# STATISTICAL ANALYSIS PLAN FOR THE N-ICE TRIAL: A RANDOMISED DOUBLE BLIND PLACEBO CONTROLLED STUDY OF THE SAFETY AND EFFICACY OF N-ACETYL-CYSTEINE (NAC) AS A PHARMACOTHERAPY FOR METHAMPHETAMINE ("ICE") DEPENDENCE

VERSION NUMBER 1.0

SEPTEMBER 2, 2020

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# 1. Administrative information

**Project title:** The N-ICE trial A randomised double-blind placebo-controlled study of the safety and efficacy of N-Acetyl-Cysteine (NAC) as a pharmacotherapy for methamphetamine ("ice") dependence

**Protocol Version Number**: 3.0 May 29, 2018, ANZCTR Number ACTRN12618000366257, Universal Trial number U1111-1210-1224

**Overall study sponsor:** This research is being conducted jointly by the NHMRC investigator team and their institutions under a co-sponsorship arrangement. Please refer to the study protocol for details.

**Funding body:** National Health and Medical Research Council

**Author:** Rebecca McKetin, National Drug and Alcohol Research Centre, University of New South Wales

Signature: _____ Date: _____

**Senior statistician:** Mohammadreza Mohebbi, Biostatistics Unit, Faculty of Health, Deakin University

Signature: _____ Date: _____

**Biostatistician:** Philip Clare, National Drug and Alcohol Research Centre, University of New South Wales

Signature: _____ Date: 02/09/2020

**Principal coordinating investigator:** Rebecca McKetin, National Drug and Alcohol Research Centre, University of New South Wales

Signature: _____ Date: _____

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Signature: _____ Date: 8/9/2020

**Senior statistician:** Mohammadreza Mohebbi, Biostatistics Unit, Faculty of Health, Deakin University

Signature: Mohebbi Date: 03/09/2020

**Biostatistician:** Philip Clare, National Drug and Alcohol Research Centre, University of New South Wales

Signature: _____ Date: _____

**Principal coordinating investigator:** Rebecca McKetin, National Drug and Alcohol Research Centre, University of New South Wales

Signature: _____ Date: 8/9/2020

## 1.1 Version history

| Version | Date | Description of Change | Brief Rationale |
|---|---|---|---|
| 1.0 | 2/9/2020 | N/A | Provide additional detail and clarification around the statistical analysis plan as detailed study protocol. |
| | | | |
| | | | |
| | | | |

# 2 Introduction

## 2.1 Rationale

Crystalline methamphetamine (aka "ice") is a significant and growing public health concern in Australia, for which there are no approved pharmacotherapies that can be delivered as scalable and cost-effective treatment options.[1,2] N-Acetyl-Cysteine (NAC) is a promising non-agonist pharmacotherapy for methamphetamine dependence.[3] NAC is a glutamatergic agent that helps restore homeostasis to brain systems compromised in addiction.[4,5] It has shown signs of efficacy in multiple addictions and particular potential for methamphetamine dependence because of its multiple actions, which aid in the management of comorbid psychiatric symptoms and which protect against methamphetamine neurotoxicity.[6] A Phase I trial (N = 23) of NAC for methamphetamine dependence in humans[7] found a large reduction in craving, good adherence to non-supervised dosing, no serious adverse events and that NAC was well-tolerated. NAC is currently an approved generic medication with a well-established safety profile that can be delivered as a prescribed take-home medication, making it a potentially scalable and cost-effective treatment option.

## 2.2 Objective

The objective of this Phase 2b trial was to test whether take-home oral NAC had a clinically relevant benefit on methamphetamine use and a range of related clinical outcomes.

Primary objective: To test whether daily oral NAC (2,400 mg/day), delivered as a take home medication, would reduce methamphetamine use relative to placebo.

Secondary objectives: To test whether daily oral NAC delivered as a take home medication would, relative to placebo, reduce the severity of methamphetamine dependence, craving for methamphetamine, methamphetamine withdrawal symptoms and psychiatric symptoms (depressive symptoms, suicidality, positive psychotic symptoms, and hostility), have an acceptable adverse event profile, and not significantly increase the use of other substances (including alcohol, tobacco, cannabis, heroin and cocaine).

## 2.3 Statistical Hypotheses

Primary hypothesis:

Daily oral NAC delivered as a take home medication will reduce methamphetamine use measured as (a) days of methamphetamine use, and (b) methamphetamine in weekly oral fluid samples, during 12 weeks of active treatment relative to placebo.

Secondary hypotheses:

Daily oral NAC delivered as a take home medication will, relative to placebo:

- reduce the severity of methamphetamine dependence, craving for methamphetamine, methamphetamine withdrawal symptoms and psychiatric symptoms (affective symptoms, positive psychotic symptoms and hostility),
- have an acceptable adverse event profile, and
- not significantly increase the use of other substances (including alcohol, tobacco, cannabis, heroin and cocaine).

# 3 Study methods

## 3.1 Trial design

A multi-site (3 site) randomised, double-blind, placebo-controlled parallel trial. Participants were randomly allocated (1:1) to receive either oral N-Acetyl Cysteine (NAC) 2,400 mg daily, or placebo, for 12 weeks.

## 3.2 Randomisation

The randomisation sequence was based on a 1:1 (treatment:placebo) permutated block randomisation, with variable block sizes, stratified by site (Melbourne, Geelong, Wollongong), gender (male vs. female) and main route of methamphetamine administration in the month prior to recruitment (any injecting vs. not injecting). The randomisation schedule was generated by the Data Safety and Monitoring Board statistician using a randomisation program prepared by the Sponsor (Associate Investigator and statistician AI Liang).

## 3.3 Sample size

Original power calculation:

Our original power calculation was based on data from the Methamphetamine Treatment Outcomes Study (MATES). Participants who did not receive treatment in this cohort showed a reduction from a mean±SD of 12.8±7.4 methamphetamine days/month at baseline to 6.0±6.7 days/month at 12-week follow-up. Our estimate of a minimal clinically meaningful reduction in use was based on outcomes for out-patient counselling derived from MATES: mean ±SD 11.2±8.8/month to 3.5±6.9/month at 12 weeks. To detect a between group difference of 6.0 vs. 3.5 days use, with 80% power and $p < 0.025$ (0.05/2 to accommodate two primary outcome measures), we would need a sample of 72 per group at 12 weeks. Assuming an 80% follow-up rate at 12 wks (based on our previous 81% follow-up in the MATES cohort) we would need to recruit 90 per group (N = 180).

Post-hoc power calculation:

We will conduct a post-hoc power analysis once we have unblinded the study. Our revised power calculation will be based on the attained sample and follow-up rate. We randomised 153 participants. 69% of assessments were completed. Data on days of methamphetamine use for the past four weeks were available for 538 of 612 (88%) of the relevant time points (i.e., Assessment 0, Assessment 4, Assessment 8 and Assessment 12), with this being 97% for Assessment 0 (149 of 153), and 85% across Assessments 4, 8 and 12 (141, 127, and 121, of 153, respectively). Oral fluid samples were taken at 1,150 (63%) of 1,835 follow-up assessments (Assessments 1-12). Oral fluid samples were not completed at 81 assessments (Melbourne 65, Geelong 14, Wollongong 2). Details of data available at each follow-up are presented in section 5.4 (Tables 3-5, Section 4.4).

