Assisting Smokers to Switch to a JUUL E-Cigarette by Devaluing Combustible Cigarettes

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Clinical Study Protocol

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LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
BMI	Body Mass Index
BUN	Blood urea nitrogen
CC	Combustible cigarette
CFR	Code of Federal Regulations
CO	Carbon monoxide
CRF	Case report form
CRM	Customer relationship management
ECG	Electrocardiogram
FDA	Food and Drug Administration
FTND	Fagerström Test for Nicotine Dependence
GCP	Good Clinical Practice
HCG	Human chorionic gonadotropin
HTTPS	Hyper Text Transfer Protocol Secure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
mCEQ	modified Cigarette Evaluation Questionnaire
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
mg	Milligram
mL	Milliliter
NRT	Nicotine Replacement Therapy

PHQ-9	The Patient Health Questionnaire
ppm	Parts per million
RBC	Red blood cell (count)
RRC	Rose Research Center, LLC.
SAE	Serious adverse event
SMS	Short Message Service
SREC	Standardized Research E-Cigarette
SOP	Standard operating procedure
SQ	Sensory Questionnaire
SSL	Secure Sockets Layer
TLS	Transport Layer Security
WBC	White blood cell (count)
WHO	World Health Organization

1 INTRODUCTION

1.1 BACKGROUND

The burden of disease and death attributable to combustible cigarette (CC) smoking is enormous, with an estimated 540,000 premature deaths annually in the United States [1]. Considerable progress has been made toward reducing the prevalence of smoking, through education about the harms of smoking, increased taxation/regulation and the greater availability of cessation treatments. However, despite a gradual reduction in smoking prevalence over the years, in 2015, 15% of the adult U.S. population, or 35 million individuals, continued to smoke [2].

The 2010 U.S. Surgeon General's Report [3] implicated combustion products, rather than nicotine, in contributing to the major smoking-related diseases. Therefore, e-cigarettes may reduce health risks to the user by avoiding combustion. Instead, they heat a solution (usually a mixture of propylene glycol and glycerol) that also contains nicotine and flavorings, in order to generate an aerosol at much lower temperatures than burning cigarettes [4]. Measures of constituents in e-cigarette aerosol show substantial reductions in most toxicants, including carbon monoxide, carcinogens (including tobacco-specific nitrosamines and polycyclic aromatic hydrocarbons), and volatile organic compounds such as acrolein, acrylamide, acrylonitrile, 1,3-butadiene and ethylene oxide [5, 6]. This reduction in toxicant yield could potentially translate into a marked reduction in risk to the smoker.

Previous studies have shown that smokers who are offered e-cigarettes as an alternative to combustible cigarettes (CCs) show substantial reductions in CC use. Nides et al. [7], for example, showed that there was a 39% average reduction in the number of cigarettes smoked daily when smokers were offered a nicotine-containing e-cigarette. A Cochrane Collaboration Review [8] summarized evidence that nicotine-containing e-cigarettes were significantly more effective than placebo in producing substantial reductions (at least 50%) in smoking; in two studies that were reviewed, 36% of smokers reduced their CC use by at least half compared to 27% with placebo (Relative risk of 1.31, 95% CI 1.02 to 1.68). Moreover, in an additional study, nicotine-containing e-cigarettes were also more effective than nicotine skin patches in reducing CC use: 61% of smokers reduced their CC use by at least half with e-cigarettes versus 44% with nicotine patch (relative risk of 1.41, 95% CI 1.20 to 1.67). Although these findings are encouraging in showing promise of e-cigarettes, they also indicate that a high percentage of smokers in these studies continued to use CC after the introduction of e-cigarettes. Population-based surveys also suggest that there is a high rate of failure to completely convert from CC to e-cigarettes. For example, the U.S. National Health Interview Survey of 2014 [9] found that, while 12.6% of adults (>90% of whom were current or former smokers) had ever tried an e-cigarette, only about 3.7% currently used e-cigarettes every day or some days. Similarly, a cross-sectional survey of 28-member states of the European Union also found that only about 9% of ever e-cigarettes users were current daily users. Although cross-sectional data cannot provide definitive conclusions about longitudinal trajectories of product use, these data suggest that the majority of smokers who try e-cigarettes do not adopt them exclusively to replace combustible cigarettes. Additionally, a recent population study found no significant reductions in toxicant exposure among dual users of combustible cigarettes and e-cigarettes, but extensive reductions of most toxicant levels were observed in exclusive e-cigarette users [9].

Therefore, much progress needs to be made in helping CC smokers make a complete transition to e-cigarettes, in order to realize the full potential of e-cigarettes as a harm reduction strategy.

To evaluate the cigarette devaluation strategy, we conducted a pilot study with six smokers, who participated in a laboratory session as well as a one-week home evaluation. Subjects (two Caucasians, three African Americans, and one "other") included one male and five females, all of them menthol smokers, with a mean age of 42 (SD=11.1), and an average baseline cigarette consumption of 9.3 (SD=2.3) cigarettes/day. Subjects had a mean FTND score of 4.7 (SD=2.3), indicating a moderate level of dependence. The e-cigarette studied was the MarkTen® brand, with 32 mg of nicotine per 800 mg of e-liquid in each cartridge.

In the laboratory session, craving for cigarettes was substantially alleviated by the use of the e-cigarette **(Figure 1)**. These data are particularly impressive given that the subject sample consisted of menthol smokers and the e-cigarette used was non-menthol.

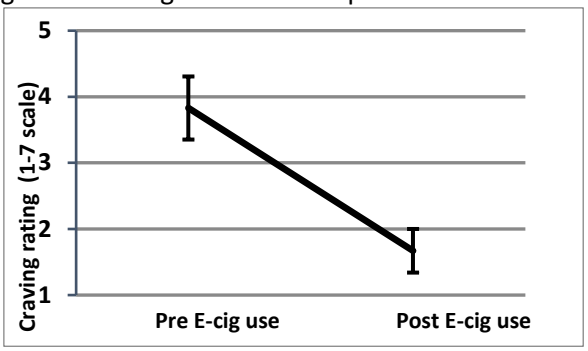

Figure 1 – Craving for cigarettes

Craving for cigarettes before and after ten puffs from an E-cigarette.

