scales	TLFB	Timeline Follow-Back
ESSI	ENRICHD Social Support Inventory	TSQM	Treatment Satisfaction Questionnaire for Medication
hCG	Human chorionic gonadotropin (urine)	UDS POC	Urine drug screen – point of care
		WURS	Wender Utah Rating Scale

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)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-092032.R2
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Date Submitted by the Author:	16-Jan-2025
Complete List of Authors:	Siefried, Krista J; University of New South Wales; St Vincent's Hospital Sydney Acheson, Liam; University of New South Wales; St Vincent's Hospital Sydney Clifford, Brendan; University of New South Wales; St Vincent's Hospital Sydney Moller, Carl; University of New South Wales Brett, Jonathan.; St Vincent's Hospital Sydney, Department of Clinical Pharmacology & Toxicology; University of New South Wales Christmass, Michael; Western Australia Mental Health Commission Dunlop, Adrian; Hunter New England Local Health District; New South Wales Ministry of Health Haber, Paul; University of Sydney - Camperdown and Darlington Campus; Royal Prince Alfred Hospital Jutras-Aswad , Didier; Centre Hospitalier de l'Université de Montréal; Université de Montréal, Department of Psychiatry and Addictology Lintzeris, Nicholas; New South Wales Ministry of Health; The University of Sydney Faculty of Medicine and Health Morley, Kirsten; The University of Sydney Faculty of Medicine and Health; Royal Prince Alfred Hospital Shoptaw, Steven; University of California Los Angeles, Family Medicine / Psychiatry and Biobehavioural Sciences Trivedi, Madhukar; The University of Texas Southwestern Medical Center Ezard, Nadine; University of New South Wales; St Vincent's Hospital Sydney
Primary Subject Heading:	Addiction
Secondary Subject Heading:	Pharmacology and therapeutics, Research methods, Public health, Mental health
Keywords:	Clinical Trial, MENTAL HEALTH, Substance misuse < PSYCHIATRY, PUBLIC HEALTH

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Title

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

Authors

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

1 The National Centre for Clinical Research on Emerging Drugs, c/o the University of New South Wales, Sydney, Australia

2 St Vincent's Hospital Alcohol and Drug Service, Sydney, Australia

3 The National Drug and Alcohol Research Centre, the University of New South Wales, Sydney, Australia

4 New South Wales Drug and Alcohol Clinical Research and Improvement Network, c/o the New South Wales Ministry of Health, Sydney, Australia

5 St Vincent's Hospital Clinical Pharmacology and Toxicology Unit and Psychiatric, Alcohol and Non-Prescription Drugs Assessment Unit, Sydney, Australia

7 Next Step Drug and Alcohol Services, Western Australia Mental Health Commission, Perth, Australia

8 Drug and Alcohol Clinical Services, Hunter New England Local Health District, Newcastle, Australia

9 School of Medicine and Public Health, the University of Newcastle, Newcastle, Australia

10 Faculty of Medicine and Health, Central Clinical School, Discipline of Addiction Medicine University of Sydney, Sydney, Australia

11 Edith Collins Centre for Translational Research, Drug Health Services, Royal Prince Alfred Hospital, Sydney, Australia

12 Research Centre, Centre Hospitalier de l'Université de Montréal (CRCHUM), Montréal, Canada

13 Department of Psychiatry and Addictology, Faculty of Medicine, Université de Montréal, Montréal, Canada

14 The Langton Centre, South East Sydney Local Health District, Sydney, Australia

15 Department of Family Medicine, The University of California Los Angeles, Los Angeles, USA

16 Peter O'Donnell Jr. Brain Institute, the University of Texas Southwestern Medical Center

Corresponding author:

Krista J Siefried

The National Centre for Clinical Research on Emerging Drugs (NCCRED)

c/o the University of New South Wales

Sydney, Australia

P: +61 410 360 102

E: krista.siefried@svha.org.au

Declarations / Conflicts of interest

KJS, LA, BC, CM, MC, AD, DJA, KM, SS, NE – none to declare.

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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 United States 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 (40mg/450mg 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 psychosocial therapy. Primary outcomes are safety (measured by treatment emergent adverse events / adverse reactions), and feasibility (measured by the time taken to recruit, the proportion of ineligible participants, retention in study, and study medication adherence). Secondary outcomes will assess methamphetamine use, craving, and withdrawal; treatment goals and expectations; physical and psychological wellbeing; 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 findings are accessible to participants and people who use methamphetamines.

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

Trial Registration: ANZCTR: ACTRN12623000866606 (protocol version 2.1 dated 08 April 2024)

Keywords: methamphetamine; substance use disorder; naltrexone; bupropion; clinical trial

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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 amongst the highest in the world [1]. MAUD is associated with increased mortality and morbidity, including from 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 United States (US) government-sponsored health plans. A recent Cochrane review found that as compared to 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 FDA 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 accuracy of measures of adherence and methamphetamine use in clinical trials.

