Statistical Analysis Plan

Project NEAT: NicotinE As Treatment

A randomized controlled trial to examine the efficacy of vaporised nicotine products and telephone quit line support compared with nicotine replacement therapy and telephone quit line support when used following discharge from residential withdrawal services

Version **3** **Dated** **19-04-2023**

Statement of Compliance

This document is a statistical analysis plan for the aforementioned clinical trial. This trial will be conducted in compliance with all stipulation of this approved protocol, the conditions of the ethics committee approval, the NHMRC National Statement on Ethical Conduct in Human Research (2007), and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

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1. Administration information

Title and trial registration

A randomized controlled trial to examine the efficacy of vaporised nicotine products and telephone quit line support compared with nicotine replacement therapy and telephone quit line support when used following discharge from residential withdrawal services

Trial registration

ANZ Clinical Trial Registration Number: [ACTRN12619001787178]

Protocol Version

Version 6, Dated 10-03-2021

2. Introduction

2.1. Background and rationale

Up to 95% of people in AOD treatment smoke tobacco. People with substance use disorders experience great difficulty quitting tobacco smoking. As a result, quit rates are close to zero, and tobacco-related diseases are the leading cause of mortality. New ways for addressing smoking in this population are needed. Vaporised nicotine products (VNPs) hold significant potential as both cessation aids and harm reduction support. There is now good evidence of safety, and emerging evidence that VNPs assist cessation. More evidence of the safety and effectiveness of VNPs for populations with high smoking prevalence rates and low quit rates is desperately needed. Many AOD withdrawal facilities are smoke-free, and service users achieve brief abstinence. However, most return to smoking immediately following discharge, representing a missed opportunity for supporting long-term abstinence. Providing smoking cessation support post discharge will assist individuals with moderate to heavy nicotine dependence to remain smoke-free in the community. The aim of this world-first trial is to test the effectiveness of VNPs at increasing smoking cessation amongst AOD residential withdrawal services. Service users (n=926) from six residential and inpatient withdrawal AOD services across three states (NSW, Victoria, and Queensland) will be recruited and randomised. Participants in the comparison condition will receive current best- practice combination nicotine replacement therapy (NRT). Participants in both groups will also receive proactive Quitline support from AOD-trained counsellors. The trial will build on our pilot study in a Victorian AOD withdrawal facility which found the design and the interventions highly feasible and acceptable to both service users and staff.

2.2. Objectives

The purpose of this trial is to test the effectiveness of VNPs and Quitline (telephone counselling) compared to current best practice combination NRT and Quitline at increasing smoking cessation among clients following discharge from an inpatient drug and alcohol withdrawal service.

2.2.1. Primary Objective

The primary objective is to examine, using a randomised controlled trial, the effectiveness of VNPs on self-reported 7-month continuous abstinence (from tobacco smoking) at 9-months follow-up.

2.2.2. Secondary objectives

Additional secondary objectives are to compare participants in the VNP + Quitline to those in the NRT + Quitline group on:

i) Biochemically verified 7-month continuous abstinence at month 9
ii) 30-day point prevalence abstinence at months 3 and 9
iii) Reduction in cigarettes smoked per day at months 3 and 9
iv) Reduction in strength and urges to smoke tobacco at months 3 and 9
v) Reduction in withdrawal symptoms at months 3 and 9
vi) Relapse episodes to smoking at months 3 and 9

Other objectives involve:

i) Assessing treatment adherence (duration/ use of products/ reasons for non-use/ engagement with telephone counselling) compared by treatment group
ii) Assess attitudes/ acceptability of the provided interventions
iii) Use of additional pharmacotherapies, visits to GPs, and use of print and online materials
iv) Assess provided interventions on mood

3. Study Methods

3.1. Trial Design

Project NEAT is a two-arm, single blinded, parallel group randomised (1:1) trial with a 6-month post intervention follow-up (or 9-months post discharge). The trial has been designed to conform to the CONSORT statement.

