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Title: Methadone-Maintained Smokers Switching to E-Cigarettes

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Medical Monitor: Dr. Michael Stein

2. Summary of the Protocol

2.a Brief Description of the Protocol

While smoking rates have declined in the United States, persons with opioid use disorder (OUD) enrolled in methadone maintenance programs continue to have smoking prevalence rates of 80-90%. Individuals with OUD receiving methadone maintenance treatment are more severely nicotine-dependent, and have higher rates of tobacco-related morbidity and mortality than those in the general population. For example, 51% of deaths among persons with OUD can be attributed to tobacco-related cause. And, smokers with OUD are 4 times more likely to experience premature mortality compared to non-smokers. Over the past decade, multiple clinical trials of pharmacotherapy have documented that methadone-maintained smokers (MMS), have very low smoking cessation rates (<10% are quit 6 months later). Given these low rates of successful quitting and the significant health consequences of smoking combustible cigarettes (CC), it is critical to identify harm-reduction strategies in this at-risk population. Electronic cigarette (EC) use has grown rapidly and substituting combustible cigarettes with EC use may decrease health risks in MMS. However, to date, few studies have prospectively examined EC use in MMS, and none in a full-scale clinical trial. Therefore, we propose to take a first step by examining the risks and benefits associated with EC use among current tobacco smokers in methadone maintenance treatment. Of particular interest would be the health effects of ECs among MMS because of MMS' difficulty with prolonged CC quitting, the severity of their nicotine dependence, greater tobacco demand, and the precedent of harm reduction wherein opioid users substitute a lower risk opioid (methadone or buprenorphine) for illicit drug use.

Participants in this randomized clinical trial will be methadone-maintained smokers interested in switching to ECs. There will be a total of 7 study visits over the course of 6 weeks: baseline, 5 weekly check-in (CI) visits, and a 6-week assessment. Baseline assessments will include biomarker measurement, carbon monoxide (CO) readings, smoking history and current cigarette use, spirometry, respiratory symptoms, and tobacco demand. After completion of the baseline visit, participants will be randomized to either: 1) 6 weeks of EC use (JUUL 5% nicotine pods) or 2) 6 weeks of nicotine replacement therapy (NRT) in the form of nicotine lozenges. EC and NRT use will begin the day after the baseline assessment. All participants will attend weekly brief assessment check-in visits where distribution of either EC or NRT will occur. Check-in assessments will include cigarette use, EC use, NRT use, CO readings, respiratory symptoms, and tobacco demand. At the 6-week assessment, baseline measurements will be repeated to determine changes in the health effects, biomarkers, and combustible cigarette use associated with 6 weeks of EC use, relative to NRT.

Type	Name	Time Frame	Brief Description
Primary	Toxicant Exposure	Baseline and 6-weeks	Toxicant exposure will be measured via first void urine. Biomarkers will include: NNAL, & NNN, 3-HPMA
Secondary	Cigarettes per Day	daily	CPD will be measured using a daily report and the Timeline Follow-back instrument (when daily report data are missing).
Secondary	Cigarettes Purchase Task (Tobacco Demand)	Baseline, 3-week check in & 6-weeks	The CPT will serve as a measure of CC reinforcement. The CPT is a questionnaire on which participants indicate how much of a product they would buy across a range of prices.
Secondary	American Thoracic Society Questionnaire (ATSQ)	Baseline and 6-weeks	Self-report measure of respiratory symptoms
Secondary	Situational Confidence Questionnaire (Quitting Self-Efficacy)	Baseline and 6-weeks	The instrument asks subjects to rate their confidence in their ability to resist smoking acrossa variety of circumstances
Secondary	Lung Functioning	Baseline and 6-weeks	The spirometry test, to measure lung functioning,will be conducted according to the American Thoracic Society guidelines. Data collected will include: FVC;

			FEV1, FEV1/FVC.

2.b. Primary and Secondary Outcome Measures

2.c Inclusion/Exclusion Criteria:

Inclusion criteria are: (1) Between 21 and 65 years of age; (2) Moderate to heavy cigarette smokers (≥ 10 cigarettes/day for > 1 yr; breath CO > 5 ppm); (3) Have been receiving methadone for at least three months; (4) Attend CODAC or SSTAR clinic at least weekly to receive methadone; (5) Speak English; (6) Have access to a phone capable of receiving phone calls and will be available over the next 6 weeks; (7) Are interested in switching to either e-cigarettes or nicotine lozenges in the next 2 weeks; (8) if a non-daily cannabis user, able to not smoke cannabis in the last 15 hours prior to study visits and (9) Give informed consent to participate in the study.