Bupropion hydrochloride is an atypical antidepressant and noradrenaline 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 RCTs (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 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 US 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 two 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, combination extended release naltrexone (32mg) / bupropion (360mg) led to significant weight loss in treatment of overweight/obesity [22]. For this reason, it is approved for this indication in the US, Canada, Europe and Australia. In theory, this improves access to this formulation.

The Trivedi study used an extended-release injectable naltrexone (380mg every three weeks) and oral extended-release bupropion (450mg daily). However, injectable

naltrexone is not widely available outside the US, Europe, Russia, and the United Kingdom. Even within the US, it is estimated to cost $1,000-$1,700USD per dose [24], rendering its likely uptake inequitable. Similarly, access to extended-release bupropion is limited outside the US, 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 wellbeing, 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 (SURGE) 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 (SPIRIT) guidelines [27], a checklist for which is available in **Supplementary 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 from patients seeking treatment at the clinic, referrals from nearby services, and by 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, Adverse Events), 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, 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 (8mg/90mg) [32]. A five-day dose escalation period will commence with one tablet on Day One, increasing to the investigational dose of five tablets (three morning, two evening) by Day Five, which commences the target maintenance dose of 40mg/450mg. The dose escalation period allows a participant to adjust to the medication,

and is slightly longer than the three 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 study drug). A five-day taper period will commence on Day 85, with medication 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: 32mg/360mg) [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 management of stimulant use. Standard of care counselling involves evidence-based motivational interviewing and cognitive behavioural therapy [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 to 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 50mg naltrexone equivalency data.

In Australia, bupropion is approved for use in nicotine dependence to a maximum dose of 300mg 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 US, 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 twice daily (32mg naltrexone and 360mg bupropion daily). This study will use a maximum dose of three tablets in the morning and two tablets in the afternoon (40mg naltrexone and 450mg bupropion daily). Study drug will be prepared by the St Vincent's Hospital Sydney clinical trials pharmacist in medication packs containing one weeks supply for the induction period, then for the remainder of the study two packs containing one weeks' 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 SMAQ adherence questionnaire [36] responses.

Stopping criteria

If a participant experiences a Grade 3 or Grade 4 Adverse Event (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 adverse events / 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 AE's, in addition to being encouraged to provide any information spontaneously at weekly study visits with study coordinators (Registered 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 pre-determined 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 known risks of the study medications, per the product label, and participant's past medical history/comorbidities. All AE's will receive final sign-off by the site PI.

Feasibility will be assessed by: (i) the time taken to recruit the sample; (ii) the proportion of ineligible participants at pre-screening and screening; (iii) retention rate in study; and (iv) 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 pre-screened 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 two weeks, however the following assessments must be completed within 24 hours of the first dose of study drug: urine for human chorionic gonadotropin (hCG); UDS POC (all drugs – must be negative for opioids); and timeline follow-back [9] for methamphetamines, opioids, alcohol, 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 (WURS) [50] to retrospectively evaluate the presence of childhood ADHD symptoms; and the ENRICHD Social Support Inventory (ESSI) [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 adverse events relating to suicidal ideation to 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 (e.g. 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 **Supplementary 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 that care about them, to drive the research agenda. One of the key priorities was a 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 is 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 $40 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 $80. An additional $40 gift card will be provided upon completion of the (optional) qualitative interview. Thus, the maximum potential reimbursement is $680 of gift cards per person.

Data Collection and Reporting

This study will use electronic data capture in the form of REDCap (Research Electronic Data Capture) [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 re-identifiable 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 no less than 15 years as per ICH-GCP guidelines [38]. Data will be published in a peer-review 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 chi-square and relative risk. For the analysis of qualitative interview data, a thematic analysis approach will be undertaken [55].

Monitoring

Data Safety Monitoring Board (DSMB)

A 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 Adverse Events (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 in the study. A copy of this is supplied in the **Supplementary text**. 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 US. 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, whilst 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. 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 300mg [14], and whilst unsuccessful in primary analysis; post hoc analyses in one study found a statistically significant effect amongst 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 two week baseline period) [57]. Similar effects were demonstrated in another study, where a planned sub-group 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 to 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 aims to be as closely representative of the underlying population as possible. Whilst 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 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 smart phone EMA app for adherence assessment and methamphetamine use. More frequent ongoing assessment of methamphetamine use may be more reliable than self-report 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 POC tests. Whilst 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 application, 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 (e.g. 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.

