DATA SAFETY MONITORING PLAN

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Targeted Pharmacological and Behavioral Treatments for

Smoking in Schizophrenia

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Summary of the Protocol

Brief Description of Protocol

The prevalence of cigarette smoking among people with schizophrenia in the United States is two- to three-times that of the general population. Smokers with schizophrenia (SS) have very low rates of smoking cessation, resulting in a disproportionate burden of tobacco-related morbidity and mortality. The overall objective of this project is to develop a novel, theory-driven intervention for smoking cessation for SS. Varenicline (VAR) reduces relapse among SS who attain abstinence, but is less effective at inducing abstinence. Contingency management (CM) interventions are highly effective at inducing abstinence in SS, but relapse rates are high once the incentives are discontinued. The combination of VAR + CM may be optimal for both inducing abstinence and reducing relapse in SS, especially if VAR reduces target mechanisms that are posited to underlie early relapse in SS: smoking urges and negative affect during abstinence (primary targets), smoking reinforcement (reward and satisfaction) during a smoking lapse (secondary targets) and cognitive dysfunction during abstinence (exploratory target). In the R21 phase of this research, we will use a laboratory model to compare the effects of VAR and placebo (PLA) on time to relapse and on these primary, secondary and exploratory target mechanisms.

Aims of the R21 Phase

Aim 1: To examine the effects of VAR versus placebo (PLA) on smoking urges and negative affect during abstinence, reinforcing effects of a smoking lapse, cognitive function and time to relapse in SS.

Aim 2: To examine the extent to which the effects of VAR on time to relapse are mediated through its effects on the target mechanisms.

In Session 1 (pre-medication baseline), we will collect baseline measures of smoking urge, withdrawal symptoms, mood, cognitive performance, a behavioral economics-based measure of cigarette demand and effects of smoking a cigarette on cigarette reward, satisfaction and mood. Next, participants will be randomized to VAR (1 mg twice daily for 3 weeks) or PLA, using urn randomization to stratify on gender and dependence. Participants will complete a week of medication use using the standard dose run-up (0.5 mg once daily on days 1-3, 0.5 mg twice daily on days 4-7, then 1 mg twice daily until the end of the medication period). In Session 2, which occurs after one week on medication, participants will complete the same laboratory assessments as in Session 1. Next, participants will undergo a 3-day abstinence period. They will come to the laboratory twice per day and will receive escalating cash incentives for breath carbon monoxide (CO)-verified abstinence. At each visit, cigarette craving and withdrawal symptoms will be measured. At Session 8 (Thursday morning), participants who have been continuously abstinent will complete the same procedure as in Sessions 1. For ethical reasons, participants who complete the study through Thursday and who wish to remain abstinent may opt out of smoking during this session and will still receive full compensation for participation, as long as they attend this lab session and complete the other session measures.

Participants will be asked to return to the laboratory on Friday morning. Breath CO will be measured and time of first lapse (single cigarette) and relapse (return to regular smoking) will be collected among those who have lapsed and relapsed. Those still abstinent (CO ≤ 4 ppm) since Session 8 will receive a small cash incentive. Next, participants will be shown how to use breath CO monitors with smart phones to record

and text us videos of themselves proving CO samples twice per day for the following week to determine time to lapse and relapse. Participants will receive $5 for each submitted sample (not contingent on CO level), paid when the smart phone and CO monitor are returned at the end of the week.

Analyses will examine the effects of VAR versus PLA on time to relapse and on smoking urges and negative affect during abstinence (primary targets), smoking satisfaction and reward during Session 8 (secondary targets), and cognitive performance (exploratory target). We will also examine the extent to which the effects of VAR on time to relapse are mediated through its effects on these mechanisms. If VAR reduces either the primary or secondary targets by ≥ 20% in ≥ 50% of the sample (go/no-go rule), this research will proceed to an R33 phase.

Aims of the R33 Phase

Aim 1: To compare the effects of VAR + mCM, VAR + non-contingent reinforcement (NR) and PLA + NR on smoking measures (CO levels, cigarettes per day) and target mechanisms (smoking urges and negative affect during abstinence, reinforcing effects of a smoking lapse, cognitive function) in SS over a 5-week period.

Aim 2: To examine the extent to which the effects of the treatments on the smoking measures are mediated through the effects of the treatments on the target mechanisms.

Aim 3: To assess the feasibility and acceptability of a multi-week VAR + mCM intervention in SS.