Exclusion criteria are: (1) Used e-cigs on > 2 of the past 30 days; (2) Currently use medications that may reduce smoking (bupropion, varenicline, nicotine replacement therapy); (3) Have unstable psychiatric conditions (e.g., past-month suicidal ideation or past-year suicide attempt, current mania or psychosis); (4) Have daily use of marijuana (self-report) which interferes with CO measurement; (5) Are currently pregnant; (6) moderate-to-severe COPD; (7) moderate-to-severe asthma; (8) medications that improve lung functioning; and (9) had a cardiovascular event in the last month.

2.d Power Calculation and Sample Size:

We estimated our sample size requirements using power analysis for the primary hypothesis (A.1.a) of better health outcomes at 6-weeks. Prior research found a dose-dependent reduction in NNAL with lung cancer risk. Based on this, it is probable that medium to large reductions in NNN, NNAL are required to yield clinically meaningful health benefits. These are consistent with our work from Project SWITCH. SWITCH reported a 39.5% reduction in mean NNAL in the EC arm and a 10.0% increase in NNAL in the cigarettes-as-usual arm. Based on reported means and a pooled standard deviation, the estimated standardized difference in means was about .69. SWITCH reported comparable effect sizes for respiratory symptoms (d = .62) and CO levels (d = .71). Here we propose to provide NRT lozenges to the comparison arm. Our past cessation studies have shown NRT treatment has low quit rates. While we expect the beneficial effect of NRT lozenges to be small, we anticipate between arm differences maybe be somewhat smaller than in Project Switch. If we assume a 35% reduction in mean NNAL in the EC arm and a 5% reduction in mean NNAL in the comparison arm, the estimated standardized difference in means is about .43. With 2:1 allocation of participants to EC vs. NRT, and assuming 15% attrition at 6-weeks, the current study has sufficient power ($1 - \beta \geq .80$) to detect a standardized difference in means of .40 or larger. In the context of a linear model with 5 controls, the study has sufficient power ($1 - \beta = .85$) to detect an increment to R^2 for treatment of .04, a small to medium effect.
We estimated statistical power for A.2.a using a repeated measures ANOVA with a 3 category within person factor (time) and 2-category between person factor (treatment). Statistical power will depend on the degree to which the intervention effect is sustained, and the strength of the correlation between repeated measurements. Assuming a standardized differences in means of .4 is sustained across 6-week assessments and a correlation of .5 between repeated measurements ($1-\beta = .92$).

Statistical power estimates for hypotheses A.3.a and A.3.b assume that n1 (# of EC/NRT exclusive users) = 37 and n2 (non EC/NRT exclusive users) = 167. In Project Switch, 26.6% of persons randomized to EC were exclusive EC users. Past studies of NRT treatment in this population have reported low rates of cigarette abstinence. We base sample estimates an overall follow-up rate of 85% and on the expectation that about 25% of persons randomized to EC will be exclusive EC users (about 34) and that 5% of persons in the NRT arm will be exclusive NRT users (about 3). For hypotheses A.3.a statistical power will be sufficient ($1-\beta = .81$) to detect standardized difference in means of .52 or larger.

Estimates for statistical power for A.3.b assume n1 = 37 and n2 = 167 and were estimated for a repeated measures ANOVA as described for hypothesis A.2.a. Statistical power will again be a function of the degree to which intervention effects are sustained over time and the magnitude of the correlation between repeated measures. Assuming a sustained standardized difference in means of .52 and a correlation of .5 between repeated measurements, estimated statistical power = .94. The design has sufficient power ($1-\beta = .80$) to detect a standardized mean difference if .42 if sustained across the 6-week assessments.