3.2. Intervention Groups

3.2.1. Group 1: VNP + Quitline

- An information pack that includes printed information on benefits of quitting (including benefits on AOD reduction); information about nicotine maintenance and elaboration of the benefits of vaping instead of smoking and the risks of vaping compared to complete abstinence. The lack of data on health risks of long-term vaping will be highlighted. Instructions on how to use VNPs and safe storage and handling will be included.
- Provision of two VNP kits + 12 weeks of liquid nicotine along with 1-week supply of NRT patches. The device (Innokin Endura T18-II starter kit) and refill liquid (Nicophar) were selected based on quality assurance and compliance with relevant standards (GMP (good manufacturing practice) for liquid). Participants will be provided with two VNPs and an initial 4-week supply of liquid nicotine, with further supplies of the refill liquid mailed or couriered to them at 4 weekly intervals. Participants will be advised to use both the NRT patches (1 week supplied) and the VNP for the first week following discharge while they are learning how to use the VNP effectively.
- *Medicine: liquid nicotine (or e-liquid).* The liquid nicotine will be manufactured to GMP standards for the trial (Nicophar brand). It will be provided to participants in 10ml dropper bottles. Each 12mg strength 10mL bottle will contain nicotine (1.2%), Glycerol (84%) and water (14.8%).
- Proactive referral to Quitline counselling (call-back service) which provides calls at pre-discharge and on days 1, 3, 7, 14 & 28 post-discharge, with an emphasis on relapse prevention. At least one call will additionally be conducted during stay at AOD treatment facility. The total number and timing of calls will be tailored to client need and smoking status, i.e. more frequent calls around relapse crises/quit attempts with an app roximate 10 calls over 12 weeks. Participants will be text messaged prior to being called as AOD clients are unlikely to pick up calls from a private number. Counsellors will be provided with training around the use of VNP, monitoring and

encouraging correct use of NRT and working with clients to address barriers to their use.

3.2.2. Group 2: NRT + Quitline

- Participants randomised to group 2: standardised smoking care will receive the following:
- An information pack that includes printed information on benefits of quitting (including benefits on AOD reduction), and instructions on how to use NRT correctly, for how long, potential side effects (and when to notify a health care provider), safe storage and handling.
- Provision of 12 weeks of nicotine replacement therapy – transdermal (e.g. patches) and oromucosal forms (e.g. gum, lozenge, mouth spray) of NRT to be used throughout the intervention period. For weeks 1–4 participants will receive: 4 x QuitX 21mg Patches 7s, 2 x Nicorette Inhalator 15mg 20s, and 3 x Nicorette Quick Mist 1mg spray. For weeks 5-8 participants will receive: 4 x QuitX 21mg Patches 7s, 2 x Nicorette Inhalator 15mg 20s, 1 x Nicorette Cool Drops 4mg 80s, and 1 x quitX Gum 4mg 100s Mint. For weeks 9–12 participants will receive 1 x Nicabate 21mg Patches 28s, 2 x Nicorette Inhalator 15mg 20, 2 x Nicorette Cool Drops 4mg 80s. This will be mailed to an address the participant supplies.
- Proactive referral to Quitline counselling (call-back service) which provides calls on days 1, 3, 7, 14 & 28 post-discharge, with an emphasis on relapse prevention. At least one call will additionally be conducted during the stay at the AOD treatment facility pre-discharge. The total number and timing of calls will be tailored to client need and smoking status, i.e. more frequent calls around relapse crises/quit attempts with an approximate 10 calls over 12 weeks. Participants will be text messaged to alert them to expect a Quitline call prior to being called as AOD clients are unlikely to pick up calls from a private number. Counsellors will monitor and encourage correct use of NRT and work with clients to address barriers to its use.