## 3.4 Framework

Superiority of active medication (NAC) over placebo.

## 3.5 Statistical interim analysis and stopping guidance

No interim analysis or stopping guidelines were included in the protocol.

## 3.6 Timing of final analysis

Analysis of primary and secondary endpoints to be analysed collectively. Analysis of tertiary endpoints and any additional analyses to take place thereafter.

## 3.7 Time points at which outcomes were measured

The time points at which each of the outcomes were assessed is shown in Table 1.

- Baseline demographic and substance use history measures were taken at the first face-to-face assessment (the Eligibility Assessment). This was conducted within the 4 weeks prior to Assessment 0.
- The primary outcome of methamphetamine use days was assessed for the past 4 weeks at Assessment 0 (baseline) and updated at each weekly assessment thereafter for the 12-week active medication phase (Assessments 1-12) to derive data on days of methamphetamine use in the past 4 weeks at Assessment 4, Assessment 8 and Assessment 12.
- The primary outcome of methamphetamine positive oral fluid tests was based on oral fluid samples taken at each weekly assessment Assessments 1-12. Oral fluid samples were not collected at Assessment 0.
- All secondary outcomes were assessed at Assessment 0 (baseline) and each weekly assessment thereafter for the 12-week active medication phase (Assessments 1-12). Weekly assessments were conducted with a time-window of -2 days to +4 days.
- Treatment satisfaction was assessed at Assessments 4, 8 and 12.
- Current concomitant medications and treatments were assessed at Assessment 0 and updated at each weekly assessment thereafter.
- Adverse events were assessed from Assessment 1, with data at Assessment 1 reflecting events since Assessment 0. Adverse events were monitored and updated at each weekly assessment thereafter.
- Contact with health and criminal justice services were assessed for the past 4 weeks at Assessment 0 and updated at each weekly assessment thereafter.
- Other quality of life and productivity measures needed for the health economics analysis (EQ-5D-5L, WPAI-GH) were taken at all assessments (A0-A12).

Two additional measures, the Beck Cognitive Insight Scale (BCIS), and the Birchwood Insight Scale (BIS), were taken at the Eligibility Assessment and on a subset of the sample at Assessment 12. These data were collected for a PhD candidature. They are not included Table 1 or covered in this Statistical Analysis Plan.

**Table 1. Time points at which outcomes were measured**

| | Eligibility Assessment | Weekly trial assessments | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| **Baseline data:** | | | | | | | | | | | | | | |
| Demographics, drug use history, CIDI (methamphetamine dependence), MINI (depression, psychotic disorders, mania), DIP (family history of psychotic disorders), RCQ, BCIS, BIS items, SAPAS, TLFB for methamphetamine use days in the past 4 weeks, days of use for other major drug classes in the past 4 weeks | x | | | | | | | | | | | | | |
| **Primary outcomes measures (timeframe):** | | | | | | | | | | | | | | |
| Oral fluid samples (taken at each weekly assessment) | | | x | x | x | x | x | x | x | x | x | x | x | x |
| TLFB for days of methamphetamine use (assessed for the past 4 weeks at Assessment 0 and updated at each subsequent assessment) | | x | x | x | x | x | x | x | x | x | x | x | x | x |
| **Secondary outcomes measures (timeframe):** | | | | | | | | | | | | | | |
| SDS (past week) | | x | x | x | x | x | x | x | x | x | x | x | x | x |
| CEQ (past week) | | x | x | x | x | x | x | x | x | x | x | x | x | x |
| AWQ (past week) | | x | x | x | x | x | x | x | x | x | x | x | x | x |
| BPRS items (past week) | | x | x | x | x | x | x | x | x | x | x | x | x | x |

**Table 2. Continued.**

| | Eligibility Assessment | Weekly trial assessments | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| **Other outcomes measures (timeframe):** | | | | | | | | | | | | | | |
| Days of other substance use (assessed for the past 4 weeks at Assessment 0 and updated at each subsequent assessment) | | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Adverse events (since previous assessment) | | | x | x | x | x | x | x | x | x | x | x | x | x |
| Concomitant Medications (current medications recorded at A0 and updated at each assessment) | | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Concomitant Treatment (current treatments recorded at A0 and updated at each assessment) | | x | x | x | x | x | x | x | x | x | x | x | x | x |
| WPAI-GH (past week) | | x | x | x | x | x | x | x | x | x | x | x | x | x |
| EQ-5D-5L (today) | | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Health service use and criminal justice involvement (past 4 weeks at Assessment 0 and updated at each subsequent assessment) | | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Treatment satisfaction - TSQM-II (no timeframe) | | | | | | x | | | | x | | | | x |

Notes. Composite International Diagnostic Interview (CIDI), Mini International Neuropsychiatric Interview (MINI), Diagnostic Interview for Psychosis (DIP), Readiness to Change Questionnaire (RCP), Standardised Assessment of Personality – Abbreviated Scale (SAPAS), Timeline Followback (TLFB), Severity of Dependence Scale (SDS), Craving Experience Questionnaire (CEQ), Amphetamine Withdrawal Questionnaire (AWQ), Brief Psychiatric Rating Scale (BPRS), Work Productivity and Activity Impairment Questionnaire – General Health V2 (WPAI-GH), EuroQol Version 5 – 5 level (EQ-5D-5L), Treatment Satisfaction Questionnaire – Medication II (TSQM),

# 4 Trial population

## 4.1 Screening data

A total of 409 participants were screened for the trial. Of these prospective participants:

- 136 failed the initial phone screening
- 9 failed the subsequent face-to-face eligibility assessment
- 109 participants passed phone screening but did not undergo the face-to-face eligibility assessment (i.e., wait-listed participants who either could not be recontacted, or were no longer interested in participating, or failed to attend the eligibility assessment).
- 2 were eligible but not randomised. These were considered to have declined to participation. One did not want to wait until the trial start date to commence medication, and the other failed to recontact the trial researchers.

Reasons for screen failure (Table 2) are based on phone screening. The most common reasons for screen failure were because the person was already receiving treatment for a substance use disorder or that they were using methamphetamine weekly or less (i.e., did not meet our screening criteria for methamphetamine dependence), while a smaller proportion had a psychotic disorder or epilepsy.