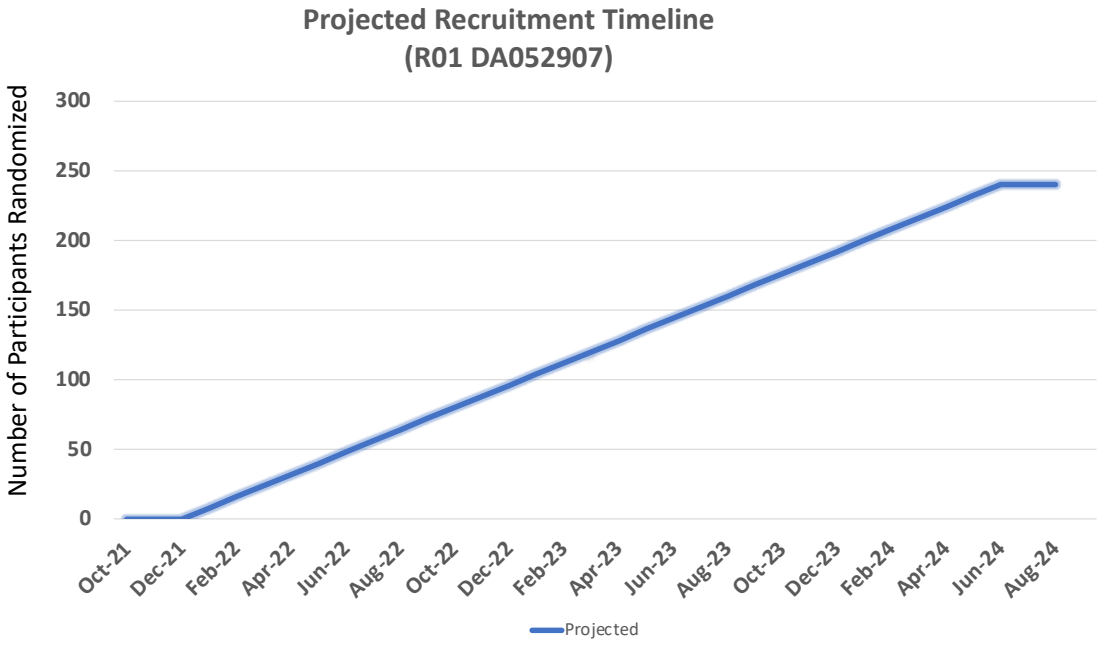
3. Trial Management:

3.a List of Participating enrolling clinics or data collection centers

1. CODAC Behavioral Healthcare in Providence, Rhode Island
2. Stanley Street Treatment and Resources (SSTAR) in Fall River, Massachusetts

3.b Projected Timetable

After staff hiring and training, participant recruitment will begin in month 3 of the study. 240 participants will be recruited over the course of 30 months and the last 3 months will be devoted to statistical analyses and dissemination of findings.



3.c Target Population Distribution

Participants in this study will consist of 240 individuals enrolled in methadone maintenance in CODAC Behavioral Healthcare (in Rhode Island) or Stanley Street Treatment and Resources (SSTAR in Fall River, Massachusetts), using tobacco cigarettes, and give informed consent to participate. Participants will be aged 21 or older. Participants will be recruited without regard to gender. All study recruitment and assessments will be conducted at CODAC, Inc. or SSTAR, both comprehensive not-for-profit outpatient treatment organizations with specific focus on substance use disorder treatment. CODAC has seven clinical sites across Rhode Island and has been a collaborative partner for the MPIs' prior research. Serving more than 1500 persons annually across the state, CODAC's patients are 15% Latinx, 8% Black/African American, and 38% female. Demographic characteristics of patients in SSTAR's methadone maintenance treatment (MMT) program have shown that approximately 41% of patients are female. However, we will attempt to recruit approximately equal numbers of men and women for the proposed project across both sites. Census data of Bristol County, MA (where SSTAR, the recruitment site, is located) shows a racial breakdown of: 88% White, 3% Black or African American, <1% American Indian or Alaskan Native, 2% Asian, <1% Native Hawaiian or Pacific Islander, and 6% other or multiracial. 6% of individuals are Latino or Hispanic. Thus, the proposed study is well-situated in communities of high OUD burden. We have considerable experience recruiting at SSTAR for previous and on-going NIH studies and CODAC is a promising site in which we expect to be able to meet recruitment goals. All CODAC and SSTAR patients receive daily methadone dosing, monthly individual counseling, referrals to psychosocial treatment, clinic- and community-based substance use support groups, and referrals to clinic case managers, as needed. No participants will be excluded from recruitment on the basis of race, ethnicity or gender. We will oversample minority populations, paying special attention to demographics of individuals who have OUD, rather than relying on demographics of the state, to attain at least 20% minority enrollment.