3.3. Randomisation

The randomisation component of the study is embedded into a REDCap project database. Participating site research assistants/ coordinators will access the randomisation module following the completion of the baseline survey with participants via the web enabled iPad. An independent statistician supervised by CI Oldmeadow from the Statistical Support Unit at Hunter Medical Research Institute (HMRI) produced the randomisation schedule using a permuted block randomisation procedure, with random blocks of size 4 or 6), stratified by site, and equal allocation ratios for the two treatment arms. This was coded using the SAS programming language and uploaded to the REDCap database.

3.4. Sample Size

Studies using continuous abstinence measures with mental illness and AOD samples have found smoking cessation rates close to zero at longer term follow-up using NRT.[1] Thus, for this trial, with our sample of heavy smokers with concurrent AOD use, we will conservatively assume a verified continuous abstinence rate of 3% at 6 months follow up in the NRT +Quitline usual care control group.

A sample of 278 smokers in each treatment group are needed to detect a difference of 6% between groups (i.e., 3% in NRT group and 9% in VNP group continuous abstinence at 9-month follow-up) using a two-tailed test with 80% power and a 5% type 1 error rate. Our pilot study at the Wellington House withdrawal unit in Melbourne recruited approximately two participants per week. Assuming similar recruitment rates and 40% attrition rate at 9 months follow-up (based on TNT trial GNT1045840)[2], we will require a sample size of 926 eligible smokers across the 6 sites. We are allowing two years for participant recruitment to achieve this, based on our pilot study.

3.5. Hypothesis

The primary null hypothesis: Compared to those allocated to current best-practice NRT +Quitline (control group), participants receiving the VNPs +Quitline (intervention group) will have an equal proportion of participants with self-reported 7-month continuous abstinence at 9-months follow-up.

3.6. Screening data

Staff members at the service will notify AOD clients that their service is currently participating in a research study to help people quit tobacco smoking. Staff members at participating services will briefly ask whether the individual identified as a current tobacco smoker on entering the service. The staff member will provide a copy of the participant information statement and will ask the AOD client if they would like the study research assistant to discuss the project further with them. If the AOD client reports no, then the AOD staff member will thank them for their time. If the AOD client reports yes then the staff member will notify the study research assistant (who may be a trained current employee of the participating AOD site or a trained research assistant/trial coordinator).

The research assistant will ask if this is a good time to discuss the project. If not the research assistant will make time the following day or so to discuss. The research assistant will **a**pproach the client and then commence the screening and enrolment log on REDCap.

3.7. Eligibility

3.7.1. Inclusion Criteria

- Aged 18 or over
- Daily tobacco smoker (10 or more cigarettes) on entering withdrawal unit
- Accessing treatment from participating services
- Receiving NRT while in treatment at participating services
- Want to quit smoking in the next 30 days
- Has capacity to consent and able to understand the participant materials and follow the study instructions and procedure (e.g., sufficient English language ability and not too unwell as judged by medical staff)

3.7.2. Exclusion Criteria

- Pregnant or breastfeeding (measured by self-report)
- Enrolled in another study

- Scheduled to be transferred to a long-term residential rehabilitation service following discharge from the withdrawal unit
- Used VNP (containing nicotine) in the last 30 days
- Currently engaged in Quitline's call-back services
- Prescribed stop smoking medication (e.g., varenicline or bupropion)
- No ready access to a phone

3.8. Recruitment

The primary mode of recruitment will be via RAs at participating services. Staff at participating services will be asked to notify potential participants about the study and to ask if they would like to speak to the RA about the study. For every client that speaks to the RA, the RA will record this in the screening and enrolment log (via iPad on REDCap). Additional recruitment strategies will be via flyers provided to participants on entry to the service, or in their pre-entry pack to the participating service, as well as flyers in the communal areas of the service to encourage self-referral.