**Table 3. Reasons for screen failures**

| | Melbourne | Geelong | Wollongong | Total |
|---|---|---|---|---|
| | n (%) | n (%) | n (%) | N (%) |
| Phone Screen failures# | 73 (40%) | 28 (24%) | 35 (32%) | 136 (33%) |
| Reason for failure[$] | | | | |
| Wrong age | 0 (0%) | 0 (0%) | 1 ( 3%) | 1 (1%) |
| Using weekly or less[a] | 30 (41%) | 11 (39%) | 11 (31%) | 52 (38%) |
| Not dependent[a] | 3 (4%) | 1 (4%) | 1 (3%) | 5 (4%) |
| In drug treatment | 32 (44%) | 14 (50%) | 8 (23%) | 54 (40%) |
| Doesn't want to reduce use | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| On OST | 8 (11%) | 6 (21%) | 2 (6%) | 16 (12%) |
| On contraindicated medication | 1 (1%) | 0 (0%) | 0 (0%) | 1 (1%) |
| Previous adverse reaction to NAC | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Psychotic disorder/bipolar | 15 (21%) | 4 (14%) | 5 (14%) | 24 (18%) |
| Recent surgery | 1 (1%) | 0 (0%) | 0 (0%) | 1 (1%) |
| Gastrointestinal ulcers | 1 (1%) | 1 (4%) | 0 (0%) | 2 (1%) |
| Renal stones | 1 (1%) | 0 (0%) | 0 (0%) | 1 (1%) |
| Epilepsy | 6 (8%) | 0 (0%) | 3 (9%) | 9 (7%) |
| Pregnant or breastfeeding | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Unwilling to do pregnancy test | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Unwilling to avoid pregnancy | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Unwilling to do oral fluid tests | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Unwilling to provide contact information | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Number screened but did not complete eligibility assessment† | 52 | 30 | 27 | 109 |
| Number who failed Eligibility Assessment | 3 | 2 | 4 | 9 |
| Number eligible but not randomized | 1 | 1 | 0 | 2 |
| **Total screened participants** | **181** | **117** | **111** | **409** |
| **Total screen failures or not randomised[@]** | **131 (72%)** | **61 (52%)** | **66 (59%)** | **256 (63%)** |

# Percentage of all participants screened

[$] Percentage of only those participants who failed the phone screen. Percentages do not add to 100% because participants can have > 1 reason for ineligibility. Phone screens terminate when it is clear that a participant is ineligible.

[a]Screening criteria used for methamphetamine dependence were more than weekly use of methamphetamine and scoring 4 or greater on the Severity of Dependence Scale (both criteria needed to be met).

†Participants who were screened but lost prior to confirmation of eligibility (includes wait-listed participants who were no longer interested or uncontactable and participants who failed to show up for their eligibility assessment)

[@]Percentage of all participants screened

## 4.2 Key eligibility criteria

Further detail on the eligibility criteria can be found in the trial protocol.

Inclusion criteria:

- Aged between 18 and 60 years
- Dependent on methamphetamine
- Seeking to reduce methamphetamine use
- Willing to provide contact details for a treating physician and their contact details for follow-up
- Able to provide informed consent and able to comply with the treatment protocol.

Exclusion criteria:

- Currently enrolled in specialist treatment services for drug addiction
- Currently enrolled in other pharmacotherapy for substance use disorders
- In need of acute psychiatric care or unstable psychiatric condition
- In need of acute care for intoxication or in need of medically supervised detoxification
- A diagnosed primary psychotic disorder (schizophrenia, schizoaffective disorder, bipolar disorder)
- Currently taking medication or other preparations that contain NAC
- Contraindications for NAC (including pregnancy, lactation or being unwilling to avoid pregnancy during the trial)

## 4.3 Recruitment

See Section 4.1 for screening data.

153 participants were eligible and randomised. Of these, 3 failed to attend their baseline assessment (Assessment 0) and hence did not receive any trial medication. One of these three participants withdrew their consent for the study because they moved interstate. One further participant attended this assessment but was withdrawn from the study because they were not able to comply with the study protocol (due to an acute psychosis). The data from their Assessment 0 was not included in the data analysis.

The remaining 149 participants received their trial medication and took their initial medication dose at Assessment 0. Of these 149 participants, 7 participants did not attend any further assessments and were considered lost to follow-up. (Details of follow-up for remaining participants can be found in Section 5.4).

Five participants were withdrawn during the study (after assessment 0), meaning they had no follow-up data after the date of withdrawal:

- One participant withdrew consent, saying that they no longer wished to participate in the study.
- Two were withdrawn by the study investigators due to non-compliance, one because they had been taking NAC from an alternative source in replacement of the trial medication, and one because they continued to take the study medication against advice, after being discontinued from the study medication due to a drug rash, and because they repeatedly failed to attend required medical or trial assessments.
- Two further participants were withdrawn for other reasons: one was incarcerated, and the other moved area and could no longer attend trial assessments.

Eight participants discontinued study medication during the trial (3 due to a drug rash, one developed seizures, and 4 disliked the medication's effects). As noted above, one of these participants was subsequently withdrawn from the study due to non-compliance with the study protocol. The remaining participants were followed up for trial assessments.

Two participants were unblinded in the context of serious adverse events, both of whom were receiving the active medication.