4. Data Management and Analysis

4.a, 4.b Data Acquisition and Transition and Data Entry Methods

Drs. Stein and Abrantes will have primary responsibility for the day-to-day monitoring of the quality of operations in all data collection. All data collected by the research team are considered part of the subject's confidential record. There are several sources of data. In most cases, data from assessments will be directly entered into the research database. Research assistants will also code all data from research interviews that is

not directly entered. This coded data will be entered into the research database. Audiorecordings of interviews with participants will be uploaded and stored on a secure server in a digital format. A study ID will be used to identify the recordings. Otherwise, they are not connected with the primary study database in any way.
All data will be collected for research purposes only and all records will be stored in locked files (physical or on computer) in locked rooms accessible only to research staff. Data gathered from people screened but who do not meet inclusion criteria or decide not to participate will be stripped of personal identifiers or links and only demographic characteristics and the reason for study exclusion will be kept. Paper forms with personal identifiers (such as consent forms or contact information) will be stored in a locked file that does not contain subject code numbers. All other data will be stored in files locked in a separate location with only code numbers identifying subjects, 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 (for collecting follow-ups), the PIs, and mandated auditing agencies during audits.

All de-identified research data will be entered into REDCap. REDCap is a secure, web application designed to support data capture for research studies, providing user-friendly web-based case report forms, real-time data entry validation (e.g. for data types and range checks), audit trails, and a de-identified data export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). Participants may complete surveys in the laboratory or anywhere they can access a web browser, including on their Internet-connected smartphone or tablet. The system was developed by a multi-institutional consortium and was initiated at Vanderbilt University. The CNE RedCap is hosted on a CNE-based server. Network transmissions (data entry, survey submission, web browsing, etc.) in REDCap are protected via Secure Sockets Layer (SSL) encryption. Access to REDCap can be restricted at different levels (e.g., research assistant, PI, and Co-Investigators). Exported data from REDCap will be stored on the Behavioral Medicine and Addiction Research's secure password-protected server.

Final Storage of Paper Data. Only the participants' study identification number will appear on any of the final paper data collection instruments. Once data have been entered and passed audit verification, paper copies of data will be housed at a facility that specializes in the storage of medical/research information. Only the subject's study identification number will be present on the forms. Any indication of the subject's name will be removed from the questionnaires prior to archiving. The destruction date of these paper files will be at least 7 years from the termination of the study and will be authorized by the Principal Investigator of the research study.

4.c Data Analysis Plan

Overview and Preliminary Analyses. We will present descriptive statistics to summarize the background characteristics, smoking behaviors, dependence, and values of outcome variables observed at baseline. Logistic regression will be used to identify significant predictors of attrition at the 6-week assessment. In addition to treatment group, evaluated predictors of attrition will include demographic characteristics, and baseline assessments of cigarettes per day (CPD), nicotine dependence, and baseline measures of outcome variables. To preserve the assumption of missing at random, baseline variables that significantly predict attrition will be included in the imputation model. The design is straight forward with primary outcomes assessed at 6-weeks. The outcomes are continuous and we envision estimating intervention effects in a general linear model framework. We will use graphical methods to evaluate the distribution of residuals. Based on that examination, we may use variance estimators that are robust to heteroskedasticity and/or analyze outcomes in a generalized linear model framework using a log link function. Planned covariates include baseline CPD, age, gender, and the baseline instance of the outcome being analyzed. A 2-tailed probability of Type I error $< .05$ will be used for all null hypothesis tests.

Missing Data. All analyses will be intent-to-treat. We will use multiple imputation by chained equations (MICE) to conduct intent-to-treat analysis. Azur et al. describe MICE as a principled method for dealing with missing data. MICE assumes data are missing completely at random (MCAR) or missing at random (MAR). Data are MAR if variables that are systematically associated with attrition are included in the model. The imputation model will include condition, baseline CPD, FTND, gender, age, the baseline instance of the outcome, and to preserve the assumption of MAR, any other baseline characteristics found to predict attrition significantly ($p < .10$). We will generate and analyze 50 data sets using the missing data facilities in Stata 15.