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Tables and Figures

Table 1 – Eligibility Criteria

Inclusion criteria	Exclusions criteria
All participants must / must be:	*All participants must not:*
▪ ≥18 years of age	▪ Be currently pregnant, breast feeding, 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: (i) dependent on opioids, (ii) in acute opioid withdrawal, or (iii) has an anticipated need for opioid-containing medications at any point during the study (e.g. planned surgery)
▪ Provide a urine drug screen (UDS) point of care (POC) test positive for methamphetamines (during screening) and negative for opioids (during screening, repeated on 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 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 [AST] or alanine transaminase [ALT] > 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

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	▪ Be concomitantly prescribed MAOIs (at least 14 days should elapse between discontinuation of MAOIs and initiation of treatment with investigational product) ▪ Have hypertension uncontrolled by a single anti-hypertensive 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

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	8mg/90mg
2	1	1	16mg/180mg
3	2	1	24mg/270mg
4	2	2	32mg/360mg
5 – 84	3	2	40mg/450mg
85	2	2	32mg/360mg
86	2	1	24mg/270mg
87	1	1	16mg/180mg
88[a]	1	0	8mg/90mg
89	0	0	0mg

[a] Day 88 is final study drug dose

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 past 28-days from Baseline to Days 28, 56, 84
Proportion of methamphetamine-positive point of care urine drug screens (POC UDS)	Point of care urine drug screens (POC UDS)	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 wellbeing 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 (AWQ) (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

SPIRIT | CONSORT OUTCOMES
Reporting Guidelines for Trial Outcomes

SPIRIT-Outcomes 2022 Checklist (for combined completion of SPIRIT 2013 and SPIRIT-Outcomes 2022 items)[a]

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
Administrative information				
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	-	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	-	Page 4
	2b	All items from the World Health Organization Trial Registration Data Set	-	Page 4
Protocol version	3	Date and version identifier	-	Page 4
Funding	4	Sources and types of financial, material, and other support	-	Page 4
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	-	Page 1
	5b	Name and contact information for the trial sponsor	-	Page 8
	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	-	Page 4
	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)	-	Pages 8, 10, 13
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	-	Pages 5-7
	6b	Explanation for choice of comparators	-	NA
Objectives	7	Specific objectives or hypotheses	-	Page 7

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
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)	-	Page 7
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	-	Page 8
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)	-	Page 8, table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (for specific guidance see TIDieR checklist and guide)	-	Pages 8-10
	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)	-	Page 10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	-	Page 10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	-	Page 9
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	-	Pages 11-12

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
	12.1		Provide a rationale for the selection of the domain for the trial's primary outcome	Page 11
	12.2		If the analysis metric for the primary outcome represents within-participant change, define and justify the minimal important change in individuals	NA
	12.3		If the outcome data collected are continuous but will be analyzed as categorical (method of aggregation), specify the cutoff values to be used	NA
	12.4		If outcome assessments will be performed at several time points after randomization, state the time points that will be used for analysis	Table 1
	12.5		If a composite outcome is used, define all individual components of the composite outcome	Page 11
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)	-	Page 12
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	-	Page 8
	14.1		Define and justify the target difference between treatment groups (eg, the minimal important difference)	NA
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	-	NA
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	-	NA

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
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	-	NA
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	-	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	-	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	-	NA
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	-	Page 12
	18a.1		Describe what is known about the responsiveness of the study instruments in a population similar to the study sample	Page 12
	18a.2		Describe who will assess the outcome (eg, nurse, parent)	NA
	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	-	Page 10

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
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	-	Page 13
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	-	Page 13
	20a.1		Describe any planned methods to account for multiplicity in the analysis or interpretation of the primary and secondary outcomes (eg, coprimary outcomes, same outcome assessed at multiple time points, or subgroup analyses of an outcome)	NA
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	-	NA
	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)	-	NA
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	-	Page 13
	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	-	Page 13
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	-	Page 11

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	-	Page 13-14
Ethics and dissemination				
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	-	Page 14
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)	-	NA
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	-	Page 11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	-	NA
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	-	Page 13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	-	Journal submission
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	-	Page 13
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	-	Page 9
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	-	Page 13
	31b	Authorship eligibility guidelines and any intended use of professional writers	-	Journal submission

Section	Item No.	SPIRIT 2013 Item	SPIRIT-Outcomes 2022 item	Location Reported[b]
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	-	NA
Appendices				
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	-	On request
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	-	NA

[a]It is strongly recommended that this checklist be read in conjunction with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) Statement paper 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 and is reproduced with permission.

[b]Indicates page numbers and/or manuscript location: to be completed by authors.

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Supplementary Table 2 - Schedule of Assessments