3.9. External Data Sources

The sole external data source is Quitline Victoria who will be collecting the following information:

- Length of call
- Number of calls
- Session content

4. ANALYSIS

4.1. Outcome Definitions

4.1.1. Primary outcome

Self-reported 7-month continuous abstinence (dichotomous: abstinent or not) at 9 months post randomization

Self-reported 7-month continuous abstinence will be assessing using the following items:

- "Do you currently smoke any tobacco products?" (response options: yes daily; yes, at least once a week; yes, less often than once a week; **no, not at all**)
- "How long ago did you last smoke every day?" (response options: Less than 1 week; 1 week to 1 month; 1 – 3 months; 4 – 6 months; **7 – 9 months; more than 9 months**) reporting either "7-9 months", "or more than 9-months".

Participants that report they are currently 'not smoking at all' AND that it has been either '7-9 months' or 'more than 9 months' since they last smoked every day are considered to have reached 7-months continuous abstinence.

4.1.2. Secondary outcomes

i) Biochemically verified 7-month continuous abstinence from tobacco smoking (dichotomous: abstinent or not)

- Self-reported 7-month continuous abstinence at 9-month survey will be verified using measures of CO in expired air. A cut-off point of 8ppm will be used to define a smoker (i.e. CO level <8ppm will be considered biochemically verified abstinent).

ii) 30-day point prevalence abstinence (PPA)

- Two items will be used to assess self-reported 30-day PPA: "Have you smoked at all, even a puff, in the last 30 days?" (response options: yes; **no**), and "How many cigarettes have you smoked in the last 30 days?" (response options: **less than 1 or just a puff**; 1 – 5; 6 – 10; 11 – 20; more than 20).
  Participants who report not having smoked in the last 30 days AND smoking 'less than 1' cigarette or 'just a puff' in last 30-days will meet 30-day PPA criteria.

iii) 7-day PPA

- Self-reported 7-day PPA will be measured by asking participants "Have you smoked at all, even a puff, in the last 7 days?" with response options a) yes, b) no. Responding 'no' will equate to self-reported 7-day PPA.

iv) Number of cigarettes smoked and percentage reduction from baseline (dichotomised: at least 50% or < 50%)

- Participants will be asked "currently how many cigarettes do you smoke per day, per week, and per month?".
- Only asked of participants who report that they are occasional/ daily smoking (if the participant reports quitting in the primary outcome they are excluded from this analysis)
- Percentage reduction in number of cigarettes smoked from baseline (dichotomised: at least 50% or < 50%)
- Reduction rate also to be calculated

v) Reducing cravings to smoke

- Frequency of cravings was assessed by one item[3]: "How often do you get cravings to smoke tobacco?" with response options: a) hourly or more often, b) several times per day, c) at least once a day, d) less than daily, or e) never.

vi) Reducing withdrawal symptoms (24 hours, 30 days)

- 24 hours (measured at baseline and 3 months)

  Nicotine withdrawal symptoms over past 24hours was measured at baseline and 3-month follow-up using the Minnesota Nicotine Withdrawal Scale (MNWS)[4], with symptoms [angry, irritable frustrated; anxious or nervous; depressed or sad; desire or craving to smoke; difficulty concentrating; increased appetite, hungry or weight gain; insomnia, sleep problems or awakening at night; restless or impatient] experienced in last 24 hours rated on an ordinal scale ranging from 0 (none), 1 (mild), 2 (moderate), to 3 (severe).

- Last 30 days (past week assessed at baseline; last 30 days at 3-month and 9-month follow-up)

  A modified version of the MNWS was used to assess withdrawal symptoms over past 30 days. At baseline participants were asked "In the week before you came here, how often were you bothered by the following problems", and at 3-month and 9-month

follow-up timepoints “In the last 30 days, how often were you bothered by the following problems?” and asked to rate the list of withdrawal symptoms from 0 (not at all), 1 (several days), 2 (more than half the days), to 3 (nearly every day).