Outcomes Analysis. In A.1., we hypothesize that persons randomized to EC will have better health outcomes at 6-weeks than those randomized to NRT. Specific outcomes include biomarkers of tobacco toxicant exposure and spirometry-determined lung functioning. The NNAL outcome continuous and as noted

previously we plan to estimate intervention effects using a general linear model. If an examination of model residuals indicates the assumptions of the linear model are not reasonably well approximated, we may use generalized linear models with alternative link (e.g., log) or exponential family error distribution (e.g., Poisson, negative binomial). We will report unstandardized and Y standardized coefficients and 95% confidence intervals to summarize the adjusted effects of intervention. As an additional measure of effect size, we will report partial omega. We will use the mi estimate facility in Stata 15 to analyze the fully populated data sets generated by the associated mi impute facility. All tests of significance will be based on 2-tailed $\alpha = .05$. We will use mixed-effects linear models to evaluate the effect of condition on cigarettes / day, tobacco demand, respiratory symptoms, and self-efficacy for quitting at 6-week assessments (hypothesis A.2.a). A Wald $\chi 2$ test will be used to test the treatment by time interaction to determine if the effect of treatment differs significantly over time. We will again use the mi estimate facility in Stata 15 to analyze the fully populated data sets generated by the associated mi impute facility and all tests of significance will be based on 2-tailed $\alpha = .05$. We plan to test hypothesis A.3.a using a general linear model. Specifically, A.3.a hypothesizes that controlling for total CC using during the 6-week trial period, persons defined as exclusive EC/NRT users will have greater decreases in tobacco toxicant exposure and improved spirometry-determined lung-function at the 6-week assessment. Here, the intervention arms are treated as a single population. Based on Project Switch, we anticipate that approximately 25% of persons randomized to the EC arm and 5% of persons randomized to NRT will be defined as exclusive users. The list of covariates will be extended to include total cigarette consumption and intervention arm. The interaction between exclusive EC/NRT use and treatment assignment will be formally tested, though given the small number of exclusive NRT users we anticipate, statistical power will be low. However, a substantively large coefficient for this interaction would suggest different processes that may merit further investigation in future research. As previously described, we will report unstandardized and Y standardized coefficients and 95% confidence intervals to summarize the adjusted effects of condition. Again we will use the mi estimate facility in Stata 15 to analyze the fully populated data sets generated by the associated mi impute facility. All tests of significance will be based on 2-tailed $\alpha = .05$. Hypothesis A.3.b will be tested using the same methods as A.2.b. We will use mixed-effects linear models to test the hypothesis that EC/NRT exclusive users will have less tobacco demand, fewer respiratory symptoms, and greater self-efficacy for quitting CC at 6-weeks. We will again use a Wald $\chi 2$ test to evaluate the treatment by time interaction to determine if the effect of condition differs significantly over time. We will again use the mi estimate facility in Stata 15 to analyze the fully populated data sets generated by the associated mi impute facility and all tests of significance will be based on 2-tailed $\alpha = .05$.

5. Quality Assurance

All research personnel will have formal training in research with human subjects (e.g., CITI training, NIH Human Subjects training). Drs. Stein and Abrantes will provide training to and supervise research assistants. Research assistants will also have training in Good Clinical Practice.

Drs. Stein and Abrantes will be responsible for quality control of this study. They will review recruitment and retention reports, and AE reports on a weekly basis. The MPIs (or their designee) will inspect BL documents (consent forms, release of information) for completeness within a week after they are signed. The MPIs (or their designee) will also conduct protocol and data quality monitoring twice a year using a checklist. This monitoring will include reviewing other study records to ensure completeness.

6. Regulatory Issues

6.a, 6.c Reporting of SAEs

Drs. Stein and Abrantes will be responsible for overseeing the daily safety of all participants. There are several ways in which they will become aware of adverse events. First, research staff will ask participants about serious adverse events (as defined by Office of Human Research Protections (OHRP); e.g., inpatient hospitalization) at each assessment. CODAC and SSTAR have licensed providers who have experience in managing psychiatric emergencies and are available during all research unit hours; the site has a standard crisis protocol in place for treatment referral. All research procedures will be supervised by Drs. Stein and Abrantes who will be on call 24-hours a day. Second, all study staff will be trained in the OHRP definitions of adverse events that are also unanticipated problems; serious adverse events; or unanticipated problems that are not adverse events. All study staff are required to report any event that might meet one of these criteria to one of the PIs immediately, both verbally and in writing. When necessary, a report of a serious adverse event will result in one of the PIs contacting the participant to further assess the event.