Participants also rated the rewarding effects of smoking their usual brand of cigarette, either preceded by use of an e-cigarette or after 60 minute deprivation. The results, depicted below in **Figure 2**, show that the reported satisfaction ratings were significantly attenuated when the usual brand cigarette was smoked immediately after the e-cigarette.

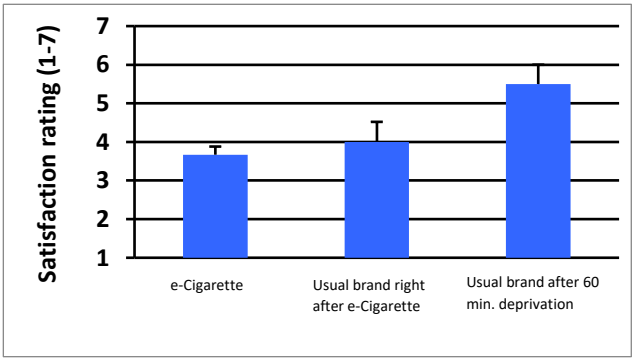

Figure 2 - Satisfaction Ratings

Satisfaction ratings of the e-cigarette and usual brand of cigarette, either preceded by e-cigarette use or after 60 min deprivation.

Moreover, the results in **Figure 2** show that the satisfaction from smoking the usual brand was reduced to a point comparable to that of the e-cigarette. This result, after a single experience, supports the hypothesis that over the course of days, the cigarette devaluation procedure will level the playing field to allow subjects to more completely switch from CC to an e-cigarette. Indeed, data collected during the subsequent seven days were quite promising and are summarized below in **Figure 3**. In this home evaluation, self-reported compliance with the pairing instruction (in the absence of coercion or financial incentives) was excellent. Participants reported using the e-cigarette immediately prior to CC over 95% of the time.

Satisfaction ratings showed a trend over time in the predicted direction. It is particularly striking that, although subjects rated their usual brands of cigarettes more satisfying initially, by the end of the seven

days there was a trend for the e-cigarette to be rated more satisfying. These results provide support for the feasibility of the cigarette devaluation procedure and suggest that this procedure will have marked effects on the rewarding value of CC and the JUUL.

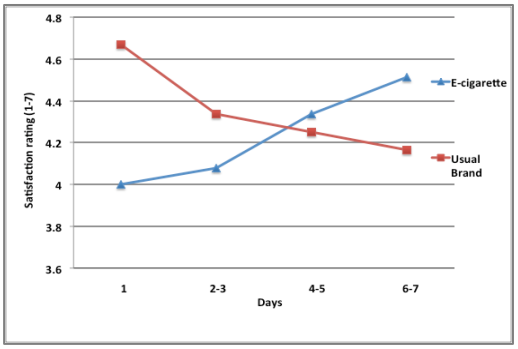

Figure 3 – Satisfaction Ratings

Satisfaction ratings over one week of cigarette devaluation.

1.2 Purpose of the Study

This study will evaluate the effects of a reward devaluation strategy on switching from CC to JUUL. There is no therapeutic intent in that smokers' nicotine/tobacco dependence will not be treated; the goal is to switch from one form of nicotine/tobacco dependence (CC) to dependence on a different tobacco product (JUUL e-cigarettes). Subjects will not be encouraged to terminate their use of e-cigarettes If they switch completely to use of JUUL. The switching strategy being evaluated is one in which smokers use the JUUL e-cigarette immediately before any combustible cigarettes (CCs) are smoked. This procedure is predicted to accomplish three goals: 1) the rewarding effects of CC will be disrupted because subjects will already have attained fairly high peak nicotine concentrations immediately before smoking the cigarette. This reduces the rewarding effect of smoking, in part from receptor desensitization that occurs following nicotine exposure, which reduces the response to a subsequent dose of nicotine, and in part from satiating the drive to smoke; 2) the use of the JUUL will become associated with the same cues that elicit smoking, thereby promoting the substitution of JUUL use for CC use; and 3) ad libitum nicotine intake from the JUUL and its rewarding effects will be maximized because, unlike CC, they will be experienced after a period of nicotine deprivation. Thus, despite a lower per-puff nicotine dose relative to CC, the pharmacologic impact and reinforcing effect will be maximized. The study will evaluate two flavors (Menthol and Virginia Tobacco), randomly assigned, to determine if flavor assignment (similar to the subjects' usual brand of CC or different than the subjects usual brand CC) has an effect on the success of this reconditioning procedure.

1.3 Study Design

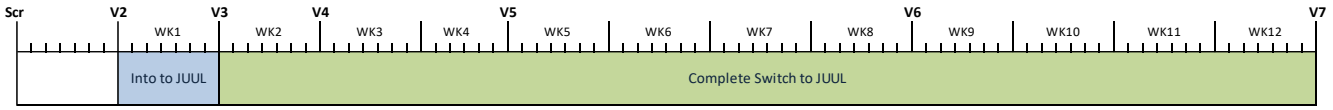

Figure 4 - Timeline

2 Study Objectives and Endpoints

2.1 Switching from CC to the JUUL

We will assess the effects of devaluation on switching from CCs to the JUUL, assessed by self-reported consumption of both products, and expired air carbon monoxide levels (CO).

2.2 Measurement of Smoking Reward

Smoking reward will be measured using the modified Cigarette Evaluation Questionnaire (mCEQ). Changes in rewarding effects over the first week will be correlated with e-cigarette use and subsequent reductions in CC smoking over the full 12-week study period.