Study day	0[a]	1[b]	7	14	21	28	35	42	49	56	63	70	77	84	112
Protocol window - days	-14	0	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3
Study Week	0	0	1	2	3	4	5	6	7	8	9	10	11	12	16
Assessments															
Pre-screening	•														
Informed consent	•														
Demographics, medical history	•														
Confirm eligibility	•	•													
Prior concomitant medication	•														
Medical review	•													•	
Weight		•	•	•	•	•	•	•	•	•	•	•	•	•	
Concomitant medication	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Concomitant psychosocial care	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Investigational Product															
Study medication dispensed		•	•		•		•		•		•		•		
Medication pack returned for pill count			•		•		•		•		•		•	•	
Safety															
Adverse events		•	•	•	•	•	•	•	•	•	•	•	•	•	•
Blood pressure, pulse, temperature	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
C-SSRS Lifetime/Recent		•													
C-SSRS Since Last Visit						•				•				•	•
Pathology															
hCG±	•					•				•				•	
UDS POC all substances	•														
UDS POC opioids		•[d]				•				•				•	
UDS POC MA		•	•	•	•	•	•	•	•	•	•	•	•	•	
Liver function tests	•														
Questionnaires															
TLFB (alcohol, MA, opioids, cigarettes/nicotine)	•	•[d]				•				•				•	•
SURGE	•	•				•				•				•	•
Daily methamphetamine use[c]		•	•	•	•	•	•	•	•	•	•	•	•	•	
Daily adherence[c]		•	•	•	•	•	•	•	•	•	•	•	•	•	
SMAQ			•	•	•	•	•	•	•	•	•	•	•	•	
WURS		•													
ESSI		•													
Promis-29		•												•	
DASS-21		•												•	
CVAS		•												•	
AWQ		•												•	
TSQM v. II														•	
Optional Interview															
Qualitative interview														◄►	

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Supplementary Table 2 - Schedule of Assessments

a	= screening	b	= baseline (Day 1, first dose of study investigational product)
•	= study activity	c	= daily smartphone EMA (self-report)
◄►	= study activity conducted any time on indicated days inclusive	±	= people of childbearing potential only
	= post-primary endpoint (taper-down and follow-up periods)	d	= TLFB, UDS POC (opioids) must be repeated on day of first dose if screening and baseline visits not combined
AWQ	Amphetamine Withdrawal Questionnaire	Promis-29	Patient-Reported Outcomes Measurement Information System-29
C-SSRS	Columbia Suicide Severity Rating Scale	SMAQ	Simplified Medication Adherence Questionnaire
CVAS	Craving Visual Analogue Scale	SURGE	Substance Use Recovery Goals and Expectations
DASS-21	Depression Anxiety Stress Scales	TLFB	Timeline Follow-Back
ESSI	ENRICHD Social Support Inventory	TSQM	Treatment Satisfaction Questionnaire for Medication
hCG	Human chorionic gonadotropin (urine)	UDS POC	Urine drug screen – point of care
		WURS	Wender Utah Rating Scale

Participant Information Sheet/Consent Form

Interventional Study - *Adult providing own consent*

St Vincent's Hospital, Sydney

Title	An Open-Label Safety and Feasibility Pilot Trial of Oral Naltrexone-Bupropion Combination Pharmacotherapy for Methamphetamine Use
Short Title	Naltrexone-Bupropion for Methamphetamine Use (NABU)
Protocol Number	2023/ETH00549
Project Sponsor	St Vincent's Hospital, Sydney
Coordinating Principal Investigator/ Principal Investigator	Professor Nadine Ezard
Associate Investigator(s)	Dr Krista Siefried Dr Carl Moller Dr Brendan Clifford Liam Acheson
Location	St Vincent's Hospital, Sydney, Alcohol and Drug Service

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project. This is because you have indicated that you currently use methamphetamine and are interested in managing, reducing, or stopping your methamphetamine use. The research project is testing a new treatment for methamphetamine use disorder. The new treatment is called naltrexone-bupropion combination therapy.

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

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

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

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:

- Understand what you have read

- Consent to take part in the research project
- Consent to have the tests and treatments that are described
- Consent to the use of your personal and health information as described.

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

2 What is the purpose of this research?

There are currently no approved medications in Australia to help treat methamphetamine dependence. This study aims to determine if it is safe and feasible for people who are using methamphetamine to be given two medications, called naltrexone and bupropion, combined together, to help manage, reduce, or stop their methamphetamine use.

Medications, drugs and devices have to be approved for use by the Australian Federal Government. A combination of naltrexone and bupropion (with the brand name Contrave® 8/90) is approved in Australia for weight reduction in obesity, however it is currently not approved to treat methamphetamine use disorder. Therefore, this is an experimental treatment for methamphetamine use disorder. This means that this medication must be tested to see if it is a safe and effective treatment for people with methamphetamine dependence.

This research has been initiated by the study doctor, Professor Nadine Ezard. This research is funded by the National Centre for Clinical Research on Emerging Drugs, University of New South Wales and a St Vincent's Clinic Foundation grant.

3 What does participation in this research involve?

If, after reading this information and discussing this research with your doctor, friends or family, you decide to take part, you will be asked to digitally sign the Consent Form confirming that you agree to participate. This study is designed to provide you with a combined formulation of naltrexone and bupropion, as well as your usual standard of care provided by St Vincent's Hospital, Sydney. This means that except for receiving the study medication, the medical care that you will receive will be the same whether you decide to take part in this research or not.

Screening and baseline assessments

Before you take part in the study, the researchers need to make sure it is safe and appropriate for you to do so. This will involve some screening procedures, including questionnaires, medical assessments, blood tests, and urine tests. These procedures are as follows:

- Review of your medical history including previous instances of substance use treatment, hepatitis C (HCV) history, and any medications you are taking currently.
- Routine medical screening, including blood pressure, pulse, temperature, and weight. All of these measures are non-invasive.
- Routine blood and urine tests, including:
    - Liver function tests (LFT) – these are blood tests that provide information about how your liver is working. These tests will require less than 5mL of blood.