Drs. Stein, Abrantes, and Herman, the project manager, will meet weekly with research assistants to review staff experiences with participants. Drs. Stein and Abrantes have each been the Principal Investigator on multiple other NIH-funded smoking studies that included patients with substance use disorders. In addition, both have served on the Data Safety Monitoring Boards of many intervention studies. Therefore, based on the sources of information detailed above, as well as direct patient contact and/or consultation with the scientific team, Drs. Stein and Abrantes will determine if the event is: a) a serious adverse event that is also an unanticipated problem; b) an unanticipated problem that is not an adverse event. The Butler Hospital IRB requires that fatalities related to the study be reported within 24 hours, all other serious adverse events related to the study be reported within 5 business/7 calendar days, and other serious adverse events related to the study be reported at the continuing review (at least annually). The chair of the IRB will then report unanticipated problems and any actions taken to remedy those problems to NIDA and OHRP within one month of the receipt of the report from Drs. Abrantes and Stein.

6.d Reporting of IRB Actions to NIDA

All SAEs will be reported to NIDA within 72 hours of the MPIs becoming aware.

6.e Report of changes of amendments to the protocol

All changes to the protocol must be approved by NIDA prior to implementation.

6.f Trial stopping rules

This study will be stopped prior to its completion if: (1) the intervention is associated with adverse effects that call into question the safety of the intervention; (2) any new information becomes available during the trial that necessitates stopping the trial.

6.g Disclosure of Conflict of Interest

Michael Stein: None
Ana Abrantes: None
Genie Bailey: None
Nikki Nollen: None
Theodore Wagener: None

7. Trial Safety

7.a Potential Risks and Benefits for Participants

Assessments: Before conducting research assessments, participants will be assured of confidentiality and told that they have the right to terminate the interview or to refuse to answer specific questions. Some interview questions may be considered sensitive and may cause emotional distress. It will be critical to make clear to participants that they can terminate the interview at any time for any reason. The interviewer will be trained to be sensitive to signs of participant discomfort and to suggest breaks where it seems appropriate.
Confidentiality: Loss of confidentiality is another possible risk. All information will be referenced to a participant identification number and will be sequestered in locked file cabinets or password protected documents in research offices at Butler Hospital. The participant's ID number can be connected to the participant's name only through a single master file, password-protected, accessible only to senior research staff.

Nicotine withdrawal effects. Participants using the full dose of JUUL or NRT distributed should experience mild to no nicotine withdrawal symptoms. On the other hand, participants who stop using cigarettes during the trial and use few study products are likely to experience nicotine withdrawal symptoms. These symptoms include anxiety, restlessness, irritability, impatience, difficulty concentrating, increased appetite, insomnia, and desire to smoke. These are moderately uncomfortable but have minimal risk of physical harm.

Expected adverse effects of electronic cigarettes. Adverse effects of e-cigs in studies in which e-cigs were distributed over a period of 24-52 weeks in general population smokers were mild. Most frequently reported in smokers without psychiatric comorbidity were: mouth irritation (21%), throat irritation (32%), and dry cough (32%). Other effects reported were: nausea (15%), sore throat (12%), headache (12%), dry mouth (9%), and mouth ulcers (3%). Effects most commonly occurred at the start of use (first 4 weeks) and waned spontaneously over time. Notably, in the sample of smokers with severe mental illness who received e-cigs for 52 weeks, there were no reports of depression, anxiety, insomnia or irritability at any time point (study weeks 4, 8, 12, 24, and 52). E-cigarette or vaping associated lung injuries (EVALI) have not been attributed to JUUL use

alone. The long-term effects of JUUL are unknown, but JUUL is provided for only 6 weeks here. At each weekly visit in the current study, participants indicate (on a checklist) incidence and severity of side effects. Checklists will be reviewed each visit by study personnel and the study physician will be available at all times to answer questions and concerns regarding symptoms.

Expected adverse effects of NRT. The most common side effects of NRT are nausea and dizziness, and irritation inside of mouth with nicotine lozenges, specifically. Much rarer effects include chest pain and heart palpitations. At each weekly check in, we will ask participants about their experience of any of these side effects. If these are experienced with the 4mg lozenge, in consultation with Dr. Stein (MPI and internist), a decision may be made to reduce to the 2mg lozenge or, if necessary, discontinue NRT.