3 Investigational Plan

3.1 Overall Study Design and Plan

This small-scale, open-label study (N= 50) will evaluate a reward devaluation strategy in which smokers use the JUUL e-cigarette immediately before any combustible cigarettes. The outcome of this strategy will be compared to the following benchmarks. Results will fall into one of the following two categories:

3.1.1 Complete switching rate of 48%

If this reconditioning procedure achieves at least a 40% (20/50 or 10/25 for matched or unmatched flavor) switching rate tested at visit 7, it will be viewed as having considerable promise, and will be advanced to larger-scale (~N=200) randomized controlled clinical trials (RCTs) to provide a rigorous evaluation of its efficacy and effectiveness. These trials may include both double-blind efficacy trials and unblinded, pragmatic, real-world effectiveness trials. Future trials will be submitted to the Institutional Review Board (IRB) as new protocols.

3.1.2 Switching Thresholds Not Achieved

If the above switching rate threshold is not met, the reward devaluation procedure will be considered unpromising, and additional studies will not be run.

3.2 Reconditioning Instructions

The JUUL will be dispensed, and subjects will be instructed to use the JUUL as often as they like. They will also be instructed to use JUUL immediately before each CC to relieve their craving as much as possible before smoking their usual brand. The JUUL will also be the first product that they are instructed to use each morning. Smokers will be told to try to completely substitute JUUL for CCs by the end of the first week of use. Subjects will be questioned by study staff to ensure that they understand these instructions.

3.3 General Study Procedures

During the product use period, daily text messaging will be used to assess JUUL and CC use, as well as to obtain a brief assessment of associated subjective rewarding effects (appendix 13). Self-reported compliance with the instruction to pair each CC with JUUL use will be assessed. At each session, expired air CO will be measured along with blood pressure, heart rate, respiratory rate and body weight. Participants will also complete questionnaires rating subjective effects of smoking and JUUL use. Subjects will be given enough JUUL e-cigarette pods to last until their next scheduled session, along with an extra 4 days' worth to allow for flexibility in case sessions need to be rescheduled. JUUL usage will be tracked not only by self-reported number of occasions used, but also by pod counts (empty and full) and determination of residual levels of partially used pods.

3.4 Study and Session Durations

The total duration for a subject will be approximately 12-13 weeks. This will allow for a grace period for scheduling the first study session and completing the 12-week product use period.

The Screening Session will last approximately two hours and the Laboratory Sessions (V2 – V7) will each last approximately one hour.

4 Study Population

4.1 Selection of Study Population

4.1.1 Inclusion Criteria

Each subject must meet all of the following inclusion criteria before enrollment at V2:

Inclusion Criteria
1. Has signed the ICF and is able to understand the information provided in the ICF.
2. Is 21 to 65 years of age (inclusive) at screening.
3. Smokes ≥ 10 commercially available CCs per day (no brand restrictions), for the last 12 months.
4. Expired air CO reading of at least 10 ppm as assessed at the screening session.
5. Interested in switching to an electronic cigarette.
6. Willing and able to comply with the requirements of the study.
7. Owns a smart phone with text message and data capabilities compatible with necessary surveys.

4.1.2 Exclusion Criteria

Potential subjects who show or report indications of or self-report a diagnosis of conditions listed below may be excluded from the study. If the study physician determines, through the course of pre-screening, a physical exam, medical history, current medications, ECG, or laboratory finding(s), that an individual has one of the conditions listed below or reveals other information that may jeopardize the subjects' safe study participation, then they may be excluded. For medical conditions that do not appear below, the subject may be enrolled if the study physician does not feel that the medical condition would jeopardize data validity or safe study participation.

Exclusion Criteria
1. Is unhealthy or cannot participate in the study for any reason (e.g., medical, psychiatric, and/or social reason) as judged by the Investigator or designated medical staff based on all available assessments from the screening period (*e.g.*, safety laboratory, vital signs, physical examination, ECG, concomitant medications and medical history).
2. PHQ-9 score greater than 9, or a score greater than 0 on item #9 ("Thoughts that you would be better off dead, or of hurting yourself in some way") at screening.

Exclusion Criteria
3. Planned use of an FDA-approved smoking cessation product during the study.
4. High Blood Pressure (systolic >150 mm Hg, diastolic >95 mm Hg) at screening.
5. Body mass index (BMI) less than 15.0 kg/m2 or greater than 40.0 kg/m2.
6. Coronary heart disease, structural cardiac disease (including, but not limited to valvular heart disease or cardiac murmurs), cardiac dysrhythmias, syncope, cardiac chest pain, or history of heart attack or heart failure.
7. Has received psychotherapy or behavioral treatments within 30 days of screening, or during the study.
8. Taking antidepressants or psychoactive medications (e.g. antipsychotics, benzodiazepines, hypnotics).
9. Use of any of these products in the past 30 days: a. Illegal drugs (or if the urine drug screen is positive for cocaine, THC, amphetamines, methamphetamines, or opiates); b. Experimental (investigational) drugs that are unknown to subject; c. Chronic opiate use.
10. Use of smokeless tobacco (chewing tobacco, snuff), cigars (except for "Black & Mild" cigars or Cigarillos), pipes, hookah, e-cigarettes, nicotine replacement therapy or other smoking cessation treatments within 14 days of screening.
11. Pregnant or nursing (by self-report) or positive pregnancy test.
12. Subject enrollment numbers met.

4.1.3 Women of Childbearing Potential

Pregnant or breastfeeding women will be excluded from the study. All females will undergo a serum pregnancy test at screening and a urine pregnancy test at every visit. Heterosexually active females of childbearing potential (not post-menopausal) must agree to use medically acceptable contraceptives during the course of the trial. Medically acceptable contraceptives include: (1) surgical sterilization (such as a tubal ligation, hysterectomy, or Essure), (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Contraceptive measures such as Plan B™, sold for emergency use after unprotected sex, are not acceptable methods for this study. Female participants will be encouraged in the consent form to notify study staff if they believe a change in their pregnancy status has occurred during the trial.

Post-menopause is defined as the time after which a woman has experienced 12 consecutive months of amenorrhea (lack of menstruation).