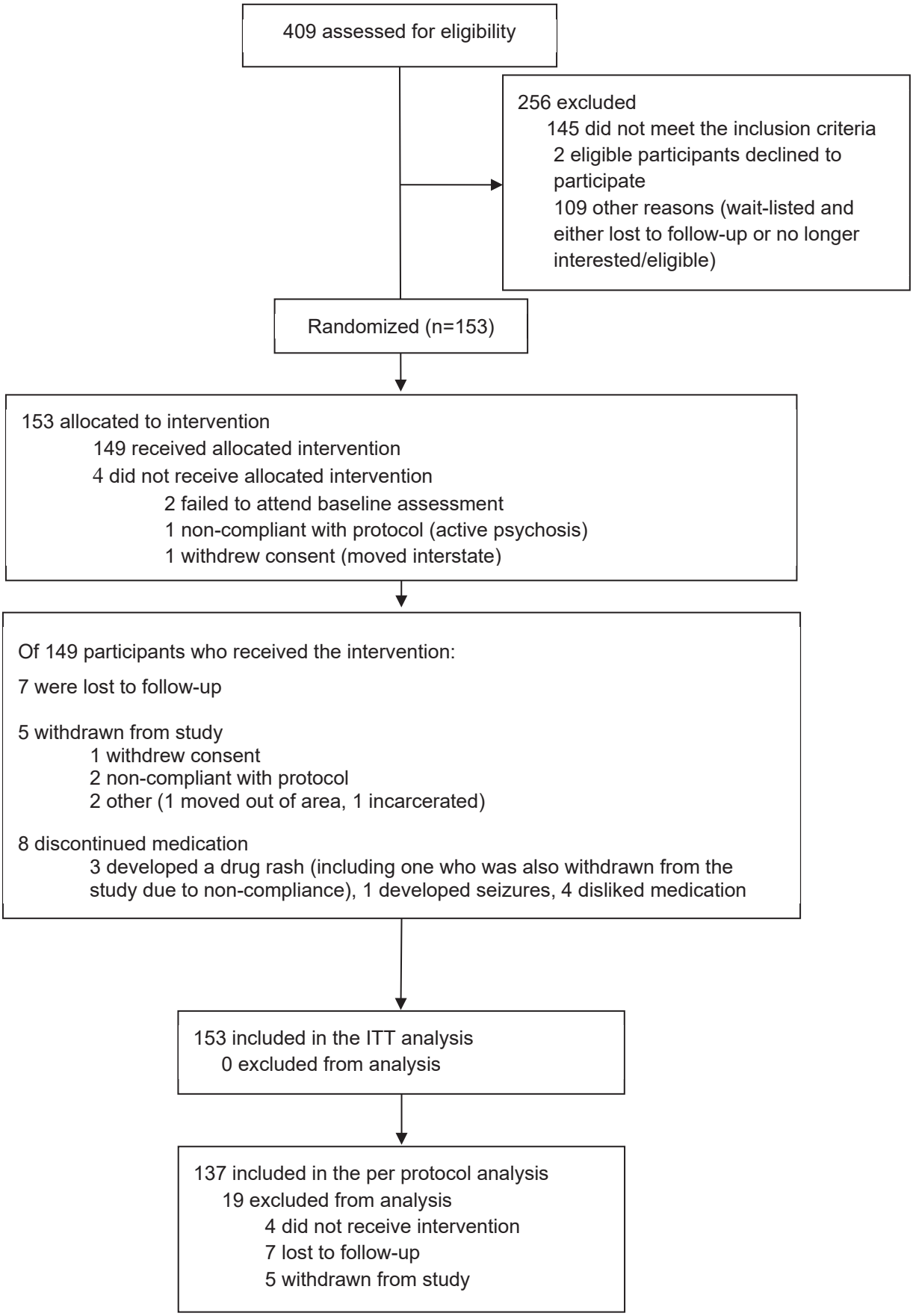


**Figure 1. Consort flow diagram**

## 4.4 Available assessment data

The overall completion of Assessments 0 – 12 for all 153 participants was 69% (1,381 of 1,989 assessments), with baseline assessment data (Assessment 0) available for 149 participants (97%), and with 142 participants (93%) completing at least one follow-up assessment (A1-A12).

Primary outcomes:

Details of the data available from Assessments 0 to 12 for each of the primary outcomes is shown in Table 3.

*Days of methamphetamine use:* Because days of methamphetamine use was updated at each assessment, data was available for participants who attended any assessment within the 4-week period (88% of data points in total). The median number of days in these time periods was 28 (interquartile range 27 to 29 days; range 7 – 60 days). Where no assessments were undertaken within the 4-week period, data were regarded as missing (12% of data points).

*Oral fluid samples:* Oral fluid test results were available for 63% of assessments. Oral fluid samples were not available for 81 of the 1,381 completed assessments, this being mostly because assessments were done by phone (e.g., where it was impractical to do a face-to-face assessment) or less often because the interview was terminated early.

Secondary outcomes: Details of missing data for secondary outcomes is presented in Tables 4 and 5. Overall, data were available for 69% of assessments. There were a small number of cases where assessments were completed but data were not collected on the secondary outcomes (e.g., because the interview was terminated or questionnaire items were skipped).

Adherence: Medication adherence data were available for 139 participants, based on 447 returned bottles (of 596 bottles dispensed) providing 1,302 weeks of adherence data.

**Table 4. Details of the number (%) of participants who completed assessments and for whom the main outcome data were available.**

| Assessment period | Number (%) of participants who attended assessment | | Number (%) of participants with data on days of methamphetamine use | | Number (%) of participants with oral fluid test results[a] | |
|---|---|---|---|---|---|---|
| | N | % | n | % | n | % |
| Assessment 0 | 150 | 98 | 149 | 97 | N/A | N/A |
| Assessment 1 | 129 | 84 | 141 | 92 | 122 | 80 |
| Assessment 2 | 118 | 77 | | | 106 | 69 |
| Assessment 3 | 111 | 73 | | | 105 | 69 |
| Assessment 4 | 109 | 71 | | | 98 | 64 |
| Assessment 5 | 100 | 65 | 127 | 83 | 91 | 59 |
| Assessment 6 | 101 | 66 | | | 96 | 63 |
| Assessment 7 | 92 | 60 | | | 84 | 55 |
| Assessment 8 | 98 | 64 | | | 96 | 63 |
| Assessment 9 | 94 | 61 | 141 | 79 | 86 | 56 |
| Assessment 10 | 88 | 58 | | | 84 | 55 |
| Assessment 11 | 89 | 67 | | | 86 | 56 |
| Assessment 12 | 102 | 98 | | | 96 | 63 |
| Total of all assessments | 1,381 | 69 | 538 | 88 | 1,150 | 63 |

[a]Oral fluid tests were not completed at 81 assessments (Melbourne 65, Geelong 14, Wollongong 2)

**Table 5 Details of the number (%) of participants for whom the secondary outcome data (CEQ, AWQ and SDS) were available.**

| | CEQ | | AWQ | | SDS | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Assessment 0 | 149 | 97 | 148 | 97 | 149 | 97 |
| Assessment 1 | 128 | 84 | 128 | 84 | 128 | 84 |
| Assessment 2 | 118 | 77 | 118 | 77 | 118 | 77 |
| Assessment 3 | 110 | 72 | 110 | 72 | 110 | 72 |
| Assessment 4 | 107 | 70 | 108 | 71 | 108 | 71 |
| Assessment 5 | 100 | 65 | 100 | 65 | 100 | 65 |
| Assessment 6 | 98 | 64 | 98 | 64 | 98 | 64 |
| Assessment 7 | 89 | 58 | 90 | 59 | 91 | 59 |
| Assessment 8 | 98 | 64 | 97 | 63 | 98 | 64 |
| Assessment 9 | 94 | 61 | 94 | 61 | 94 | 61 |
| Assessment 10 | 87 | 57 | 87 | 57 | 87 | 57 |
| Assessment 11 | 88 | 58 | 89 | 58 | 89 | 58 |
| Assessment 12 | 100 | 65 | 101 | 66 | 101 | 66 |
| Total of all assessments | 1,366 | 69 | 1,368 | 69 | 1,371 | 69 |

**Table 6. Details of the number (%) of participants for whom the secondary outcome data (psychiatric symptoms) were available.**

| | Hostility | | Psychotic symptoms | | Depression | | Suicidality | |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % |
| Assessment 0 | 149 | 97 | 149 | 97 | 149 | 97 | 149 | 97 |
| Assessment 1 | 128 | 84 | 128 | 84 | 128 | 84 | 128 | 84 |
| Assessment 2 | 118 | 77 | 118 | 77 | 118 | 77 | 118 | 77 |
| Assessment 3 | 109 | 71 | 109 | 71 | 109 | 71 | 109 | 71 |
| Assessment 4 | 107 | 70 | 107 | 70 | 107 | 70 | 107 | 70 |
| Assessment 5 | 100 | 65 | 100 | 65 | 100 | 65 | 100 | 65 |
| Assessment 6 | 99 | 65 | 99 | 65 | 99 | 65 | 99 | 65 |
| Assessment 7 | 91 | 59 | 91 | 59 | 91 | 59 | 91 | 59 |
| Assessment 8 | 98 | 64 | 98 | 64 | 98 | 64 | 98 | 64 |
| Assessment 9 | 94 | 61 | 94 | 61 | 94 | 61 | 94 | 61 |
| Assessment 10 | 87 | 57 | 87 | 57 | 87 | 57 | 87 | 57 |
| Assessment 11 | 89 | 58 | 89 | 58 | 89 | 58 | 89 | 58 |
| Assessment 12 | 101 | 66 | 101 | 66 | 101 | 66 | 101 | 66 |
| Total of all assessments | 1,370 | 69 | 1,370 | 69 | 1,370 | 69 | 1,370 | 69 |

## 4.5 Baseline characteristics

Baseline descriptive data: Baseline descriptive statistics include the demographics of the sample (e.g., age, sex, employment status, marital status, income, years of schooling, tertiary qualifications, prison history), methamphetamine use history (duration of use, days used in the past month, main route of administration), and other substance use. This baseline descriptive data will be collected at the eligibility assessment. Table 6 details each of the baseline variables and how they will be presented.