Effects of using too much nicotine. Smoking topography characteristics of e-cigs differ compared to tobacco cigarettes, and the rate of increase in blood nicotine from e-cigs appears to be slower. These smoking characteristics facilitate nicotine titration so we believe it is unlikely that participants will obtain more nicotine from e-cigs than desired. However, participants may increase their daily nicotine intake if they continue to smoke tobacco cigarettes at their baseline rate while using JUUL or NRT. Based on our experience with participants who smoke while receiving nicotine replacement therapy (e.g., nicotine patch), participants who smoke cigarettes while using e-cigs may report increased heart rate (without associated symptoms), mild anxiety, mild difficulty sleeping, and mild nausea. We will warn participants of these potential symptoms during the informed consent process and as needed in study assessment visits. While medical effects of smoking while also using e-cigs have not been studied, continuing to smoke cigarettes while using the nicotine patch is not medically harmful even in patients with coronary artery disease and even when 42 mg NRT was administered.

Benefits

The risks to participants are judged to be acceptable relative to the anticipated benefits. By participating in the clinical research project, participants may benefit from the intervention that they will receive. Participants who replace tobacco cigarettes with e-cigs or NRT may reduce their exposure to inhaled tar and other combustion products, and to toxicants associated with these products. The results will be used to advance the understanding of the health outcomes related to these two products among high-risk smokers. Given this level of risk(s) to the patients and the likelihood that some will benefit from the additional treatment (or from the additional assessment contacts) and the even greater possibility of benefits to the larger population of smokers, the risk/benefits ratio seems favorable.

7.b. Collection and reporting of AEs and SAEs

See 6.a

7.c Management of SAEs and other study risks

See 6.a and 7.a.

8. Trial Efficacy

8.a Plans for interim Analysis of efficacy data

There are no plans for interim analysis of efficacy data.

9. DSM Plan Administration

9.a Responsibility for data and safety monitoring

The Data Safety Monitoring Board will be comprised of 2 individuals independent from this research project. No member of the board will be a collaborator with the MPI on any other studies or have co-published with the MPIs in the past 3 years. They will be qualified to review the patient safety data generated by this study. They will review rates of adverse events to determine any changes in participant risk and will make appropriate recommendations for changes in protocol, which will be submitted to the Butler Hospital IRB and NIDA for review.

9.b Frequency of DSM

Study progress and safety will be reviewed by the MPIs monthly (and more frequently if needed). Semi-annually, a progress report will be generated for the DSMB's review. The full DSMB will be convened twice per year to review the semi-annual report and discuss data and participant safety.

9.c. Content of DSM Report

The DSM report will include a brief description of the aim of the trial, baseline and demographic information, recruitment and retention, regulatory issues or data quality issues that have arisen, and AE/SAEs. *The DSM report will be sent to the NIDA Program Officer annually.*

The study team will specifically generate the following for the DSM report:

- Interim CONSORT document (number screened, number consented, reasons not eligible, status of all participants enrolled in the study, number completed the study vs. withdrawn)
- Actual vs. expected enrollment numbers
- Gender, age, race, and ethnicity of enrolled participants
- List and description of deaths, unanticipated problems, and SAEs
- Summary table of AEs
- List of protocol deviations, if any
- Ongoing quality assurance and quality control procedures and findings.

The DSMB will determine whether 1) AE rates are with pre-study assumptions, 2) whether continuation of the study is justified, and 3) conditions under which the study would be prematurely terminated.

10. DSM Board Plan

10.a Members and Affiliation

1. Alayna Tackett, Ph.D. – Assistant Professor of Preventive Medicine, University of Southern California, Keck School of Medicine, USC Institute for Addiction Science
2. David Strong, Ph.D. – Professor, Herbert Wertheim School of Public Health and Human Longevity Science, University of California, San Diego

10.b Frequency of Meetings

See 9.b

10.c Conflict of Interest

None.

10.d. Protection of Confidentiality

Only de-identified data will be presented in DSMB reports.

10.e Monitoring Activities

See 9.a

10.f Communication plan to IRB, NIDA, and FDA

DSMB reports will be submitted to both the Butler Hospital IRB and NIDA.