4.2 Recruitment Strategies

Subjects will be selected through an IRB approved generic recruitment advertisements which are designed to recruit subjects into the volunteer database for future smoking and tobacco related research at the Rose Research Center. For this database, many of the subjects have provided basic smoking history data, along with demographic information, which will allow for screening and selection of potentially interested subjects.

Subjects who call in will be screened into the volunteer database, and if they pre-qualify, will be offered the option to prescreen for this protocol.

Subjects will be contacted only with IRB approved appropriate materials and information, submitted along with this protocol. These documents will include a brief description of the study and information on how to prescreen for participation. Subjects will be contacted by phone, email and/or text messages which prompt interested subjects to prescreen through an electronic screen form.

4.2.1 Pre-Screening

Pre-screening will be completed prior to the screening visit (V1) for all subjects. Participants will be provided with a set of IRB approved questions directly related to the inclusion and exclusion criteria. Based upon the outcome of these questions, potential participants may be scheduled for a screening visit (V1).

4.3 Subject Retention in the Study

All candidates who schedule a screening visit (V1) will receive a series of email, text, and/or telephone reminders; candidates are also permitted, through these communications, to confirm, cancel, or reschedule their appointments.

4.4 Discontinuation of Subjects from Study

Discontinued subjects will include both subjects who withdraw from the study (subject's decision) and subjects who are discontinued from the study (following Investigator's decision). A subject can only be discontinued from the study after randomization at visit 2. Subjects that are not randomized are considered screen failures.

Subjects will be informed that they are free to withdraw from the study at any time. Subjects should be questioned for the reason for withdrawal from the study, although they are not obliged to disclose this information.

Subjects discontinued from the study cannot re-enter the study.

4.4.1 Subjects will be discontinued from the study for any of the following reasons:

- Withdrawal of informed consent.
- Any adverse effect or condition that would jeopardize continued safe study participation.
- Pregnancy test is positive (for female subjects).
- Discontinuation is considered to be in the best interest of the subject, or for other subjects participating in the study, as judged by the Investigator.

4.4.2 Subjects may be discontinued from the study for any of the following reasons on the judgment of the Investigator:

- No-show to appointments and unable to reschedule within the visit window.
- The misuse or abuse of study related equipment.
- Noncompliance to study procedures.

4.5 Lost to Follow-up

For subjects lost to follow-up, a reasonable number of attempts to contact the subject (including written correspondence and/or phone calls) will be made and documented in the source documents. The date of the last contact (e.g. last visit, last phone call) will be recorded in the source document. When the PI(s) or designee(s) declare(s) a subject is lost to follow-up, the lost to follow-up date will be recorded and will correspond to the date of the end of study (EOS) of the subject.

4.6 Violation of Inclusion/Exclusion Criteria

Subjects who, after signing the ICF, do not meet the inclusion and exclusion criteria will not be enrolled in the study and will be considered screen failures. Re-screening for the study is not permitted.

4.7 Subject Compensation

There will be a payment of $25 for the Screening Session (V1) and $75 at the completion of each study session V2 through V7. Subjects will also receive an additional payment of $5/day for responding to daily text messages during the 12-week product use period.

If subjects are asked by study staff to return to the center to complete or redo parts of the screening in situations of equipment malfunctions or other circumstances that are beyond the subjects' control, subjects may be reimbursed for mileage.

Subjects who decide to withdraw from the study will be paid for the part of the study they have completed.

4.8 Session and Response Windows

4.8.1 V2 Session Window

Participants may attend V2 up to 30 days post Screening Session (V1).

4.8.2 All other visit Windows

Participants may attend sessions up to four-calendar day's pre or post the scheduled visit.

4.8.3 SMS Response Window

The SMS response window will be open until the next SMS message is sent.

5 JUUL E-CIGARETTE DEVICE AND PODS

5.1 DESCRIPTION OF JUUL

The JUUL is a breath-actuated, rechargeable closed e-cigarette system. Each JUUL pod is pre-filled with 0.7 mL of e-liquid. The e-liquid ingredients include: glycerol, propylene glycol, flavor, nicotine (5% by weight), and benzoic acid.

5.2 DESCRIPTION OF JUUL PODS

Each JUUL Pod contains 0.7mL with 5% nicotine by weight, approximately equivalent to one pack of cigarettes or 200 puffs. Multiple flavors are available, but this study will focus on "Virginia Tobacco" and "Menthol" flavored pods, with subjects randomly assigned to one of these flavors (see Section 1.3 regarding randomization scheme). At Visit 2, subjects will be allowed to use the two different flavors *ad libitum*, presented in counterbalanced order (randomly assigned), with a 10-minute period between each trial use. Research staff will inquire whether the subjects are willing and able to use the JUUL (either flavor) during the study, to determine eligibility, and prior to randomization of flavor assignment.

Subjects will be provided with enough pods of their assigned flavor to use during the study (150% of reported usage, with each pod approximately equivalent to one pack of cigarettes). JUUL Pods are sealed system cartridges for use in the JUUL e-cigarette. Each pod is contained in tamper resistant blister packs of four pods.

5.3 PRODUCT USE TIMEFRAME

The maximum amount of time the JUUL will be in use will be for twelve weeks, plus up to an additional four days (to allow for the scheduling window). Subjects will be instructed on how to use the JUUL e-cigarette prior to dispensing.

5.4 ACCOUNTABILITY AND COMPLIANCE

5.4.1 Dispensing Product

The JUUL will be dispensed by the Investigator or designated study staff, as per study design. Subjects will be dispensed pods initially at 150% based on their daily smoking habits as reported at baseline (one pod per pack of cigarettes smoked per day). Subjects may come into the office between visits to get additional supplies if needed. Each dispensation and collection of the product will be recorded.

5.4.2 Storage and Accountability

All JUUL products will be stored in a locked, limited-access area at the study site and kept at a controlled room temperature (defined as 20 - 25°C [68 - 77°F], with excursions permitted to 15 - 30°C [59 - 86°F]). JUUL products should not be exposed to extreme heat or cold.