- A dip-stick urine drug test for methamphetamine and opioids. This will require approximately 2-3 tablespoons (50mL) of urine.
- A pregnancy blood test will also be conducted if you are of childbearing potential.

- A series of baseline questionnaires to assess your:
  - Use of substances (including methamphetamine, opioids, alcohol, cigarettes, etc.) over the past 4 weeks (Timeline Follow Back (TLFB) method)
  - Craving for methamphetamine
  - Withdrawal from methamphetamine
  - Thoughts of suicide and acts of suicidal behaviour
  - Feelings of depression and anxiety
  - Quality of life
  - Social support
  - Care received outside St Vincent's Hospital
  - Physical health symptoms

These screening and baseline procedures are expected to take between one and two hours. These procedures can be completed over more than one clinic visit if necessary, but all procedures must be completed with 14 days of consenting to participate in the study.

Medication

This study involves a commercially available medication (branded as Contrave® 8/90) which contains naltrexone hydrochloride and bupropion hydrochloride. The medication is in tablet form and is taken orally (swallowed). You will be required to take this medication daily for 88 days (just under 13 weeks). The maximum number of tablets to be taken is 5 per day. The medication will be provided to you once a week for the first week, then every two weeks for the remainder of the study. The medication will be provided in a pack containing one weeks' supply for the first week, then two weeks' supply from then on, of the medications, separated into daily doses. Each pack will contain a maximum of 70 tablets of the medication, separated into morning and afternoon doses for each day. When you pick up your study medication you will be asked to return the previous pack, with any unused medication to study staff.

The dose of medication will start low and will be increased gradually each day over the first five days of the study, as follows:

- Day 1: 1 tablet morning (1 tablet per day)
- Day 2: 1 tablet morning & 1 tablet evening (2 tablets per day)
- Day 3: 2 tablets morning & 1 tablet evening (3 tablets per day)
- Day 4: 2 tablets morning & 2 tablets evening (4 tablets per day)
- Day 5: 3 tablets morning & 2 tablets evening (5 tablets per day)

From day 5 onwards the medication dose will remain at 5 tablets per day until the end of Week 12 (up to day 84 inclusive). Then the dose will be gradually decreased in Week 13, as follows:

- Day 85: 2 tablets morning & 2 tablets evening (4 tablets per day)
- Day 86: 2 tablets morning & 1 tablets evening (3 tablets per day)
- Day 87: 1 tablet morning & 1 tablet evening (2 tablets per day)
- Day 88: 1 tablet morning FINAL DOSE (1 tablet per day)

Daily medication reporting

Every day during the medication period (88 days) you will asked to report whether you have taken the daily medication dose by responding yes/no to a message sent to your mobile phone.

Daily methamphetamine reporting

Every day during the medication period (88 days) you will be asked to report whether you have consumed methamphetamine within the last 24 hours by responding to a message sent to your mobile phone.

Weekly clinic visits

After enrolling in the study and completing all the screening and baseline measures, you will be required to attend St Vincent's Hospital, Sydney, Alcohol and Drug Service once a week for 13 weeks, plus a visit at Week 16. The purpose of these visits is to provide you with the study medication for each week (provided fortnightly),to monitor you for any medication related side effects, and to test your urine for methamphetamine. Each visit will take approximately one hour.

Each week, you will be asked about care received outside St Vincent's Hospital, other medications you are taking, and physical health symptoms. Your blood pressure, pulse, temperature, and weight will be recorded at each weekly visit. You will provide a urine sample for a point of care methamphetamine screen, and every four weeks for opioid screening and for pregnancy if you are of childbearing potential. In addition, every four weeks you will be asked about your drug consumption (methamphetamine, opioids, alcohol, and cigarettes/nicotine). At the study visit on Day 84, you will also be asked to complete many of the same questionnaires that you completed at the start of the study (baseline), assessing feelings of suicide, depression and anxiety, quality of life, social support, craving,

Optional Psychological Therapy

You will be offered psychological therapy as part of this study as per routine care at St Vincent's Alcohol and Drug Service. This psychological therapy is optional and it is up to you whether you would like to take part. Whether you decide to take part in the psychological therapy or not will not affect the care you receive or your participation in the study.

Optional Interview

We would also like to interview you about your experiences related to taking part in the study. This interview is optional, and you can participate in the main study without participating in the interview. At the Week 13 clinic visit you will be asked if you would like to take part in the interview. Your decision will not affect the care you receive in any way, or your participation in the rest of the study.

Interviews will be semi-structured, meaning that the interviewer will have questions to ask you, but some questions may be changed or skipped depending on what you wish to talk about.

Interviews will conducted one-on-one with a trained research staff member. The interview will take approximately 30 minutes. The interview will focus on your goals around managing your methamphetamine use, your expectations around taking the study medication, your experiences of taking the study medication, any concerns relating to the study medication, and your experience of taking part in the study in general.