Baseline values for outcome measures: All primary and secondary outcome measures will be presented for Assessment 0 (i.e., in addition to presenting the follow-up data for these outcomes) with the exception of oral fluid test results (because these were not taken at Assessment 0). See Table 7 for details on how each of these measures will be reported.

Analysis of baseline characteristics: The distribution of each measure will be inspected and a judgement will be made regarding whether the data conform to model assumptions (e.g. normality). Descriptive statistics will be presented as the mean (standard deviation) for continuous parametric measures and median (inter-quartile range) for highly skewed measures. Group differences will be tested using chi-square tests for categorical outcomes, a median comparisons test for skewed continuous data and t-tests for normally distributed continuous data. Spearman correlations will be used to examine correlations for skewed data.

**Table 7. Description of baseline characteristics**

| Baseline measure | Description | Presentation |
|---|---|---|
| Demographics | | |
| Age | Age in years | Mean (SD) |
| Sex | Male (vs. female) | n, (%) |
| Immigrant | Born outside of Australia (vs. born in Australia) | n, (%) |
| Married | Married/de-facto (vs. single, separated, divorced, widowed) | n, (%) |
| Unemployed | Unemployed (vs. full-time, part-time, casual employment or home duties) | n, (%) |
| Income | Net legal income in the past fortnight (< $400, $400-799, $800-1119, >$1200) | n, (%) |
| Schooling | Years of completed school (primary and secondary) | Median (IQR) |
| Qualifications | Completed tertiary qualifications (Nil, Trade/technical, University) | n, (%) |
| Prison history | Ever been to prison (i.e., served a prison sentence) | n, (%) |
| Methamphetamine use | | |
| Treatment history | Ever started drug treatment for methamphetamine use (e.g., detox, rehab, drug counselling) | n, (%) |
| Duration of use | Years since first use of methamphetamine | Median (IQR) |
| Injecting | Main way participant took methamphetamine in the past month (inject vs. smoke, snort, swallow or no use) | n, (%) |
| Days of use in the past 4 weeks | TLFB days of methamphetamine use in the past four weeks | Median (IQR) |
| Other substance use | Days of other substance use (summed across all drug types) in the past 4 weeks | Median (IQR) |

Notes. Inter-quartile range (IQR), standard deviation (SD), Timeline Followback (TLFB),

**Table 8 Description of outcome measures reported at Assessment 0**

| Outcome measure | Description | Presentation |
|---|---|---|
| Days of methamphetamine use | TLFB days of methamphetamine use in the past four weeks (at A0) | Median (IQR) |
| Severity of methamphetamine dependence | SDS score for the past week | Mean (SD) |
| Methamphetamine craving | CEQ score for the past week | mean (SD) |
| Methamphetamine withdrawal | AWQ score for the past week | mean (SD) |
| Psychotic symptoms | Score of 3 or greater on any of the BPRS items of suspiciousness, unusual thought content and hallucinations | n (%) |
| Hostility | Score of 4 or greater on the BPRS hostility item | n (%) |
| Depression | Score of 4 or greater on the BPRS depression item | n (%) |
| Suicidality | Score of 3 or more on the BPRS suicidality item | n (%) |

Notes. Inter-quartile range (IQR), standard deviation (SD), Timeline Followback (TLFB), Severity of Dependence Scale (SDS), Craving Experience Questionnarie (CEQ), Brief Psychiatric Rating Scale (BPRS),

# 5 Statistical Principles and definitions

## 5.1 Confidence intervals and p values

All tests will be two-tailed. Significance for each of the primary outcomes will be $p < 0.025$ to adjust for having two primary outcome measures (i.e., 0.05/2). Significance for the secondary outcomes will be $p < 0.01$ to adjust for multiple secondary outcomes. Significance for all other tests will be set at 0.05. Confidence intervals will be 95%. Bootstrapped confidence intervals will be used for outcomes that are highly skewed.

## 5.2 Analysis populations

*The intention to treat (ITT) dataset* will include all randomised participants, regardless of whether they received the intervention or were followed up.

*The modified intention to treat analysis dataset* will include randomised participants who took at least one dose of trial medication and who also completed at least one follow-up assessment.

*The safety analysis dataset* will include randomised participants who took at least one dose of trial medication and who completed at least one follow-up assessment (i.e., had some safety data).

*The Per-Protocol Analysis Dataset* will include randomised participants who took at least one dose of the study medication, for whom data was available for at least one follow-up assessment, and who were not withdrawn from the study for reasons unrelated to the study medication. See Figure 1, Section 4.3 for details.

## 5.3 Protocol deviations

Protocol deviations were defined as noncompliance with the clinical trial protocol or approved Human Research Ethics Committee protocol, or the guidelines for Good Clinical Practice in Australia. These deviations were reported to the Data Safety and Monitoring Board (DSMB). The number of trial participants withdrawn from the study, discontinued from the study medication, and unblinded, will be reported. The number of protocol deviations per participant will be reported. Serious deviations from the protocol (e.g., protocol violations) will be reported and, if necessary, sensitivity analysis will be performed to assess their impacts.

# 6 Analysis

## 6.1 Outcome definitions

**Primary outcomes**

The main outcome is days of methamphetamine use during the active (12 week) trial phase. There are two measures of this primary end point, as described below.

(1) Days of methamphetamine use, assessed using the Timeline Follow Back (TLBF)[8], taken for the past 4 weeks at Assessment 0, and updated at each follow-up interview. The outcome in the analysis will be days of methamphetamine use in the past 4 weeks at Assessment 0 (baseline), Assessment 4 (week 4), Assessment 8 (week 8) and Assessment 12 (week 12). This will be modelled as days of methamphetamine use over the number of days observed during the four-week period (as this varied depending on the actual assessment dates).

(2) Methamphetamine positive oral fluid samples, taken at each weekly follow-up during the 12-week active medication period (Assessments 1-12). Each oral fluid sample was considered positive for methamphetamine if it contained ≥ 25 ng/ml of methamphetamine.

**Secondary outcomes**

All secondary outcomes were assessed at each assessment (Assessment 0-12)

Methamphetamine craving: Methamphetamine craving will be the total score on the Craving Experience Questionnaire,[9] assessed for the past week.

Severity of methamphetamine dependence will be the total score on the Severity of Dependence Scale,[10] assessed for the past week.

Methamphetamine withdrawal symptoms will be the total score on the Amphetamine Withdrawal Questionnaire[11], assessed for the past week.

Psychiatric symptoms: Symptoms of psychosis, hostility, depression and suicidality were assessed for the past week at each assessment using the Brief Psychiatric Rating Scale (BPRS)[12]. The cut-points on the BPRS items used to define symptoms has changed from the study protocol for symptoms of psychosis, hostility and suicidality due to the low severity of symptoms. The final cut-points are listed below.