5.4.3 Compliance

Compliance will be ensured by strict distribution of the product and collection of devices (used and unused) which will be documented in appropriate logs.

6 STUDY PROCEDURES AND ACTIVITIES

Personnel performing study assessments must have appropriate and documented training. An overview of all study assessments is shown in the schedule of events (Section 7.7). Study personnel will adhere to standard operating procedures (SOPs) for all activities. Appropriate medical advice will be provided by qualified staff (licensed providers) to the subject in case of any medical findings requiring health care.

6.1 INFORMED CONSENT AND GUIDANCE

Prior to any study assessments being performed, the subject will be asked to provide their written consent to participate in the study on an informed consent form (ICF). All assessments must start after the time of ICF signature by the subject for study participation.

Designated staff, under the supervision of the Principal Investigator, will obtain informed consent from each participant. The person obtaining consent provides the participants with a printed document that explains the procedures and risks. Designated staff will answer any questions. A signed copy of the informed consent form will be given to each participant. Participants are informed that they may withdraw from participation in the study at any time without penalty.

Because of the nature of this study and the number of questionnaires that subjects are expected to complete, we do not recruit potential subjects who do not read, are blind, or who do not read/understand English. We are not equipped to validate alternate versions of our questionnaires, most of which are not published. Questionnaires cannot be administered orally by a translator or by technicians to illiterate or blind subjects because the data obtained would not be comparable to self-administered questionnaires.

6.2 SAFETY LABORATORY AND OTHER ASSESSMENTS

An overview of all assessments is provided in the schedule of events (Section 6.4).

Non-fasting blood samples and urine samples will be collected by qualified and trained site personnel. Subjects should be in a seated position during blood collection.

The maximal total volume of blood drawn for each subject will be around 30 mL for clinical chemistry, hematology, and serum pregnancy (for females).

Samples for clinical chemistry, hematology, and serum pregnancy test will be sent to LabCorp for analysis. Urinalysis will also be performed by LabCorp.

The results of the clinical chemistry, hematology and urine analysis safety panel will not routinely be given to subjects to send or be sent to their physician to include in their medical record. However, if the subject's laboratory results are clinically relevant (including positive pregnancy tests), the research medical staff will send the subject a copy of the laboratory results. Subjects who are accepted into the study but need medical follow-up due to minor abnormalities in laboratory results (at any session) will also receive a copy of the laboratory results.

6.2.1 Safety Laboratory

Safety laboratory includes clinical chemistry, hematology, and urinalysis and will be assessed at Visit 1.

6.2.1.1 Clinical Chemistry

Clinical Chemistry	
Sodium	Chloride
Potassium	Carbon dioxide
Blood urea nitrogen (BUN)	Creatinine
Glucose	Calcium
Total protein	Albumin
Bilirubin	Alkaline phosphatase (AP)
Aspartate aminotransferase (AST)	Alanine aminotransferase (ALT)

6.2.1.2 Hematology

Hematology	
Red blood cell (RBC) count	WBC count
Hemoglobin	Differential white blood cell (WBC) count
Hematocrit	Platelet count
Mean corpuscular volume (MCV)	Mean corpuscular hemoglobin concentration (MCHC)
Mean corpuscular hemoglobin (MCH)	

6.2.2 Urine Samples

Urine samples will be collected for the urine drug screen (at screening session), urine pregnancy test (at all sessions except screening), and safety urinalysis (at screening session). The urine drug screen and pregnancy tests will be performed by study personnel at the study site. The urine sample collected for urinalysis will be sent to LabCorp for testing.

In case of any positive pregnancy test, the Investigator or designee will inform the participant about the risks associated with smoking during pregnancy.

In the event of a positive urine drug test for cocaine, THC, opiates, amphetamines, or methamphetamines at the screening visit (V1), subjects are notified that they have been excluded from study participation because of a positive drug test.

Urinalysis
pH
Red blood cell traces
Bilirubin
Protein
Glucose
Specific gravity
Nitrite
WBC Esterase

Table 1 - Urinalysis Assessments

Drug Screening
Amphetamine
Cocaine
THC
Methamphetamine

Opiates

Table 2 - Drug Screening

6.2.3 Serum Pregnancy Test

Serum pregnancy test will be performed during the screening visit for all females.

Serum Pregnancy Test
Quantitative human chorionic gonadotropin (HCG) test

6.2.4 Urine Pregnancy Test

The urine pregnancy test will be performed by study personnel on site for all females at each visit (except screening).

6.2.5 Electrocardiogram (ECG)

ECG recording will be performed as per the site's standard operating procedures. A standard 12-lead ECG will be recorded after the subject has rested for at least 5 minutes in a supine position.

The following parameters will be documented: heart rate, PR interval, QRS interval, QT interval, and QTc interval. Every ECG has to be assessed as normal, abnormal – not clinically significant, or abnormal – clinically significant.

ECG print-outs will be interpreted by a qualified physician or licensed medical provider. Any print-outs of ECGs on thermo-sensitive paper must be photocopied and stapled together for inclusion in the source documents and signed by the Investigator or designee.

6.2.6 Vital Signs

Vital signs (systolic and diastolic blood pressure, pulse rate, temperature and respiratory rate), will be measured in sitting position after the subject has rested for at least 5 minutes. After two minutes of standing, a second blood pressure reading (systolic and diastolic) and pulse rate will be obtained at the screening visit (V1).

6.2.7 Physical Examination

A complete physical examination, including auscultation and palpation will be performed. A complete physical examination will include review of general appearance, hair and skin, head, eyes, ears, nose and throat, neck, chest, abdomen, dentition, cardiovascular, musculoskeletal and neurological systems. The physical examination is to be conducted by a designated fully trained representative.

Appropriate medical recommendations will be provided to the subject if any medical findings requiring health care are identified.