vii) Relapse episodes

- **Instance of relapse at 3-month** follow-up will be determined by:
  Answering ‘daily’ or ‘yes, at least once a week’ to question of “*do you currently smoke any tobacco products”*
  OR
  Answering ‘less often than once a week’ or ‘not at all’ to current smoking status **AND** answering ‘yes’ to question “*since you left service, have you smoked every day for a week or more?*”
- **Time to relapse at 3-month follow-up** is assessed by the question “How soon after discharge did you go back to smoking (your first smoke after discharge)?” with response options a) as soon as I could get a cigarette that day; b) later on the day I got out; c) on the day after I got out; d) 2-7 days after I got out; e) more than a week after I got out but less than 1 month; f) more than a month after I got out.
- **Instance of relapse at 9-month follow-up** is determined by:
  Answering ‘not at all’ to *current smoking status* AND responding ‘yes’ to question “Since you quit smoking, have you smoked every day for a week or more (even just puffs)? (yes/no)”
  OR
  Current (daily or occasional) smokers who report a quit attempt within past 6 months that lasted ≥2 days

vii) Abstinence from all nicotine/ tobacco products

- This will be measured by asking participants "Are you currently using any form of nicotine products, including vapourised nicotine products and tobacco products other than cigarettes? Check all that apply” with response options a) no; b) yes, nicotine patches; c) yes, oral nicotine products; d) yes, nicotine vaping products; e) yes, some other form of tobacco product. Responding ‘no’ will equate to ‘Abstinence from all nicotine/ tobacco products.’

4.1.3. Baseline participant characteristics (demographic, clinical, and psycho-social)

i) Motivation to quit

- At baseline participants are asked “How motivated are you to stay off cigarettes after you leave this facility?” (response options: not very motivated; moderately motivated; very motivated; extremely motivated)
- At 3-month follow-up, participants who report abstinence from smoking are asked “How motivated are you to remain quit from smoking?’ (response options: not very motivated, moderately motivated, very motivated, extremely motivated).

ii) Confidence in ability to quit this time (self-efficacy)

- At baseline all participants are asked: “If you decide to stay off the smokes completely when you leave, how confident are you that you would succeed?” (response options: not at all confident; slightly confident; moderately confident; very confident; extremely confident)
- At 3-month and 9-month follow-ups, *participants who are current smokers* are asked “If you decided to quit smoking permanently in the next 6 months, how confident are you that you would succeed?” (response options: not at all confident; slightly confident; moderately confident; very confident; extremely confident)
- At 3-month and 9-month follow-ups, *participants who report abstinence* are asked “How confident are you that you will succeed in staying quit in the long term?” (response options: not at all confident; slightly confident; moderately confident; very confident; extremely confident)

iii) Difficulty in quitting

- At baseline all participants asked “How hard do you think it would be for you to stay quit smoking permanently (after you leave this facility)?” (response options: impossible; very hard; hard; easy; very easy).
- At 3-month follow-up, *participants who are current smokers* are asked “How hard do you think it would be for you to quit smoking permanently?” (response options: impossible; very hard; hard; easy; very easy).
- At 3-month follow-up, *participants who report abstinence* are asked “How hard do you think it would be for you to stay quit smoking permanently?” (response options: impossible; very hard; hard; easy; very easy).

iv) Nicotine dependence

- Two-item Heaviness of Smoking Index[5] consisting of: number of cigarettes per day and timing to first cigarette.
- Scoring: low heaviness of nicotine dependence= 0-2, moderate 3-4, and heavy 5-6.

v) Alcohol use

- Participants who reported alcohol use (baseline: in 30 days before admission; 3-month follow-up: in time since discharge; 9-month follow-up: current use) were presented a single item from the AUDIT[6]: “How many standard drinks containing alcohol do you have on a typical day when you are drinking?” (response options: 1-2; 3-4; 5-6; 7-9; 10 or more).

4.1.4. Adverse events

Any adverse events reported during the study and follow up period. The number of adverse events will be tabulated by intervention arm. Incidence ratios to be calculated.

4.1.5. Analysis populations

The primary analysis population will be the intention to treat (ITT) population, defined as all participants that were randomised to an intervention arm. Participants

that drop out of the study will have their outcomes imputed using the methods described in the "missing data section".