SS will be randomized to one of 3 conditions for a 5-week period: (1) VAR plus a mobile CM intervention, (2) VAR plus a non-contingent reinforcement (NR) control condition, and (3) PLA plus the NR condition. During the first week, participants will undergo a standard 7-day medication (VAR or PLA) dose run-up period and will receive voucher-based reinforcement for texting videos of themselves providing CO samples twice per day, regardless of CO level. In Weeks 2-5, participants will continue to text video samples twice per day and will receive voucher reinforcement that is either contingent upon abstinence, or contingent only upon submitting the video (NR). Participants will visit the laboratory each week to complete assessments of smoking, craving, withdrawal symptoms, mood, subjective effects of smoking and psychiatric symptoms. They will also complete the CPT, cognitive battery, measures of quit interest, and provide a saliva sample for cotinine analysis at the beginning and end of the intervention period. At the end of the intervention, participants will be provided with brief advice to quit smoking and will be offered referrals to community treatments. They will also be administered a debriefing questionnaire in which they are asked to guess their medication condition and asked about the intervention acceptability, their willingness to participate in longer CM trials, and their willingness to receive prize-based incentives rather than vouchers.

Two weeks after Session 6, participants will be contacted by phone and asked about the frequency and quantity of cigarette and other nicotine/tobacco product use since the end of the active treatment period. Those indicating that they have been abstinent in the last 7 days will be provided with taxi transportation and compensation to provide CO verification of abstinence. Participants will be asked whether they have contacted and attended any community cessation treatments, and about their current interest in treatment. Participants will again be offered referrals to cessation treatments in the community. This assessment, including CO verification of abstinence, will be repeated 2 weeks later.

Analyses will examine (1) the effects of the study conditions on smoking measures (CO levels, cigarettes per day) and the target mechanisms (craving and negative affect during abstinence, reinforcing effects of a smoking lapse, cognitive function); (2) the extent to which the effects of the treatment conditions on smoking are mediated through the effects on the target mechanisms; and (3) the feasibility and acceptability of a multi-week VAR + mCM intervention in SS.

Primary and Secondary Outcome Measures

Primary Outcome Variables:

- Primary target measures: Questionnaire on Smoking Urges (QSU) total score, Minnesota Nicotine Withdrawal Scale (MNWS) negative affect score (average of the anger, depression, anxiety and difficulty concentrating items).
- Secondary target measures: Cigarette Evaluation Questionnaire (CEQ) Satisfaction scale (mean of ratings on the satisfaction, taste and enjoyment items), Reward scale (mean of ratings on the calm, feel more awake, less irritable, help to concentrate and reduce hunger items), and Craving Reduction scale (single item).
- Latency to relapse (hours between the start of Session 8 and time of relapse, collected in person at Friday's session and by videoed CO sample in the follow-up week.

Secondary Outcome Variables:

- Expired breath carbon monoxide (CO) level
- Salivary cotinine level
- Cognitive performance measures (response times, errors of omission, errors of commission) on the WAIS-IV Coding task, Continuous Performance Test-3, 2-letter search task, WAIS-IV letter-number sequencing task, Wisconsin Card Sorting Task
- Diener and Emmons Mood Scales
- Cigarette Evaluation Questionnaire (CEQ) Enjoyment of Respiratory Sensations scale (single item) and Aversiveness scale (mean of ratings on the dizziness and nausea items).
- MNWS items not included in primary variables: insomnia, restlessness, increased appetite
- Demand indices on the Cigarette Purchase Task (CPT): intensity (consumption at zero price), Omax (maximum amount of money allocated to cigarettes), break-point (first price at which participant reports zero consumption) and Pmax (price at which Omax occurs).
- Other smoking measures: Fagerström Test for Nicotine Dependence (FTND), Smoking Stage of Change questionnaire, Contemplation Ladder
- Psychiatric symptom measures: Brief Psychiatric Rating Scale (BPRS), Calgary Depression Scale for Schizophrenia
- Movement disorder measures: Abnormal Involuntary Movements Scale, Simpson-Angus Scale, Barnes Akathisia Rating Scale
- Feasibility outcomes (R33 phase only): median number of sessions attended, percentage of video samples submitted, percentage of those who indicate that they would be willing to participate in a longer CM trial, responses to open-ended questions on the debriefing questionnaire

- Adverse events: Number and type of serious adverse events, adverse event ratings (analyzed individually using one maximum value over the study duration for each person for each expected effect, including the baseline value of each item).

Inclusion/Exclusion Criteria

Inclusion Criteria:

1) Men and women
2) Ages 18-65
3) Have schizophrenia or schizoaffective disorder
4) Would like to quit smoking within the next 6 months
5) Have smoked at least 10 cigarettes per day in the past year
6) Have breath CO level > 10 ppm
7) Able to speak, read and comprehend English well enough to complete study procedures

Exclusion Criteria:

8) Pregnant, breast-feeding, or unwilling to use medically-approved contraception
9) Currently using VAR, bupropion or nicotine replacement therapy for smoking cessation
10) Medical disease that would preclude participation in the opinion of the medical monitor
11) Unstable psychiatric conditions (hospitalization or change in dose of chronic medication in past 30 days)
12) Body mass index (BMI) < 15 or > 38 kg/m^2
13) Past-month suicidal intention, with or without a specific plan
14) Positive urine drug screen or breath alcohol level > 0.01% at screening (one re-test allowed)