6.2.8 AE/SAE Reporting

Any adverse events (such as cough, sore throat, nausea) since the last session or during the laboratory sessions will be assessed. AEs/SAEs will be assessed using face-to-face interviews at the indicated time points, and spontaneous reporting from the time of ICF signature until the EOS for the subject.

6.2.9 Questionnaires

The questionnaires will be administered to the subjects using paper questionnaires and/or an electronic data collection system. The results of questionnaires will be transcribed into the Case Report Form (CRF) as needed.

6.2.9.1 mCEQ – The modified Cigarette Evaluation Questionnaire

The Cigarette Evaluation Questionnaire was initially developed in the PI's laboratory and used in numerous studies to assess the effects of pharmacological treatments on the rewarding effects of cigarette smoking. The mCEQ (Appendix 8) is a widely used and validated questionnaire that will be used to assess the degree to which subjects experience the reinforcing of smoking, providing five subscale scores: smoking satisfaction (satisfying, tastes good, enjoy smoking), psychological rewards (calms down, more awake, less irritable, helps concentrate, reduces hunger), aversion (dizziness, nauseated), enjoyment of respiratory tract sensations (single-item assessment), craving reduction (single-item assessment). Subjects will be asked to assess the 12 items of the questionnaire on a 7-point scale, ranging from “not at all” to “extremely”.

6.2.9.2 Smoking History Questionnaire

The Smoking History (Appendix 7) is a questionnaire designed to help assess the subject’s current and past smoking habits. This questionnaire will be used to check eligibility criteria.

6.2.9.3 Registration Form

The Registration form (Appendix 3) is an internal questionnaire designed to collect demographic information about subjects.

6.2.9.4 FTND -- The Fagerström Test for Nicotine Dependence

The Fagerström Test for Nicotine Dependence (Appendix 11) is a six-item questionnaire developed by Karl-Olov Fagerström and is used to determine an individual’s level of nicotine dependence. The scores obtained on the test allow the classification of nicotine dependence in three different levels: mild (0-3 points), moderate (4-6 points), and severe (7-10 points).

6.2.9.5 PHQ-9 -- The Patient Health Questionnaire

The PHQ-9 (Appendix 2) is used to screen for depression and is used to help determine eligibility.

6.2.9.6 Reasons to Smoke

The Reasons to Smoke questionnaire (Appendix 12) is used to determine the most important reasons to smoke for each subject.

6.2.9.7 ABOUT – Assessment of Behavioral Outcomes

The ABOUT questionnaire (Appendix 9) is a self-report instrument that measures dependence in a directly comparable way across different tobacco- and nicotine-containing products.

6.2.9.8 Employment History

The Employment History (Appendix 10) is an internal questionnaire designed to collect information about a subjects’ social economic status.

6.2.10 Expired Air CO Breath Test

Subjects will exhale into the Vitalograph CO monitor for determination of CO breath levels. This will be performed at each visit.

6.2.11 Medical History and Concomitant Disease

Relevant medical history and concomitant disease will be documented at the screening visit (V1). Medical history is defined as any condition that started and ended prior to screening. A concomitant

disease is defined as any condition that started prior to screening and is still ongoing at V1 (this may also include findings detected during the screening visit (V1)).

6.2.12 Prior and Concomitant Medication

All medication taken 30 days prior to the screening visit (V1) and during the study will be documented. Medications which are stopped before the screening visit (V1) will be considered as prior medication. Medications which are started prior to the screening visit (V1) and which are still being taken by the subject during the study, as well as medications that are initiated after the screening visit (V1) will be considered as concomitant medications. This applies to both prescription and over-the-counter products (e.g., vitamins).

Records of prior and concomitant medications taken include the drug name (preferably both generic and trade name), route of administration, dose/unit, frequency of use, indication, the start and, if applicable, the stop date. Any therapy changes (including changes of regimen) during the study have to be documented.

6.2.13 Demographics

Sex, date of birth, race and ethnicity will be recorded for each subject.

6.2.14 Body Height and Body Weight

Body weight will be measured at each visit. Height and weight will be measured at screening, and body mass index (BMI) will be calculated.

6.3 JUUL Product Use Period

During the 12-week product use period, daily text messaging will be used to assess JUUL and CC use, as well as to obtain a brief assessment of the associated subjective rewarding effects and craving. Self-reported compliance with the protocol (instruction to pair each CC with JUUL use) will also be assessed.

6.4 6-Month Follow-Up

Participants who complete the study, will be contacted six months after the complete switch day utilizing an automated SMS messaging system, to ascertain their current smoking status and use of e-cigarettes.

6.5 SCHEDULE OF EVENTS

Visit Assessments and Procedures		Screening Session	Laboratory Sessions						Product Use Period 12 Weeks
		V1	V2	V3	V4	V5	V6	V7	PM SMS
Informed Consent and Guidance		•							
Inclusion/Exclusion Criteria		•							
Enrollment/Randomization			•						
Prior and Concomitant Medication		•	•	•	•	•	•	•	
Questionnaires	Smoking History Questionnaire	•							
	Registration Form	•							
	Employment History		•						
	Medical History/Review of Systems	•							
	Payment Verification Form	•	•	•	•	•	•	•	
	Reasons to Smoke		•						
	Modified Cigarette Evaluation Questionnaire (mCEQ)		•	•	•	•	•	•	
	The Fagerström Test for Nicotine Dependence (FTND)		•	•				•	
	Assessment of Behavioral OUTcomes (ABOUT)		•	•				•	
	Patient Health Questionnaire (PHQ-9)	•							
	Craving Assessment Question (via daily SMS text)								•
	Satisfaction Assessment Question (via daily SMS text)								•
	e-Cigarette Usage (via daily SMS text)								•
	Smoking Status (via daily SMS text)								•
Safety Laboratories		•							
Serum Pregnancy Test (Females)		•							
Urine Pregnancy Test (Females)			•	•	•	•	•	•	
Urine Drug Screen		•							
CO Breath Test		•	•	•	•	•	•	•	
ECG		•							
Vitals	Blood Pressure	•	•	•	•	•	•	•	
	Heart rate	•	•	•	•	•	•	•	
	Temperature	•							
	Respiratory rate	•	•	•	•	•	•	•	
	Weight	•	•	•	•	•	•	•	
Height		•							
Physical Examination		•	•#	•#	•#	•#	•#	•#	
JUUL Flavor Assessment and Questionnaire			•						
Reconditioning Instruction			•						
Collect Used/Unused JUUL Pods				•	•	•	•	•	
Dispense JUUL Pods			•	•	•	•	•		

#Targeted examination as needed

Figure 5 - Schedule of Events

7 RISK / BENEFIT INFORMATION

7.1 POTENTIAL RISKS

Continuing to smoke carries significant health risks; however, the participants in the studies will have expressed no intention to quit smoking within the brief study duration, and hence will not be exposed to significant additional risks.