Interviews will be conducted in a private treatment or interview room at St Vincent's Hospital, Sydney. Interviews will be conducted between Days 84 and 112 (Weeks 13 and 16) of the study. Interviews will be audio recorded and then transcribed (written down) in full.

Reimbursement

Participation in this study requires attending St Vincent's Hospital, Sydney, Alcohol and Drug Service every week for 13 weeks, in addition to taking the study medication daily, and one visit four weeks later. Each weekly visit will take approximately one hour. Given the time burden imposed by participation in this study, you will be reimbursed for your time and associated expenses. Reimbursements are a fixed amount and will be made after each weekly visit that you attend. If you consent to take part in the study and complete all the screening and baseline assessments within 14 days of consenting, you will receive a $40 gift card. If you attend your Week 1 clinic visit and complete the required assessments, you will receive an additional $40 gift card. Reimbursements of $40 gift cards will be made for each subsequent weekly visit where all required assessments are completed. An additional $40 gift card will be provided upon completion of the (optional) qualitative interview. Thus, the maximum potential amount of reimbursement over the entire duration of the study is $680 of gift cards per person.

Day	Screen	0	7	14	21	28	35	42	49	56	63	70	77	84	112	Interview
Amount	$40	$40	$40	$40	$40	$40	$40	$40	$40	$40	$40	$40	$40	$80	$40	$40*

* Optional qualitative interview

4 What do I have to do?

There are no lifestyle restrictions or dietary restrictions associated with this project. You may continue to do everything that you normally would. There are some medication restrictions, which means that certain medications should not be taken while you are taking the study medications. These include medications commonly taken for depression and other mental health conditions, and medications or other substances containing opioids. During the screening process, the study doctor will ask you about the medications that you are currently taking. It is important that you tell the study doctor what medications you are taking to ensure that it is safe for you to participate in the study. We also ask that you inform the study doctor if there are any changes to your medications or substance use at any point during the study.

If you take part in this study, you are asked to commit to taking the medication provided as instructed, in accordance with the requirements of the study. It is your responsibility to ensure the provided medications are stored safely and to not allow any other person access to the provided medications.

It is desirable that your local doctor (i.e. your GP) be advised of your decision to participate in this research project. If you have a local doctor, we strongly recommend that you inform them of your participation in this research project.

5 Other relevant information about the research project

You will be participating in a single group pilot study. In this study, all participants receive the same treatment. There will be a maximum of 20 participants taking part in this study.

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

There are no additional costs associated with participating in this research project. All medication, tests and medical care required as part of the research project will be provided to you free of charge.

This research involves collaboration with researchers from St Vincent's Hospital Sydney and the University of New South Wales.

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

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be asked to sign this Participant Information and Consent Form electronically and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with St Vincent's Hospital, Sydney.

7 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at St Vincent's Hospital. Other options are available; these include psychological therapies such as cognitive behavioural therapy and motivational interviewing. Your study doctor will discuss these options with you before you decide whether or not to take part in this research project. You can also discuss these options with your local doctor.

This research study differs from standard care for methamphetamine use, as there are currently no medications approved for the treatment of methamphetamine use in Australia.

8 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research; however, possible benefits may include reducing or stopping your methamphetamine use. Participation in this research may help to develop effective, evidence-based medication treatment options for people who use methamphetamine.

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

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

Although the side effects associated with naltrexone and bupropion at the doses provided in this study are well understood, there may be side effects that the researchers do not expect or do not know about, which may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get at any point during the study.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your study doctor may need to stop your treatment. Your study doctor will discuss the best way of managing any side effects with you.

The most commonly reported side effects associated with Contrave® 8/90 (combined naltrexone hydrochloride and bupropion hydrochloride) are nausea, constipation, vomiting (≥1/10 people), dizziness, dry mouth, and headache (≥1/100 to <1/10 people). Gastrointestinal symptoms are generally self-limited and self-resolving within 4 weeks. Contrave® can cause an increase in blood pressure as well as an increase in resting heart rate.

Side effects associated with naltrexone alone are typically mild and transient, meaning that they do not last long. Serious side effects are uncommon, however liver damage is possible at very high doses (4 to 6 times the weekly dose of this study). The following side effects have been reported among people taking naltrexone for alcohol dependence, however these may be caused by alcohol withdrawal itself, rather than the direct effects of naltrexone:

- Nausea (10 out of 100 people)
- Headache (7 out of 100 people)
- Dizziness (4 out of 100 people)
- Nervousness (4 out of 100 people)
- Fatigue (4 out of 100 people)
- Insomnia (3 out of 100 people)
- Vomiting (3 out of 100 people)
- Anxiety (2 out of 100 people)
- Sleepiness (2 out of 100 people)

The following common side effects have been reported among people taking bupropion for smoking cessation, for which a possible causal relationship with bupropion has been established. It is possible that some of these side effects may be caused by nicotine withdrawal itself, rather than the direct effects of bupropion:

Very common (at least 10 out of 100 people)

- Insomnia
- Headache
- Dry mouth
- Nausea and vomiting

Common (1-10 out of 100 people)

- Fever
- Asthenia (physical weakness or lack of strength)
- Dizziness
- Agitation
- Anxiety
- Tremor
- Concentration disturbance
- Depression
- Loss of appetite
- Abdominal pain and constipation
- Hypersensitivity reactions such as urticaria (hives), rash, pruritus (itchiness), sweating
- Visual disturbance (e.g. blurred vision, double vision), etc.), taste disorders

Bupropion is associated with an increased risk of seizures. This risk is dose dependent, meaning that the risk increases as the dose increases. At a daily dose of 450 mg, there is an approximately 4 in 1,000 chance (0.4% chance) of experiencing a seizure. If you have a pre-existing increased risk of seizure, including history of epilepsy or seizure disorder, or an acute eating disorder, or are currently undergoing acute alcohol withdrawal, you will not be able to participate in this study.

The use of bupropion has been associated with an increased risk of suicidal thinking and behaviour. If you experience thoughts of suicide, or are worried about them, talk with your study doctor. In the weekly clinic visits, your study doctor will also ask you about suicidal thoughts and behaviours.

The effects of naltrexone hydrocholoride and bupropion hydrochloride on the unborn child and on the newborn baby are not known. Because of this, it is important that research project participants are not pregnant or breast-feeding and do not become pregnant during the course of the research project. You must not participate in the research if you are pregnant or trying to become pregnant, or breast-feeding. If child-bearing is a possibility for you, you will be required to undergo a pregnancy test prior to commencing the research project. If you can make someone pregnant, you should not make someone pregnant or donate sperm for at least one month after the last dose of study medication.

All participants must avoid pregnancy during the course of the research and for a period of one month after completion of the research project. You should discuss effective methods of avoiding pregnancy with your study doctor.

If you do become pregnant whilst participating in the research project, you should advise your study doctor immediately. Your study doctor will withdraw you from the research project and advise on further medical attention should this be necessary. You must not continue in the research if you become pregnant.

You should advise your study doctor if you have made someone pregnant while participating in the research project. Your study doctor will advise on medical attention for your partner should this be necessary.

If you become upset or distressed as a result of your participation in the research, the study doctor will be able to arrange for counselling or other appropriate support. Any counselling or support will be provided by qualified staff who are not members of the research project team. This counselling will be provided free of charge.

This research project involves the collection of information about your use of drugs. Participation in the research project includes urine analysis to determine the presence of methamphetamine and opioids. That information will be stored in a re-identifiable (or coded) format. In the event that SVHS is required to disclose that information, it may be used against you in legal proceedings or otherwise. These legal obligations apply whether you are involved in a research study or not. That is, participation in this study will not change the legal obligations that SVHS has in relation to information collected from you.

Having a blood sample taken may cause some mild discomfort, bruising, minor infection or bleeding. If this happens, it can be easily treated.

10 What will happen to my test samples?

This study includes the collection of both blood and urine. These collections are a mandatory component of the research. The samples collected from you are part of routine care and will be used to help determine if it is safe for you to participate in this study. All samples collected for routine care will be individually identifiable, meaning your name will be on the sample. This is standard procedure in the hospital, and your privacy will be maintained as per hospital procedures. All physical samples will be destroyed immediately upon analysis and will not be stored for any future use.

11 What if new information arises during this research project?

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

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

12 Can I have other treatments during this research project?

Whilst you are participating in this research project, you may not be able to take some or all of the medications or treatments you have been taking for your condition or for other reasons. It is

important to tell your study doctor and the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the research project. Your study doctor should also explain to you which treatments or medications need to be stopped for the time you are involved in the research project.

13 What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by St Vincent's Hospital up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

14 Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:

- Unacceptable side effects
- The medications being shown not to be effective
- The medications being shown to work and not need further testing
- Decisions made by local regulatory/health authorities

15 What happens when the research project ends?

Should you require treatment for methamphetamine dependence in the future, you will be offered the clinic's usual care of counselling and psychosocial support and follow-up. The study drugs naltrexone and bupropion are currently not licensed for use outside of clinical trials for the treatment of methamphetamine use in Australia. When the study is finished, you should speak to your Doctor about the treatment options available to you.

If you would like to find out about the results of the research, please advise your study coordinator who will be able to email you a one-page summary of the findings after the analysis is completed.

Part 2 How is the research project being conducted?

16 What will happen to information about me?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. All information that is collected about you for the purposes of this study will be recorded with a code number instead of your name. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

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

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified.

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

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

After the study has been completed, all study-related documents will be stored securely for 15 years in line with national research guidelines, and then securely destroyed.