Power Calculation and Sample Size

R21 phase:

A total of 48 randomized participants are planned for the R21 phase. This sample size is based on Aim 1, which is to determine effects of VAR versus PLA on smoking urges and negative affect during abstinence, reinforcing effects of a smoking lapse, cognitive function and time to relapse in SS. A repeated-measures design with 48 total participants provides 80% power to detect main and interaction effects on the primary targets (smoking urges and negative affect during abstinence) and secondary targets (reinforcing effects of a smoking lapse) of at least d = .40 in size, assuming a moderate within-subject autocorrelation. While this effect size is somewhat smaller than those detected by West et al. (2008) for effects of abstinence on urges and negative affect during abstinence and smoking satisfaction and reward from relapse (d's = .32-.44), abstinence was not controlled or biochemically verified after target quit date in that study, and, as the authors noted, it is possible that the effects that they observed were due only to those who were completely abstinent. With our rigorous control of abstinence, which includes twice-daily CO testing and a stringent abstinence criterion, we believe that we will detect smaller effects. We are not determining sample size based on Aim 2 (which is to examine the extent to which the effects of VAR on time to relapse are mediated through its effects on the target mechanisms), but we should be able to

detect medium-sized group effects on latency to second lapse, and estimate the size of mediation relationships that would be detectable as significant. We anticipate 20% attrition between enrollment and randomization. Therefore, we anticipate needing to enroll up to 60 participants (30 per group) to include 48 in the intent-to-treat sample.

R33 phase:

A total of 48 randomized participants are planned for the R33 phase. With 20% attrition estimated between enrollment and randomization, we anticipate needing to enroll up to 60 participants (20 per group) to include 48 in the intent-to-treat sample. Given that the PAR-14-230 funding announcement indicates that Stage 1B pilot studies funded through this R33 mechanism "are not expected to have sufficient power to conduct a strong test of efficacy", we have not attempted to power this study to detect significant differences among the groups. We will focus on determining the feasibility and initial efficacy (i.e., effect sizes) of this intervention to determine if a larger-scale trial is warranted.

Trial Management

List of Participating Sites:

Brown University

Projected Timetable

Recruitment (cumulative)

R21 phase:

Year 1: 24 participants
Year 2: 48 participants

R33 phase:

Year 3: 16 participants
Year 4: 32 participants
Year 5: 48 participants

Target Population Distribution (e.g., women, minorities, etc.)

Age Range: Participants will be 18-65 years of age. Those under 18 will be excluded because the efficacy and safety of VAR in children has not been established.

Gender: Both men and women will be included. About 60% male participants are anticipated because schizophrenia is more prevalent among men (Aleman et al., 2003).

Racial and ethnic groups: Ethnicity/race will not be a selection/exclusion factor for study participation. Based on census data and our recent studies, we anticipate that 75% of participants will be Caucasian, 20% African American or multiracial, 4% Asian, 1% Native American and 15% Hispanic.

Data Management and Analysis

Data Entry, Acquisition and Transmission

Data will be entered directly by the participant or by the Research Assistant. Research materials include paper or computer-administered (Qualtrics or REDCap) questionnaires and tasks, structured clinical interviews, videos of participants providing a breath CO sample, breath samples for analyzing carbon monoxide and alcohol levels, saliva samples for analyzing cotinine, and urine samples for assessing tobacco toxicity biomarkers, illicit drug use and pregnancy.

All data will be collected for research purposes only. All forms will be marked with only subject ID, session number and date. All records will be stored in locked files (physical or on computer) in locked rooms accessible only to research staff. Data gathered from people who attend the screening but do not meet inclusion criteria or decide not to participate will be stripped of personal identifiers or links and only the reason for study exclusion will be kept.

Personal information (participant name, address, telephone number, email address, locator contact information) must be collected so that the research assistant can contact people to schedule assessments, call with session reminders and arrange transportation to sessions. These data will be stored in a locked file that does not contain ID code numbers. All other data will be stored in files locked in a separate location with only code numbers identifying subjects and no personal identifiers. A cross-index of code numbers and participant names will be kept in a separate, password-protected computer file that is available only to research staff, PI, and mandated agencies during audits (e.g., study sponsor and Brown University IRB).

Saliva specimens for cotinine analysis will be marked with a study ID number, stored in the locked laboratory suite, and sent to a commercial laboratory for analysis. We will track samples sent and analysis results received using a form stored on a password-protected computer.