Secondary analysis population will include the 1) completers, defined as all participants that were randomised to receive an intervention, and returned for a follow-up survey with complete data (i.e., complete case analysis); 2) the intention to treat population, Participants that drop out of the study will have their outcomes imputed using the methods described in the "missing data section". 3) the per protocol analysis excluded participants with major protocol violations (e.g. death, pregnancy, study withdrawal, loss to follow-up, non-adherence, non-compliance). Self-reported adherence was defined as having been sent all 12 weeks' study medication from the study team AND a quitline referral. Self-reported medication compliance was defined as current or previous use of NRT (use of patches for ≥7weeks AND any oral form use) or VNP (use for ≥7weeks) according to group assignment.

4.2. Analysis Methods

4.2.1. Descriptive statistics

Descriptive statistics will be used to summarize the baseline demographic and clinical characteristics overall and for intervention and control groups. Counts and percentages for categorical data, and means, standard deviations (or medians, interquartile ranges) for continuous data.

4.2.2. General Statistical methodology

Statistical inference for assessing differences between groups for all outcome measures will be within a Bayesian framework. This involves for each outcome specifying a likelihood function, and a prior distribution. Together these form the posterior distribution for the parameters of interest.

4.2.3. Samples from the posterior distribution

Posterior summaries: samples from the posterior distribution will be obtained using the No U-Turn Sampler (NUTS) with 4 Markov chains, as implemented in the brms R package.[7]

4.2.4. Assessment of convergence

Visual inspection of chains, histograms of posterior distributions for all model parameters, Effective sample size, Rhat <=1.1 indicating chains have converged. If chains have not converged then we will initially attempt to increase the number of iterations, and then try stronger prior distributions.

4.2.5. Assessment of fit

Posterior predictive checks will be used to compare the observed data with the data predicted from the models to look for any discrepancies that might indicate poor model fit. If models indicate poor fit, stronger prior distributions or alternate model distributions will be explored.

4.2.6. Summaries of the posterior distribution

Posterior mean: The mean of the converged posterior distribution for the parameter reflecting the between group differences (either absolute or relative) will be presented as the point estimate to 2 decimal places

Intervals: 95% credible intervals will be calculated using the highest posterior density (HPD) method and presented to 2 decimal places.

Probability of direction: The one-sided probability that the difference between treatment and control is greater than zero will be presented (representing a beneficial treatment effect). This is calculated as the proportion of posterior samples that are of sign that is favorable to the intervention (either +'ve or –'ve)

Bayes Factors: The relative evidence of a treatment effect compared to no treatment effect will be calculated. The marginal likelihood of models with and without the treatment effect will be calculated using a bridge sampler as implemented in the brms R package[7]. The ratio of these likelihoods is the Bayes factor. A Bayes factor greater than 1 indicates there is more evidence the treatment is effective compared to no treatment effect. Bayes factor categories[8] can be interpreted as substantial (3.2 to 10), strong (10 to 32), very strong (32 to 100), decisive (>100).

4.3. Statistical models

4.3.1. Primary outcome model

The primary outcome of interest will be assessed in the ITT population using a generalized linear mixed model (GLMM) with logit link function including a random intercept for site and treatment group as a fixed effect. Priors on the treatment parameter (difference in log odds between treatment arms) will be non informative and a power prior (normal distribution) based on previously published data will be used in the sensitive analysis. The random intercept will be modelled on the log-odds scale and assumed distributed as a normal distribution with mean 0 and variance assumed to be distributed from as a half Student-T of 3 degrees of freedom.

4.3.2. Secondary outcome models

Secondary abstinence outcomes will be assessed in the ITT population, other secondary outcomes in the completers and the ITT population. GLMM will be used to assess the difference in outcomes at follow up between treatment groups or changes from baseline.

All single endpoint outcomes will include a normally distributed random intercept for site (on the scale of the canonical link function for the specific distribution family) and treatment group as a fixed effect with a non informative prior for the treatment effect. The random intercept will be modelled from a normal distribution with mean 0 and a hierarcahical variance parameter that is distributed as a half Student-T of 3 degrees of freedom.