- Psychosis: 3 or greater on any of the items of suspiciousness, unusual thought content or hallucinations
- Hostility: 4 or greater on the hostility item
- Depression: 4 or greater on the depression item
- Suicidality: 3 or more on the suicidality item

**Other outcomes**

The use of other major drug classes: The use of other drug classes was assessed in the past 4 weeks at baseline and updated weekly during the trial. The measure used in the analysis will be the sum of the days of other drug classes used in the past 4 weeks at baseline (Assessment 0), Assessments 4, 8 and 12 respectively. Drug classes included will be tobacco, alcohol, cannabis, ecstasy, cocaine, heroin, inhalants, other hallucinogens. This will be modelled as the number of days over the possible days of use during the days observed (e.g., total days of use for all drug types during the 4-week assessment period / 28 days x 8 to account for 8 drug classes).

Adverse events: Data on adverse events were collected using a structured and pre-defined series of open-ended questions. Adverse events were reviewed and updated at each weekly assessment. Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) by System Organ Class (SOC). Adverse events were counted once only for a given participant. The event counted was the event with the highest severity (coded as mild, moderate or severe). Causality was coded as not related, possibly related, or probably related. The definitions for adverse events, serious adverse events, severity and causality can be found in the protocol.

Treatment satisfaction: Treatment satisfaction was assessed using the Treatment Satisfaction Questionnaire – Medication version 2 (TSQM II)[13] at Assessments 4, 8 and 12. The TSQM II includes subscales for convenience, perceived effectiveness, and side-effects, as well as a composite global satisfaction score. The outcome used will be the global satisfaction score, which is a percentage score

where higher scores reflect higher satisfaction. The scoring algorithm used will be that published by Aktinson et al.[13] We will report the average percentage across all four timepoints, and percentages at each timepoint only if relevant.

Medication adherence: Medication adherence data will be based on eCAP$^{TM}$ technology that records the date and time of medication bottle opening. Each bottle opening is counted as one dose, and multiple bottle openings recorded within a 10-minute interval are recorded as a single event, based on the time of the initial bottle opening (to avoid recording miscellaneous events that occur during a single dosing episode).

Adherence data will be reported as the percentage of adherent medication doses for the time observed from the available eCAP$^{TM}$ data (i.e., based on the date of the first to the last eCAP$^{TM}$ bottle reading for each medication bottle). The numerator in this calculation will be the number of adherent doses. The denominator will be the number of possible adherent doses during the timeframe of the recorded data. A maximum of 2 doses were allowed per calendar day. No compliance band was used to assess whether doses were taken morning and evening.

## 6.2 Analysis methods

The analysis plan below is based on blinded data that did not include the treatment allocation variable. After unblinding, model assumptions will be checked (e.g., distribution of the outcome, cell sizes and model convergence and model fit) and models will be modified as necessary; any covariates that need to be included in the model will be identified.

### Analysis of the primary outcome

Analysis of the primary outcome (methamphetamine use) will be based on the intention-to-treat dataset. Missing data will be imputed.

There are two measures of the primary outcome: (1) days of methamphetamine use, and (2) methamphetamine positive oral fluid samples. The p value will be set at 0.025 to adjust for having two primary outcome measures. The analysis of each of the primary outcome measures is described below.

Interpretation of the two primary outcome measures: The two primary outcome measures will be considered separately because they are qualitatively different: days of use reflects the frequency of methamphetamine use, whereas a positive oral fluid sample reflects any use (i.e., a negative test reflects complete abstinence from methamphetamine). Any discrepancy between the effect on each outcome will be interpreted accordingly.

#### *Days of methamphetamine use*

Descriptive analysis: Descriptive data on days of methamphetamine use will include the median number of days at each time point, with interquartile ranges reported, and variance estimates (i.e., standard errors and confidence limits) will be bootstrapped.

Main model: The effect of the medication on days of methamphetamine use will be tested using a condition (active [1] versus placebo [0] condition) versus time (Assessment [0] versus Assessment 4 [1], Assessment 8 [1] and Assessment 12 [1]) interaction. A negative binomial generalised linear mixed model will be used to test this effect. The outcome variable in the model will be repeated measures on days of methamphetamine use observed in the past 4 weeks at baseline (Assessment 0), 4

weeks (Assessment 4), 8 weeks (Assessment 8) and 12 weeks (Assessment 12). An exposure term (i.e. offset) will be included in the model to adjust for the exact number of days in each of these periods, because this can vary depending on the actual assessment dates. A random intercept term for participant identifier will be included in the model to account for clustering of data on repeated assessments. A random intercept for site will be included in the model only if it significantly improves model fit ($p < 0.05$).

A secondary analysis will test the treatment effect at each time point (weeks 4, 8 and 12) relative to baseline. This will be based on a condition (active [1] versus placebo [0]) versus time contrast (Assessment 0 [0] versus Assessment 4 [1], Assessment 8 [2] and Assessment 12 [3]), where time is entered into the model as a factorial term, providing separate condition by time interaction effects, relative to baseline, for Assessment 4, Assessment 8 and Assessment 12. All other model parameters will be as for the main model.

Rationale for the average treatment effect and related model assumptions:

In the main model, the condition by time interaction effect represents the average treatment effect across the 12-week medication period. This average treatment effect assumes the equivalence of treatment effects at each time point (i.e., 4 weeks, 8 weeks and 12 weeks) and no time trend in the treatment effect.

We chose to test for an average treatment effect across the 12 weeks of medication because there was substantial uncertainty about whether any time trends could be expected, and what form these might take. The effects of NAC on drug craving are evident within 48 hours, and although two previous small scale trials[7,14] have provided descriptive evidence suggesting larger effects over time, this has not been demonstrated in larger trials: for example, a larger RCT[15] did not find a significant differential treatment effect by time.

Because we assume constancy of the treatment effect across the 12-week follow-up, we will interpret this average treatment effect in light of outcomes at each timepoint (from the secondary analysis) and we will also undertake a sensitivity analysis after unblinding that incorporates any observed time trend in the treatment effect in the model (e.g., models the treatment effect as a linear time trend, if this is apparent in the data).

Interpretation of the treatment effect from the model (i.e., interaction effect rate ratio): The main treatment effect will be the time (baseline vs. active medication phase) x condition (active vs. placebo) interaction effect. This interaction effect represents the rate ratio of change in days of methamphetamine from baseline to follow-up (i.e., rate of days of use at baseline/rate of days of use at follow-up) for the active condition, over the rate ratio of change from baseline to follow-up for the placebo condition. That is:

r = (days of use at follow-up/days of exposure at follow-up) / (days of use at baseline/days of exposure at baseline)

$r_p$ = r in placebo group

$r_a$ = r in active group

The interaction coefficient representing the treatment effect is the rate ratio (rr) of these two parameters, i.e., $r_a / r_p$.

***Methamphetamine positive oral fluid tests***

Descriptive analysis: Descriptive data on the proportion of positive oral fluid samples in each group at each week across the active trial phase will be presented.

Main model: The effect of NAC on methamphetamine positive oral fluid samples will be tested using a main effect of treatment condition (active [1] versus placebo [0]) on positive oral fluid samples (12 test results per participant, taken at weeks 1-12). The outcome measure will be whether the person had a methamphetamine positive oral fluid sample at each time point (no [0], yes [1]) with 12 repeats per person. A generalised linear mixed model with a logistic link will be used to test this effect. A random intercept term for participant identifier will be included in the model to account for clustering of data on repeated assessments. A random intercept for site will be included in the model only if it significantly improves model fit ($p < 0.05$).