Data Analysis Plan

R21 phase

Variables will be examined for distributional assumptions associated with analyses to be used and transformed if necessary. Groups will be compared on demographic and other individual difference measures using t-tests for continuous measures and chi-square tests for categorical measures. Analyses of the effects of Group (VAR, PLA) and Time (Sessions 2-8) on QSU and MNWS-negative affect scores will be conducted using generalized estimating equation (GEE) models (Zeger et al., 1988), which allow for varying numbers of observations per participant (to minimize bias due to attrition) while controlling for autocorrelation (AR1 structure). GEE will also be used to analyze the effects of Group and Time (Screening, Sessions 2 and 8) on BPRS and other psychiatric symptom scores. Mixed 2 x 2 Analysis of Variance tests (ANOVAs) will be used to examine effects of Group and Abstinence (Sessions 1 and 8) on CEQ scale scores,

cognitive measure scores (with baseline scores covaried), CPT demand indices and within-session changes (post- minus pre-smoking) in CO level and positive and negative mood scale scores. Significant interactions will be followed by simple effects tests. Those who opt not to smoke in Session 8 will not be included in the Group x Abstinence analyses of CEQ, or pre-to-post smoking changes in CO or mood, but will be included in all other analyses (only one SS opted not to smoke in Session 8 in our previous study, Tidey et al., 2014). Latency to relapse will be defined as hours between the start of Session 8 and time of relapse, collected in person at Friday's session and by videoed CO sample in the follow-up week. We will follow up for one week after Friday's session, which is 8 days after Session 8. Thus, the maximum latency until second lapse will be 192 h, at which point data will be censored. Lapse latencies will be compared in VAR vs. PLA using a t-test. We will examine whether gender and FTND score (≤ 5 vs. ≥ 6) moderate the effects of VAR by adding these factors (separately) to each model.

Mediation of the relationship between group and lapse latency will be examined using an SPSS macro (Preacher & Hayes, 2004). Hypothesized mediators will include baseline Calgary scale, cognitive performance and Contemplation Ladder scores, Session 8 QSU and MNWS scores, Session 8 CPT and CEQ Reward and Satisfaction scores, and Session 8 cognitive performance scores. Simple mediator models will be used to investigate the direct effect of medication on relapse latency (c path) with no mediator in the equation, as well as the medication → mediator path (a), the mediator → latency path (b), and the effect of medication on latency with the mediator in the equation (c' path). The indirect effect of medication on latency via each mediator (c - c') is equal to the product of the coefficients of the "a" and "b" paths (i.e., "ab"). If ab is not normally distributed, 10,000 bootstrap resamples will be used to obtain lower and upper 95% confidence intervals (CI) for each indirect effect (Preacher & Hayes, 2008). All variables will be standardized first so that path coefficients can be directly compared across variables with different metrics. In addition, step-wise regression will be used to examine whether screening BPRS scores (entered in Step 1) and Session 8 BPRS scores (Step 2) predict latency to relapse. The SPSS mainframe statistical package (SPSS, Inc., Chicago, IL) will be used for GEE, mediation and regression analyses. All other analyses will be conducted using SPSS Statistics Version 20 for Windows (IBM, Armonk, NY). Differences will be considered significant when $p \leq .05$.

R33 phase

Following intent-to-treat principles, all randomized participants will be included in analyses. Baseline characteristics of the groups will be compared using ANOVAs for continuous variables and chi-square tests for categorical variables. CO levels from participants' videos will be averaged to provide a single CO measure for each week. Effects of the treatment groups on dependent measures (CO, total and consecutive abstinent CO samples, cigarettes per day, cotinine, QSU, MNWS, mood, CEQ, Stage of Change, Contemplation Ladder, cognitive scores (baseline co-varied), BPRS, Calgary Scale, AIMS, Simpson-Angus and BARS scores), will be analyzed with generalized linear mixed models (GLMMs) with Group (VAR + CM, VAR + NR, PLA + NR) as the between-subjects factor and Session as the within-subjects factor. We will examine main effects and the Group x Session interaction. This approach controls for correlations from repeated measurements and for person-level covariates. Baseline data will be imputed for missing. Differences will be considered significant when $p \leq .05$ and effect sizes will be calculated (Cohen, 1988). We will examine whether gender and FTND score (≤ 5 vs. ≥ 6) moderate treatment effects by adding these factors (separately) to each model. To examine whether reductions in smoking are mediated by changes in proposed targets, once the Group x Session GLMMs have been conducted, we will add concurrent QSU, MNWS and CEQ Reward and Satisfaction scores as covariates in these models to see the extent to which

smoking outcomes are attenuated by the mediators. We will use the same procedure to explore whether cognitive performance mediates smoking outcomes.

Feasibility outcomes include: median number of sessions attended, percentage of video samples submitted and percentage of those who indicate that they would be willing to participate in a longer CM trial. Responses to open-ended questions on the debriefing questionnaire will be described. Number and type of serious adverse events are expected to be rare so will be reported descriptively. Adverse event ratings will be analyzed individually using one maximum value over the 5 weeks for each person for each expected effect, including the baseline value of each item.