17 Complaints and compensation

If you suffer any injuries or complications as a result of this study, you should contact the study team as soon as possible and you will be assisted in arranging appropriate medical treatment. In the event of loss or injury, the parties involved in this research project have agreed that you may be entitled to seek compensation for any injuries or complications resulting from the study if your injury or complication is sufficiently serious and is caused by unsafe Investigational Product or by the negligence of one of the parties involved in the study (for example, the researcher, the hospital, or the treating doctor). You may wish to seek legal advice to explore your options. You do not give up any legal rights to compensation by participating in this study.

If you receive compensation that includes an amount for medical expenses, you will be required to pay for any medical treatment required for your injury or complication from those compensation monies. If you are not eligible for compensation for your injury or complication under the law, but are eligible for Medicare, then you can seek medical treatment required for your injury or complication free of charge as a public patient in any Australian public hospital. If you are not eligible for Medicare you may be able to claim compensation back via your private health insurance.

18 Who is organising and funding the research?

This research project is being conducted by St. Vincent's Hospital, Sydney and is being funded by the National Centre for Clinical Research on Emerging Drugs (NCCRED), the University of New South Wales. NCCRED is funded by the Australian Government Department of Health and Aged Care. Funding has also been obtained by a St Vincent's Clinic Foundation grant.

St. Vincent's Hospital, Sydney, may benefit financially from this research project if, for example, the project assists St. Vincent's Hospital, Sydney to obtain approval for a new drug.

You will not benefit financially from your involvement in this research project even if, for example, your samples (or knowledge acquired from analysis of your samples) prove to be of commercial value to St. Vincent's Hospital, Sydney.

In addition, if knowledge acquired through this research leads to discoveries that are of commercial value to St. Vincent's Hospital, Sydney, the study doctors or their institutions, there will be no financial benefit to you or your family from these discoveries.

St. Vincent's Hospital, Sydney will receive a payment from the University of New South Wales, National Centre for Clinical Research on Emerging Drugs for undertaking this research project.

No member of the research team will receive a personal financial benefit from your involvement in this research project (other than their ordinary wages).

19 Who has reviewed the research project?

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

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007-updated 2023)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

20 Further information and who to contact

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

If you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor (clinical contact person) as follows:

Clinical contact person

Name	Nadine Ezard
Position	Principal Investigator
Telephone	02 8382 1111
Email	Nadine.Ezard@svha.org.au

If you have any general enquiries about the study or want any further information concerning this study, you can contact the general enquiries contact person as follows:

General enquiries contact person

Name	Clare Smylie
Position	Research Officer
Telephone	02 8382 1233
Email	clare.smylie@svha.org.au

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

Complaints contact person

Name	Research Office Manager
Position	Research Office Manager
Telephone	02 8382 4960
Email	svhs.research@svha.org.au

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

Reviewing HREC approving this research and HREC Research Officer details

Reviewing HREC name	St Vincent's Hospital, Sydney HREC
Position	Research Officer
Telephone	02 8382 4960
Email	svhs.research@svha.org.au

Local HREC Office contact (Single Site -Research Governance Officer)

Name	Research Governance Officer
Position	Research Governance Officer
Telephone	02 8382 4960
Email	svhs.research@svha.org.au

ST VINCENT'S HOSPITAL SYDNEY
A FACILITY OF ST VINCENT'S HEALTH AUSTRALIA

Consent Form - *Adult providing own consent*

Title	An Open-Label Safety and Feasibility Pilot Trial Oral Naltrexone-Bupropion Combination Pharmacotherapy for Methamphetamine Use Disorder
Short Title	Naltrexone-Bupropion for Methamphetamine Use (NABU)
Protocol Number	2023/ETH00549
Project Sponsor	St Vincent's Hospital, Sydney
Coordinating Principal Investigator/ Principal Investigator	Professor Nadine Ezard
Associate Investigator(s)	Dr Krista Siefried Dr Carl Moller Dr Brendan Clifford Liam Acheson
Location	St Vincent's Hospital, Sydney, Alcohol and Drug Service

Declaration by Participant

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

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

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to St Vincent's Hospital, Sydney concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

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

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

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

Name of Participant (please print) _____

Signature _____ Date _____

Declaration by Study Doctor/Senior Researcher†

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

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

Signature _____ Date _____

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

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

Form for Withdrawal of Participation - *Adult providing own consent*

Title	An Open-Label Safety and Feasibility Pilot Trial Oral Naltrexone-Bupropion Combination Pharmacotherapy for Methamphetamine Use
Short Title	Naltrexone-Bupropion for Methamphetamine Use (NABU)
Protocol Number	2023/ETH00549
Project Sponsor	St Vincent's Hospital, Sydney
Coordinating Principal Investigator/ Principal Investigator	Professor Nadine Ezard
Associate Investigator(s)	Dr Krista Siefried Dr Carl Moller Dr Brendan Clifford Liam Acheson
Location	St Vincent's Hospital, Sydney, Alcohol and Drug Service

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with St Vincent's Hospital, Sydney.

Name of Participant (please print) _____

Signature _____ Date _____

Declaration by Study Doctor/Senior Researcher†

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

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

Signature _____ Date _____

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

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