**Analysis of the secondary outcomes**

Analysis of the secondary outcomes will be based on the modified intention-to-treat database. The main analysis of the secondary outcomes will not use imputed data. This approach has been taken because secondary outcomes were not collected at the eligibility assessment, making imputation difficult for participants who failed to attend any assessments.

Treatment effects for secondary outcomes will be examined using a series of generalised linear mixed models. The outcome in these models will be the secondary endpoint at each Assessment (i.e., time-varying data across Assessments 0-12). The treatment effect for each secondary outcome will be tested using a condition (NAC [1] vs. placebo [0]) by pre-test (Assessment 0 [1]) vs. post-test (repeated measures for assessments 1-12 [1]) interaction. This interaction effect will reflect the ratio of change from baseline to follow-up in the active over the placebo group (as for the main outcome measure, days of methamphetamine use). A random intercept term for participant identifier will be included in the model to account for clustering of data on repeated assessments. A random intercept for site will be included in the model only if it significantly improves model fit ($p < 0.05$).

It is expected that linear models will be used for the continuous outcomes (CEQ, AWQ, SDS). Highly skewed outcomes will be normalised using a log function, or, if that fails, other model options will be examined to identify the best model fit. A logistic link will be used for categorical outcomes (i.e., psychiatric symptoms). A Poisson or negative binomial link will be used for count data, and may be used for categorical outcomes with small cell sizes, where this produces superior model fit.

**Sensitivity analyses**

- Sensitivity analyses will be conducted that repeat the primary outcome analyses (for each of the primary outcome measures), but which use the modified intention-to treat-dataset and which do not impute missing data.
- Sensitivity analyses will be conducted that repeat the secondary outcome analyses, but which use imputed missing data.
- A sensitivity analysis will be conducted that is the same as the primary analysis of days of methamphetamine use, but which collapses the data across the three follow-up time points, such that the outcome is the total days of methamphetamine use across the 12 week medication period.
- Sensitivity analyses will also be conducted that include baseline variables that differ significantly ($p < 0.05$) between the active vs. placebo condition as covariates in the model.

- Sensitivity analysis will be undertaken based on post-hoc confirmation of time trends in the data, and inclusion of these in the main model when estimating the treatment effect (e.g., estimating the treatment effect with time as a linear slope).

**Additional analyses**

Per-protocol analysis: A per protocol analysis will be undertaken on the subset of randomised participants who took at least one dose of the study medication, for whom data was available for at least one follow-up assessment (i.e., were not lost to follow-up), and who were not withdrawn from the study for reasons unrelated to the study medication. The per protocol analysis will use non-imputed data. See Figure 1 in Section 4.3 for detail.

Treatment complier effect: The average treatment complier effect will be based on the modified intention-to-treat dataset, where adherence data is also available, and it will use non-imputed data. The complier effect will be estimated using an instrumental variable approach.[16] The treatment effect in this analysis will be based on the main effect of condition on the outcome across Assessments 1-12. Baseline days of methamphetamine use will be included as a covariate in the model, should this differ significantly ($p < 0.05$) between groups. Estimated exposure to the medication will be modelled by regressing condition allocation and baseline covariates on adherence (% of non-missed doses). The predictors of adherence from the resultant model will be regressed onto the outcome (days of methamphetamine use/methamphetamine positive oral fluid samples), in lieu of the condition allocation to estimate the treatment complier effect.

Mediation of medication effects by exposure to other treatments: A mediation analysis will be conducted to examine whether any treatment effects were mediated by any concomitant treatment received for substance use disorders during the 12-week trial period (with treatment exposure being the total number of treatment episodes reported across Assessments 1-12). Mediation will be assessed using the 'explained fraction' approach, as described by Whitehead et al.[17]: [odds ratio (OR)a – 1] – (ORb – 1)]/(ORa – 1), where ORa represented the OR for the unadjusted relationship between treatment condition and methamphetamine use, and ORb the relationship between treatment condition and treatment exposure. This analysis will be based on the main effect of condition on the outcome across Assessments 1-12.

Subgroup analyses: No subgroup analyses were planned under the protocol and the study was not powered to detect outcomes for subgroups. Post-hoc comparisons will be conducted to examine whether main treatment effects are modified by (a) sex (men vs. women), (b) route of administration (injecting vs. non-injecting use), and (c) site (Melbourne, Geelong, Wollongong). These factors were incorporated into the randomisation strata, meaning that participants were randomly assigned within site, sex, and route of administration.

## 6.3 Missing data

Missing data will be imputed using multiple chained equations (fully conditional specification). For imputed data on days of methamphetamine use in the past four weeks, the exposure time (offset) will be set at 28 days. Variables considered for inclusion in the imputation model will be (a) days of methamphetamine use in the past 28 days at the eligibility assessment, and (b) baseline variables that are significantly ($p < 0.05$) correlated with missingness for the outcome variable (Tables S1-3). For the primary outcome of days of methamphetamine use, correlates of the number of missing data points on days of methamphetamine use will be considered (Table S1). For the primary outcome of methamphetamine positive oral fluid samples, the number of assessments where oral fluid test results

were missing will be considered (Table S2). And, for all other outcomes, the number of missed follow-up assessments will be considered (Table S1). Based on Monte-Carlo error, the number of imputations used will be based on the percentage of cases with missing data, rounded up to the nearest 10 (e.g. for 15% missing data, M=20 imputations will be used (White, Royston & Wood, 2011).

If adequate imputation models cannot be derived, the alternative strategy will be to conduct the main analysis on the modified intention-to-treat dataset, including covariate adjustment for baseline variables that are correlated with missingness (as defined above).

Details of any imputation models will be included in online supplementary material on publication.

### 6.4 Harms

Safety analyses will report the number and percentage of participants reporting adverse events and serious adverse events in each treatment condition, by System Organ Class (SOC); treatment conditions will be compared using a Pearson's Chi-Square test. For serious adverse events, expectedness and causality will also be noted.

### 6.5 Exploratory analyses and embedded studies

Exploratory analyses that have been planned to-date are detailed in the protocol. No statistical analysis plan has been developed for these exploratory analyses. Nor have any other exploratory analyses had been planned at the time of writing this Statistical Analysis Plan. If the intervention is effective, cost analyses will be undertaken. These will be detailed in a subsequent Health Economic Analysis Plan. Data collected to facilitate this analysis include: (1) the EQ-5D-5L[18] version 2.1, taken Assessments 0-12, (2) the Work Productivity and Activity Impairment Questionnaire – General Health V2 (WPAI-GH) taken at Assessments 0-12, and (3) data on health service utilisation and criminal justice contact over the active medication phase (Assessments 0-12).

### 6.6 Statistical software

All analyses will be conducted in Stata Version 16.0. Where models cannot be run in Stata Version 16.0 (e.g., due to lack of model options) they will be conducted in alternative appropriate software.

## 7 Related documents

The Trial Protocol, Trial Masterfile, Statistical Masterfile and Data Management Plan are held at the University of New South Wales with the Principal Coordinating Investigator, Rebecca McKetin. Each site Principal Investigator holds a copy of the Masterfile.