Quality Assurance

Procedures in place to ensure the validity and integrity of the data

It will be made clear to participants that all information obtained during assessments is confidential and that no information will be shared with the participants' clinicians unless the participant requests this in writing. All investigators and staff associated with this project have been trained, and new hires will be trained, on human research ethics in accordance with the requirements of the local institutions during initial project approval.

The PI will train and closely monitor the Research Assistant on the procedures to be used in this study. Such monitoring will consist of frequent in-person discussion of study visits at the beginning of the study and less frequent monitoring as the study progresses. The PI and Research Assistant will meet at least weekly to discuss any study issues and their resolution.

Questionnaires administered during the screening interview will be read to participants and filled out by the Research Assistant, to maximize accuracy and completeness of these data. After enrollment, questionnaires that are administered at repeated time points during the study (e.g., QSU) will be completed by participants. The first time that participants complete these questionnaires, the Research Assistant will go over the questionnaires to ensure that participants understand the questions. Subsequently, the Research Assistant review the questionnaire instructions with participants and will be available to the participant to answer any questions he/she may have. Questionnaires will be reviewed for completeness while the participant is present. On computerized forms or tasks, participants cannot accidentally skip a question, but may choose not to answer questions. Biochemical measures (expired breath CO, urine pregnancy, urine drug) will be analyzed immediately, while the participant is present. If necessary (e.g., if the sample volume is insufficient for analysis), the Research Assistant can gather another sample immediately and re-analyze.

Standard operating procedures and case report form templates will be developed to ensure that data are collected consistently during the study. Each visit will have a checklist of all measures that need to be obtained and the order in which these measures are to be administered. Once a participant has completed all study procedures and all open events have been closed, the PI will review the participant's binder and sign a form indicating study completion for that participant. Oversight of the study and adherence to protocol procedures will be conducted by the PI or another study staff member (e.g., post-doctoral fellow) who has been trained and is supervised by the PI.

VAR and matching PLA will be prepared by a pharmacist by compounding VAR tablets or placebo lactose powder to capsules that are identical in appearance. The standard VAR dosing will be used: 0.5 mg/day on days 1–3, 0.5 mg twice daily (morning, evening) on days 4–7, then 1 mg twice daily to the end of the medication period. VAR and PLA will be distributed in identical 7-day medication blister packs, marked with the participant's study identification number and letter code.

A medication randomization table will be created by the PI. The Research Assistant will be provided with a copy that has letter codes (A, B, C, or D) instead of medication names. When the Research Assistant enrolls a participant, the Research Assistant will enter the participant's name and ID number on a row the table, note the medication letter code for that row on the participant's enrollment form, and take the medication pack with that letter code. The Research Assistant will then provide the Data Manager with a copy of the randomization table so that the data manager can update his records.

Dr. Tidey will remain blind to medication condition during each phase (R21 phase, R33 phase). The Data Manager will break the blind for Dr. Tidey at the end of each phase. The Data Manager will break the blind for the medical monitor (Dr. Swift) in case of adverse events requiring medical intervention.

Regulatory Issues

Reporting of SAEs

Serious events as defined in 21 CFR 312.32 will be reported to the Brown University IRB, the NIDA Project Officer, and the DSMB. The Brown University IRB requires that fatalities and all other SAEs related to the study products be reported within 5 days of receiving notice of the event. SAEs related to the study will be reported to NIDA within 72 hours.

Reporting of IRB actions to NIDA

Actions taken by the Brown University IRB in response to AEs/SAEs will be reported to NIDA in the annual noncompetitive continuation application, as will reports of changes or amendments to the protocol as a result of an AE/SAE. Recommendation for trial study discontinuation, for significant changes or amendments to the protocol, or other significant findings as a result of a study related SAE will be reported immediately to the NIDA Program Officer by the PI.

Reporting of changes or amendments to the protocol

All proposed changes/amendments to the protocol will be discussed with the NIDA Project Officer prior to implementation. Amendments will then be filed with the IRB. IRB approval of such amendments and an updated DSMP will be forwarded to the NIDA Project Officer, and the original amendment approvals will be filed in the primary document manual.

Trial stopping rules

The trial will be stopped if the Brown IRB recommends trial discontinuation due to SAEs, if the trial is not progressing due to lack of participant recruitment, or if advised by the DSMB.

Disclosure of any conflict of interest in the DSMB

Potential conflicts of interest in the DSMB will be disclosed to the Brown University IRB and to the NIDA Project Officer if they arise. The investigators will devise an appropriate course of action in light of a potential conflict of interest, and the PI will report and document the action taken to resolve the conflict.