7.1.1 Use of JUUL

The common risks associated with e-cigarette use include coughing, dry mouth, throat irritation, sore throat and shortness-of-breath.

7.1.2 Nicotine Toxicity

The e-cigarette may deliver less of various tobacco smoke constituents than participants' usual brands of cigarettes, and in some cases, may deliver more nicotine. However, participants control their nicotine intake and many studies have shown that smokers effectively limit their nicotine intake from cigarettes to avoid symptoms of nicotine toxicity (e.g., nausea, vomiting, sweating, headache, dizziness, jittery, palpitations, or in the case of extreme cases of nicotine overdose, convulsions, respiratory paralysis and death).

7.1.3 Tobacco Withdrawal

To the extent that nicotine or other tobacco smoke constituent intake is reduced or eliminated, participants may experience tobacco withdrawal symptoms, including craving, difficulty concentrating, mood disturbance and increased appetite/weight gain.

7.1.4 Blood Draw

The risks associated with venipuncture are minimal and include momentary discomfort and/or bruising. Infection, bruising, excess bleeding, clotting, and fainting are also possible, although unlikely.

7.2 Protection Against Risks

The risks to which participants will be exposed are comparatively minor, because it is unlikely when using the e-cigarette that they will be exposed to higher levels of toxicants than when smoking their cigarettes. Smokers are very experienced in regulating their nicotine intake to avoid excessive amounts [10]. Additionally, participants will be screened medically and monitored throughout the study.

Study participants will receive detailed instructions on the use of the tobacco products distributed to them, in order to minimize the possibility of misuse. JUUL e-cigarette cartridges are sealed systems. Subjects will be instructed to keep all nicotine/tobacco products away from children and pets.

Participants will be instructed to report any side effects to study staff, who will communicate these reports to the medical staff. The most appropriate course of action will be determined, which may include options for termination of exposure to study-related clinical materials (e.g., e-cigarettes). Participants will, however, be reminded that they have the option to withdraw from the study at any time and will be referred to local quit-smoking resources if interested at the end of the study. Subjects will also be given a 24-hour emergency contact number in the event that side effects or adverse events occur between sessions.

8 QUALITY CONTROL AND QUALITY ASSURANCE

8.1 TRAINING OF STAFF

The Investigator or designee will ensure that appropriate training relevant to the study is provided to all staff involved in the study, and that any new information relevant to the performance of this study is forwarded in a timely manner to the staff.

8.2 AUDITS AND INSPECTIONS

Good Clinical Practice regulations require independent inspections of clinical program activities. Such inspections may be performed at any time before, during and/or after the study.

Authorized representatives of regulatory agencies and/or an IRB may perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed and accurately reported according to the protocol, ICH/GCP guidelines and all applicable regulatory requirements.

The Investigator and study staff are responsible for maintaining a comprehensive and accurate filing system of all study-related documentation that will be suitable for inspection at any time by regulatory agencies. By signing this protocol, the Investigator or designee understands and agrees to provide access to the necessary documentation and files.

9 REPORTING OF ADVERSE EVENTS

9.1 DEFINITIONS

9.1.1 Adverse Event

An Adverse Event (AE) is defined as any untoward medical occurrence that may present during participation in the study and which may or may not have a causal relationship with study procedures and/or products tested in this study. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the study procedures and/or products.

Any increase in the severity and/or the frequency of a concomitant disease is considered an AE.

9.1.2 Serious Adverse Event

A Serious Adverse Event is any adverse event that:

- results in death;
- is life-threatening;
- results in inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability / incapacity;
- results in a congenital anomaly / birth defect;

- requires immediate medical or surgical intervention.

Important medical events that may not result in death, be life-threatening, nor require hospitalization may be considered an SAE, when, based on appropriate medical judgment, an SAE may jeopardize the subject, or the subject may require medical or surgical intervention to prevent one of the outcomes listed in the above definitions.

The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Any pre-planned hospitalizations that are known at the time of signing the ICF will not be recorded as an SAE; however, they will be recorded as AE only. Any AE that occurs during this pre-planned hospitalization will be considered according to the above definitions.

9.2 COLLECTION OF SAFETY EVENTS FROM SUBJECTS

Information recorded when collecting AE will include: verbatim description of the AE, seriousness assessment, start and stop dates and times, circumstances leading up to the event, clinical elements such as clinical course, specific vital signs and test results that may explain the pathophysiology of the event, as well as alternative explanations to its occurrence, the action taken with the investigation product due to the AE, the subject`s disposition in the study after the occurrence of the AE, and the final outcome of the AE.

Any exacerbation/worsening or increased frequency of an AE or pre-existing condition shall be evaluated and recorded.

AEs should be collected using face-to-face interviews with the subject.

Whenever a medically meaningful diagnosis is available to comprise a set of reported signs and/or symptoms, it should be preferentially provided as the AE or SAE term, rather than the individual signs and/or symptoms. Otherwise, each one of those signs and/or symptoms should be reported separately as event terms.