# 8 Roles and responsibilities

Rebecca McKetin (Principal Coordinating Investigator)
Associate Professor
National Drug and Alcohol Research Centre
Street address: 22-32 King Street Randwick
UNSW SYDNEY NSW 2052 AUSTRALIA
T: +61 (2) 9385 0294 / + 61 406538259
E: r.mcketin@unsw.edu.au

Mohommadreza Mohebbi (Statistician)
Dr Mohammadreza Mohebbi - Senior research fellow, Biostatistics Unit
Faculty of Health, Deakin University, Melbourne Campus at Burwood
Building BC, Room BC4.121, 221 Burwood Highway, Burwood, VIC 3125, AUSTRALIA
Phone: +61 3 9246 8993
Email: m.mohebbi@deakin.edu.au

Philip Clare (Biostatistician)
Dr. Philip Clare – Research Fellow/Biostatician
National Drug and Alcohol Research Centre
Street address: 22-32 King Street Randwick
UNSW SYDNEY NSW 2052 AUSTRALIA
T: +61 (2) 9385 0333
E: p.clare@ unsw.edu.au

Other study investigators (see Protocol for details).

# 9 Appendix

## 9.1 Baseline variables

All variables are from the eligibility assessment. Spearman correlates are with (a) the number of data points missing for days of methamphetamine use in the past 4 weeks (at assessments 0, 4, 8 and 12) (Table S1), (b) the number of missing data points for oral fluid samples when assessments were completed (Table S2), and (c) the number of missed assessments (Assessment0-12) (Table S3).

Table S1. Correlates of the number of missing data points for days of methamphetamine use

| Baseline variable | Spearman's rho | P value |
|---|---|---|
| Age | -0.17 | 0.032 |
| Male | 0.02 | 0.825 |
| Born outside of Australia | -0.09 | 0.286 |
| Married/defacto | 0.04 | 0.592 |
| Unemployed | -0.03 | 0.688 |
| Income (past fortnight net legal income) | | |
| < $400 | -0.04 | 0.627 |
| $400-799 | 0.06 | 0.496 |
| $800-1199 | -0.10 | 0.216 |
| >$1200 | 0.05 | 0.530 |
| Years of schooling | -0.16 | 0.044 |
| Tertiary qualifications | | |
| No tertiary education | -0.06 | 0.436 |
| Trade or technical | 0.14 | 0.092 |
| University | -0.12 | 0.127 |
| Prison history | 0.15 | 0.062 |
| Ever started drug treatment for methamphetamine use | 0.13 | 0.122 |
| Injecting main route of methamphetamine use | -0.13 | 0.097 |
| Days of methamphetamine use in the past 4 weeks at eligibility | 0.07 | 0.383 |
| Duration of methamphetamine use (years) | -0.13 | 0.123 |
| Days of other drug use (summed across all drug types) at eligibility | -0.03 | 0.714 |
| Any use of substance in the past month at eligibility | | |
| Heroin | 0.03 | 0.713 |
| Other opioids | 0.03 | 0.727 |
| Cocaine | 0.23 | 0.004 |
| Ecstasy | 0.03 | 0.735 |
| Hallucinogens | 0.03 | 0.711 |
| Inhalants | -0.02 | 0.804 |
| Cannabis | -0.12 | 0.152 |
| Tobacco | -0.02 | 0.849 |
| Alcohol | 0.01 | 0.886 |
| Benzodiazepines | 0.02 | 0.774 |
| Antipsychotics | 0.02 | 0.780 |
| Antidepressants | -0.15 | 0.066 |

Table S2. Correlates of the number of missing data point for methamphetamine positive oral fluid samples

| Baseline variable | Spearman's rho | P value |
|---|---|---|
| Age | -0.28 | 0.000 |
| Male | 0.01 | 0.910 |
| Born outside of Australia | -0.07 | 0.403 |
| Married/defacto | 0.10 | 0.218 |
| Unemployed | -0.00 | 0.965 |
| Income (past fortnight net legal income) | | |
| < $400 | 0.08 | 0.336 |
| $400-799 | 0.03 | 0.732 |
| $800-1199 | -0.18 | 0.029 |
| >$1200 | 0.05 | 0.523 |
| Years of schooling | -0.07 | 0.424 |
| Tertiary qualifications | | |
| No tertiary education | -0.04 | 0.628 |
| Trade or technical | 0.06 | 0.429 |
| University | -0.04 | 0.587 |
| Prison history | 0.10 | 0.231 |
| Ever started drug treatment for methamphetamine use | 0.13 | 0.102 |
| Injecting main route of methamphetamine use | -0.18 | 0.028 |
| Days of methamphetamine use in the past 4 weeks at eligibility | 0.10 | 0.238 |
| Duration of methamphetamine use (years) | -0.16 | 0.043 |
| Days of other drug use (summed across all drug types) at eligibility | -0.07 | 0.423 |
| Any use of substance in the past month at eligibility | | |
| Heroin | 0.01 | 0.904 |
| Other opioids | 0.06 | 0.431 |
| Cocaine | 0.23 | 0.004 |
| Ecstasy | 0.10 | 0.240 |
| Hallucinogens | 0.06 | 0.498 |
| Inhalants | -0.05 | 0.541 |
| Cannabis | -0.07 | 0.379 |
| Tobacco | 0.01 | 0.951 |
| Alcohol | 0.13 | 0.116 |
| Benzodiazepines | 0.12 | 0.156 |
| Antipsychotics | -0.03 | 0.745 |
| Antidepressants | -0.16 | 0.049 |

Table S3. Correlates of the number of missed assessments

| Baseline variable | Spearman's rho | P value |
|---|---|---|
| Age | -0.20 | 0.013 |
| Male | -0.02 | 0.811 |
| Born outside of Australia | -0.07 | 0.421 |
| Married/defacto | 0.06 | 0.447 |
| Unemployed | -0.01 | 0.887 |
| Income (past fortnight net legal income) | | |
| < $400 | 0.05 | 0.508 |
| $400-799 | 0.06 | 0.464 |
| $800-1199 | -0.19 | 0.016 |
| >$1200 | 0.05 | 0.548 |
| Years of schooling | -0.11 | 0.182 |
| Tertiary qualifications | | |
| No tertiary education | -0.01 | 0.892 |
| Trade or technical | 0.07 | 0.402 |
| University | -0.09 | 0.255 |
| Prison history | 0.11 | 0.178 |
| Ever started drug treatment for methamphetamine use | 0.07 | 0.383 |
| Injecting main route of methamphetamine use | -0.18 | 0.023 |
| Days of methamphetamine use in the past 4 weeks at eligibility | 0.08 | 0.306 |
| Duration of methamphetamine use (years) | -0.15 | 0.072 |
| Days of other drug use (summed across all drug types) at eligibility | -0.00 | 0.987 |
| Any use of substance in the past month at eligibility | | |
| Heroin | 0.04 | 0.618 |
| Other opioids | 0.03 | 0.681 |
| Cocaine | 0.20 | 0.015 |
| Ecstasy | 0.10 | 0.263 |
| Hallucinogens | 0.04 | 0.649 |
| Inhalants | -0.04 | 0.611 |
| Cannabis | -0.05 | 0.512 |
| Tobacco | 0.01 | 0.942 |
| Alcohol | 0.17 | 0.039 |
| Benzodiazepines | 0.00 | 0.955 |
| Antipsychotics | 0.01 | 0.920 |
| Antidepressants | -0.14 | 0.083 |

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