Trial Safety

Potential Risks and Benefits for Participants

Potential risks of participation

1) Survey Questionnaires: The interview will include questions about medical history, psychiatric history and symptoms, and drug and alcohol use. Answering these personal questions could make the participant feel uncomfortable. However, the questions we ask are commonly used in research and clinical practice, and the participant will not be required to answer any question he/she is not comfortable answering. Answers to these questions will be kept confidential.

2) Breach of Confidentiality: The risk of the interview is loss of privacy if other people find out the results. We will work to ensure that the participant's confidentiality is kept, and a Certificate of Confidentiality will be obtained from NIDA to further protect confidentiality. Study data will be identified only by numeric code and stored in locked file cabinets, or on password-protected computers. A master list of participant names and contact numbers will be kept completely separate from other information about participants in order to facilitate study visit scheduling and coordination. Only those with a need to know (for assessments of adverse events) or mandated auditors will have access to the master list linking names and code numbers. Clinically important assessment data such as new concomitant medications or adverse events will be made available to the medical monitor so that he can evaluate the participant coordinate an effective response. All study staff have received (and new staff will receive) mandatory human subjects' protections training. All are highly experienced with relevant ethical principles, particularly around confidentiality. Digital video files of CO samples will be deleted once these data have been coded.

3) Coercion: Coercion can arise from the payments that participants can earn for participation. Payments are considered compensation for assessment and travel time, and the rate is consistent with local standards for research. The R21 study includes high-value cash incentives for abstinence, which is necessary for experimentally-controlling smoking abstinence in this study as we demonstrated in a previous study (Tidey et al., 2014). Participants are free to discontinue at any time and will receive compensation for the sessions that they complete at the same rate and in the same form as those who complete that study. As an added protection for participants, those who initiate and maintain abstinence in this study through Thursday and wish to remain abstinent can opt out of the post-abstinence smoking assessment and still receive full compensation, as long as they attend the visit for the same amount of time as those who smoke and complete the other assessments. The R33 study includes a contingency management (CM) system, in which participants will receive voucher-based incentives for abstinence. Incentive values are in line with those offered in other CM studies for smoking cessation (e.g., Dallery et al., 2013).

4) Nicotine Withdrawal: Participants may experience some discomfort when abstaining from smoking. Symptoms can include irritability, frustration, anxiety, depressed mood or sadness, desire or craving to smoke, difficulty concentrating, and increased appetite or hunger. These feelings can be uncomfortable but they are normal, temporary, and usually mild.

5) Effects of Varenicline (VAR): The results of the largest study to date of varenicline's efficacy and safety in smokers with and without psychiatric disorders found no increase in neuropsychiatric adverse events attributable to varenicline relative to nicotine patch or placebo (Anthenellie et al., 2016). The most frequent adverse event associated with varenicline is mild to moderate nausea, occurring in 25-45% of users, diminishing over time, and not leading to varenicline discontinuation (Anthenelli et al., 2016; Cahill et al., 2009; Ebbert et al., 2010; Evins et al., 2014; Leung et al., 2011). Other common adverse events include insomnia, abnormal dreams and headaches; serious adverse events have been rare in randomized, controlled phase III studies, and there have been no treatment-related deaths and no known contraindications (Anthenelli et al., 2016; Aubin et al., 2014; Evins et al., 2014). Nevertheless, patients receiving VAR should and will be monitored in this study for changes in psychiatric symptoms including mood and suicidality. Co-Investigators Rohsenow, a licensed clinical psychologist, and Swift, an addictions psychiatrist, will assess and assist with any participants who experience increases in psychiatric symptoms during the study. We will ask participants to sign a medical release form that will allow us to inform their psychiatrist or other healthcare provider that they are participating in a research study in which they may be receiving VAR under double-blind conditions.

6) Changes in Psychiatric Symptoms Secondary to Changes in Smoking Behavior. Changes in smoking can affect how well some psychiatric medications work due to changes in CYP1A2 enzyme activity. We believe the risks of these events are low given the low incidence of such changes in clinical trials, including a trial that included over 4000 smokers with psychiatric disorders (Anthenelli et al., 2016; Evins et al., 2014). However, we will inform participants about these risks and ask participants to provide us with written permission to notify their treating clinician that they are in a study in which they may receive VAR and a behavioral treatment (R33 phase only) that may affect their smoking rate. Adverse events will be collected weekly using a checklist and open-ended questions. In addition, psychiatric symptoms will be assessed with the BPRS and Calgary Scale at every in-person session and movement disorders will be assessed with the AIMS, Simpson-Angus Scale and BARS at the screening and last session. Moderate-to-severe increases in symptoms (e.g., change from mild/moderate category to severe) will trigger review by Dr. Swift or Rohsenow, who will meet with the participant if needed. Serious adverse events and unexpected related adverse events will be reported to the Brown University IRB as noted above (see **Regulatory Issues** section). Participants will be given contact information so that they can reach the PI, Dr. Swift, Dr. Rohsenow, or study staff at any time to report adverse events. Participants reporting suicidal intention at any time (score ≥ 4 on the Columbia Suicide Severity Rating Scale, suicide plan endorsed on the Calgary Depression Scale for Schizophrenia, or spontaneous reports) will be put in contact with Dr. Swift or Rohsenow immediately. The clinician will speak with the participant in person if suicidality is reported during a study visit or by phone if it is reported by phone. The clinicians will then determine the next steps to be taken. Having 2 clinicians on this study increases the likelihood that at least one will be available. However, if neither is available, other qualified clinicians at our research center will speak with the participant. The PI will follow any steps recommended by the clinician (i.e., to continue or discontinue participation).