For outcomes with multiple time points, the models will additionally include participant id as a random intercept, and parameters for time with an interaction between time and treatment group as fixed effects, all on the scale of the canonical link function for the specific distribution family. Non-informative priors will be used for fixed effects. Participant id

random intercept will be modelled from a multivariate normal distribution with mean 0 and covariance matrix with a non-informative prior (LKJ-Correlation and half Cauchy priors implemented in the brms R package).

A GLMM with a binomial distribution and logit link function will be used to model abstinence outcomes (biochemically verified 7-month continuous abstinence, self-reported 30 day and 7 day point prevalence, abstinence at 3 and 9 months).

Number of cigarettes smoked per day will be compared at each time point using a GLMM with a negative-binomial distribution and log link function. Percentage reduction of at least 50% in the number of cigarettes smoked per day will be assessed with GLMM with a binomial distribution and logit link function.

Craving scores and relapse episodes will be compared using a GLMM with multinomial distribution and a cumulative logit link function, or binomial distribution and logit link depending on the distribution of responses.

Withdrawal scores will be compared using a GLMM with normal distribution and identity link function.

Abstinence from all nicotine/ tobacco products will be modelled using GLMM with a binomial distribution and logit link function.

4.4. Sensitivity analysis

A series of sensitivity analysis will be performed assessing how robust the results are to:

1) missingness (see Missing Data section),
2) abstinence defined using stricter thresholds for CO (<=5 ppm and <=3 ppm),
3) adjusting for baseline characteristics that were potentially not well balanced between the groups at baseline.
4) the choice of prior for Bayesian analysis. A power prior (normal distribution) for the treatment effect using previously published data will be assessed. Non-informative priors for all other parameters will be used.

The primary outcome will be assessed for sensitivity to missingness by assuming missing at random (MAR) (Russel Standard will be used as the primary imputing method for the main analysis) and for the choice of prior. If evidence of the primary outcome treatment effect is shown, additional analysis by assuming missing not at random (MNAR) will be conducted using pattern mixture models (see Missing Data section).

Secondary outcomes will be assessed for sensitivity to missingness by assuming MAR, and if both the primary and secondary outcome show a treatment effect, additional analysis by assuming MNAR will be conducted using pattern mixture models (see Missing Data section).

4.5. Missing Data

It is anticipated that there will be two main mechanisms that will enable missing data will be observed in the data sources for the primary and secondary outcome: 1) participant that have not completed the follow-up CATI surveys (at 3 or 9-months) and are considered lost to

follow-up; and 2) participants that were successfully reached at follow-up; however, the outcome is missing. It is expected the first scenario is most likely.

The main analysis will be conducted in the intention to treat population. The primary method of imputing missing data will follow the recommendations of the Russel Standard, and assume those with missing data to be not abstinent.

A sensitivity analysis will be conducted under the missing at random assumption and, if evidence of a treatment effect is shown then missing not at random (MNAR). The analysis will be conducted using multiple imputation by chained equations with predictive mean matching models (PMM). PMM models will use analysis variables (treatment, site, time and outcomes) plus variables known to be predictors of abstinence (???) and any variables found to be predictive of missingness. Chisq or t-tests on baseline psychometrics will be used to assess association with missingness on the primary outcome to include in the PMM models. The number of imputations will be the higher of the percentage missing or 25 and 20 iterations will be used. The stability of the results will be explored through increasing the number of imputations. Pattern mixture models will be used to assess the sensitivity of the missing at random assumption. A tipping point approach will be used by varying our assumptions regarding the outcome proportion for those with missing data in the treatment group until a positive treatment effect is nullified. This sensitivity analysis will enable a better understanding of the variability of the missing data and will be used to assess the impact of missing on the outcomes of the study.

4.6. Statistical Software

The cleaning, coding, and analysis of the data sets will be completed using Statistical Analysis System (SAS) version 9.4 and R (R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

4.7. References

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