Potential benefits of participation

Given the short exposure to VAR and CM, no direct benefits to participants are expected. Participants will have the chance to learn more about the effects of smoking, and to help us learn more about the potential efficacy of this treatment approach.

Collection and reporting of AEs and SAEs

While participating in the trial, adverse events and concomitant medications will be assessed at every study visit. Medical events will typically be identified during the administration of the Health Changes Questionnaire. Other events may be identified by spontaneous reports.

Questionnaire items that will be reviewed:

Health Changes Questionnaire: If the participant answers **'YES'** to **Questions 1, 2, 3b** or **3c**, the interviewer should administer the 'Medical Event Form.'

1) ***Have you had any negative changes in your physical or mental health since your last visit?***
2) ***Have you had any changes in medication since your last visit?***
3) *Since your last visit, have you received any form of medical care?*
    a. *Have you received any preventive care?*
    b. ***Have you needed to seek immediate medical care, gone to the emergency room, or been hospitalized since your last visit?***
    c. ***Have you received any care for an illness, injury, or other medical complaint that did not require emergency care?***
    d. *Have you received any follow-up care?*

For the participant's protection, participants will be withdrawn immediately from the study if any of the following occur:

1) Cardiovascular disease (CVD) event: Typically includes MI (heart attack), PTCA (angioplasty/stenting), bypass surgery, stroke, peripheral vascular disease (arterial blockages in arms or legs leading to procedure or surgery). Less common CVD problems would be new cardiac arrhythmias (e.g., new atrial fibrillation) or new valvular disease (e.g., mitral or aortic regurgitation).
2) DVT/PE (deep vein thrombosis/pulmonary embolism, i.e., blood clots in the venous system).
3) Suicide Attempt: A participant will be withdrawn if he/she attempts suicide at any time during participation in the study.
4) Psychiatric Hospitalization: A participant will be withdrawn if he/she is hospitalized for psychiatric reasons at any time during participation in the study.
5) Pregnancy: If participant indicates she is pregnant or has a positive pregnancy test at any session, she will be withdrawn from the study, and this event will remain open until delivery. At that time the medical monitor will contact the participant to ask a few questions about the baby's health and will update the open 'Medical Event Form'.

The following will be monitored and can lead to the participant being withdrawn by the PI or medical monitor:

1) Any hospitalization or debilitation in which participation in the study could be detrimental to the recovery process. This will be self-reported by the participant and will be reviewed by the PI and medical monitor to determine whether continued participation in the study is appropriate.
2) If a participant is behaving in an inappropriate or threatening manner, admits to lying about eligibility criteria, including omitting previous medical diagnoses and medications, is participating in other research studies that could affect the primary outcome measures, or does not follow study instructions, then the PI can withdraw him or her at the PI's discretion.

Serious adverse events (SAEs): Information about all serious adverse events will be collected and recorded on a standard Serious Adverse Event Report Form. A serious adverse event is an undesirable sign, symptom or medical condition which:

1. is fatal or life-threatening
2. requires or prolongs hospitalization
3. results in persistent or significant disability/incapacity
4. constitutes a congenital anomaly or a birth defect
5. is medically significant, in that it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

A hospitalization would not be considered to be a serious adverse event if it is for the routine treatment or monitoring of the studied indication (smoking), not associated with any deterioration in condition, is treatment, which was elective or pre-planned, for a pre-existing condition unrelated to the indication under study and did not worsen, is admission to a hospital or other institution for general care, not associated with any deterioration in condition, is treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above, and not resulting in hospital admission.

Any SAE occurring after the participant has signed the informed consent and until the participant has stopped study participation must be reported. Investigator responsibilities for notification of SAEs are described above (see **Regulatory Issues** section).

Management of SAEs or Other Study Risks

The study medical monitor will review all AEs. A study participant may be discontinued from the study if the medical monitor and/or PI determines it is the best decision in order to protect the safety of a participant. In the event that a participant either withdraws from the study or is discontinued due to an AE/SAE, the participant will have appropriate follow-up medical monitoring until the problem resolves, stabilizes, or is clearly unrelated to the study medication. Any AE that remains open will be reviewed and closed at the last visit (R21 phase) or the last follow-up phone call (R33 phase).

Trial Efficacy

Plans for Interim Analysis of Efficacy Data

Data will be analyzed at the end of the R21 phase to determine if the results support moving to the R33 phase (i.e., if the go/no-go target has been met). No other interim analyses are planned.

DSM Plan Administration

Responsibility for data and safety monitoring

The PI (Dr. Tidey) will be responsible for monitoring data integrity and participant's safety, executing the DSM plan and complying with the reporting requirements to the IRB, DSMB and NIDA. The PI will provide an annual summary of the Data Safety and Monitoring Board (DSMB) report to NIDA along with the progress report.

Frequency of DSM reviews

The PI and Research Assistant will meet at least weekly during the project, and the larger group (PI, Co-Investigators, Research Assistant and Data Manager) will meet at least monthly throughout the project. During these meetings, the progress of the trial, data quality, recruitment, retention, and other factors that may affect study outcomes will be reviewed. Adverse events will be reviewed to determine if there are any changes in participant risk. The investigators and staff are available to meet outside of the scheduled meetings, if concerns regarding a particular participant or another problem should arise.

The DSM Board will meet twice per year as described in the DSM Board section below.

Content of DSM report

The DSM report will include enrollment information, demographics and characteristics of the participants, the expected versus actual recruitment rates, quality assurance or regulatory issues that may have occurred during the year, a summary of adverse events and SAEs, protocol violations, and any actions or changes to the protocol. Also included will be any and all actions by the IRB.

Data Safety and Monitoring Board (DSMB)

Members and Affiliation

1. Mary Brunette, M.D., (Chair), Associate Professor of Psychiatry, Geisel School of Medicine at Dartmouth and Medical Director, Bureau of Behavioral Health, NH Department of Health & Human Services Expertise: smoking cessation treatment research for people with schizophrenia (Mary.F.Brunette@Hitchcock.org)
2. Cori Cather, Ph.D., Director of Psychology Services, Schizophrenia Program, Massachusetts General Hospital, and Assistant Professor of Psychology, Harvard Medical School Center for Addition Medicine, Boston, MA. Expertise: assessment of VAR and other medication treatments for smoking in people with schizophrenia (ccather@mgh.harvard.edu)
3. Marc Steinberg, Ph.D., Associate Professor of Psychiatry and Associate Director of the Division of Addiction Psychiatry, Robert Wood Johnson Medical School, Rutgers University, New Brunswick NJ. Expertise: laboratory and smoking cessation treatment research in people with schizophrenia (steinbml@rwjms.rutgers.edu)

4. Andrea Weinberger, Ph.D., Assistant Professor of Psychology, Yeshiva University, NY, NY. Expertise: laboratory and smoking cessation treatment research in people with schizophrenia and major depression (andrea.weinberger@einstein.yu.edu)

Frequency of meetings

This Board will meet at regular intervals (every 6 months) to evaluate the progress of the trial, data quality, recruitment, participant demographics, study retention, and other factors that may affect study outcome. This meeting will be conducted as a conference call. Included in the review will be protocol violations, quality of data collection, overall data flow and study drop outs and reasons. The Board will also review the participants' ability to achieve study requirements and the rates of adverse events to assess trends and determine whether there has been any change in participant risk. The DSMB will review all serious or unexpected adverse events and provide recommendations. The review will ensure that subject risk does not outweigh the study benefits. A brief report will be generated from each of these meetings for the study record and forwarded to the Brown Institutional Review Board (IRB) and to the NIDA Program Officer with the progress report.

The DSMB will be available to convene outside of the regular meetings, if necessary. If concerns should arise regarding a particular subject, or any troublesome trends in the experiences of participants, they will make appropriate recommendations for changes in protocol, as needed.

Conflicts of interest

No board members will be affiliated with the grant other than through their work on the board. Each member will complete a conflict of interest disclosure form prior to each meeting. Ad hoc specialists may be invited to participate as non-voting members at any time if additional expertise is desired.

Protection of confidentiality

During DSMB meetings, only de-identified data, including blinded study site and condition type, will be provided to the board. All data and discussion during the meeting will be confidential.

Monitoring activities (initial and ongoing study review)

The DSMB's charge will include evaluating the standard procedures for monitoring developed by the investigators. The DSMB will begin by reviewing the study protocol and data and safety monitoring plan. This review will include protocol design, the appropriateness of the inclusion/exclusion criteria, the randomization plan, the definition of participants (e.g., screened, enrolled, randomized, treated, drop out, lost to follow-up), assessment and subjective measures and study biomarkers. The DSMB will ultimately establish the criteria for safety concerns, discontinuing a participant, and how to deal with missing visits/data.

Communication plan to IRB and NIDA

We will inform the IRB and the NIDA Program Officer of any significant action taken as a result of the DSMB findings. We will inform the subjects of any changes in risk.

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