9.2.1 Period of Collection

All existing health conditions identified during the Screening Period will be recorded as concomitant disease and the subject's eligibility will be reviewed. Any AEs which occur during the screening session will be captured by the study site staff and assessed by the Investigator or designee in order to establish relationship or relatedness in respect to study products or procedures.

Any new, clinically relevant, abnormal finding detected during the study or worsening of a pre-existing condition/concomitant disease will be documented as an AE and/or SAE.

All ongoing AEs at the end of study participation will be followed-up by the Investigator or designee until they have improved, resolved, stabilized (i.e., no worsening of condition), or until an acceptable explanation has been found. The Investigator or designee will refer the subject to their General Practitioner for follow up of those AE when appropriate.

9.3 Assessment of Adverse Events

9.3.1 Intensity of Adverse Events

For each AE, the intensity will be graded on a 3-point intensity scale:

- Mild: The AE is easily tolerated and does not interfere with daily activity.
- Moderate: The AE interferes with daily activity, but the subject is still able to function.
- Severe: The AE is incapacitating and requires medical intervention.

9.3.2 Relationship to Study Procedures

In general, all AEs and/or SAEs will be assessed by the Investigator or designee as either 'related' or 'not related'.

- Not related: The temporal relationship of the clinical event to study procedures makes a causal relationship unlikely, or, concomitant medication, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
- Related: The temporal relationship of the clinical event to study procedures makes a causal relationship possible, and concomitant medication, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

9.4 Follow-up of Non-serious and Serious Adverse Events

Any non-serious AE that is ongoing during the safety follow-up period will be actively followed-up by the Investigator during that period until it has improved, resolved, stabilized (i.e., no worsening of the condition), or an acceptable explanation has been found (e.g., a chronic condition).

All SAE will be followed up by the Investigator or designee, despite their continuation after the EOS, until their improvement, resolution, stabilization (i.e., no worsening of the condition), or an acceptable explanation has been found (e.g., a chronic condition).

9.5 Reporting of Safety Events

The Principal Investigator will report all serious adverse events relating to the study in an expedited manner to the Advarra Institutional Review Board (IRB) office and all applicable regulatory authorities in accordance with standard operating procedures.

9.6 Reporting and Follow-Up of Pregnancies

All subjects who are determined to be pregnant after enrollment (V2) will be discontinued from the study. This subject's data will be censored, and that subject will be replaced. Advice on the risk of smoking and smoking cessation will be provided by the study staff and subjects will be referred to the respective health care facility/health care provider for further support.

The Investigator or designee is responsible for informing the IRB of any pregnancy that occurs during the study and its outcome, according to local regulations.

9.7 Adverse Event Leading to Discontinuation

If a subject is discontinued from the study because of an AE, the Investigator or designee will follow up until the AE(s)/SAE(s) has/have improved, resolved, stabilized (*i.e.*, no worsening of condition), or until an acceptable explanation has been found.

10 Data Management

10.1 Data Collection Procedures

The results from the clinical assessments will be recorded in the source data file by the Investigator or their authorized designee and then captured in the case report forms (CRFs), unless specified otherwise in the final protocol. Trained study personnel will be responsible for capturing the data from the observations, tests, and assessments specified in the protocol and in the source documents and transferring the data to the CRFs.

The Investigator has ultimate responsibility for the collection and reporting of all data related to the clinical study and ensuring that the data are accurate, authentic/original, legible, timely (contemporaneous), enduring, and available when required. Any corrections made to source documents must be clearly recorded, without obscuring the original values and be accompanied by the date of change, reason for change, and identification of the person making the change. CRF data will be verified against the source documents at the study site by appropriate staff. Instances of missing or unclear data will be discussed with the Investigator for resolution.

10.2 Protocol Deviations / Noncompliance

Protocol deviations are defined as deviations from the study procedures described in this document, whether intentional or unintentional, that may affect the subject (their rights, safety, or well-being) or affect the data (completeness, accuracy or reliability).

Noncompliance that meets the above definition must be reported to the IRB within 10 days of becoming aware of the noncompliance.

10.3 Data Capture

All data are collected from subjects using paper documents or an electronic data capture system. All applicable data, as specified in the protocol, will be transferred to the database or applicable Case Report Forms.

10.3.1 Salesforce.com

Data will be collected for recruitment and screening purposes as stated within the IRB generic recruitment protocol. Unrelated to that protocol, pre-screening questionnaires will be attached to potential participant's records on whether they qualify or are disqualified for this study. Questionnaires utilized for this study will be permanently attached to that potential volunteer's record unless that information is requested to be removed by the participant.

Salesforce acts as a database for potential study participants and will retain responses to general demographic and lifestyle questions, which could help determine prequalification status for specific study participation.

Salesforce.com utilizes some of the most advanced technology for internet security available today. Access to the site is accomplished using industry standard Secure Socket Layer (SSL) technology. Information is protected using both server authentication and data encryption, ensuring that the data are safe, secure, and available only to registered users at Rose Research Center (RRC). Data are completely inaccessible to other groups.

Salesforce.com provides each RRC user a unique user name and password that must be entered at each login. Salesforce.com issues a session "cookie" only to record encrypted authentication information for the duration of a specific session. The session "cookie" does not include the username or password of the user. Salesforce.com does not use "cookies" to store other confidential user and session information, but instead implements more advanced security methods based on dynamic data and encoded session IDs. In addition, salesforce.com is hosted in a secure server environment that uses a firewall and other advanced technology to prevent interference or access from outside intruders.

Salesforce.com also offers the ability to allow only specific IP ranges to log in to the system. This ability alongside double authentication methods keep the system up to date with some of the most advanced security measures in place on the internet today.

10.3.2 Medrio

All smoking behavioral and self-report measures will be captured initially using Medrio. Medrio is an electronic data collection system that records and performs analysis and reporting of data. Participant data will be kept within Medrio's secure servers and may only be transmitted for a secure (SSL) download to our local server. Medrio's servers are protected by high-end firewall systems, with vulnerability scans performed regularly. All services have quick failover points with redundant hardware, and complete encrypted backups are performed regularly. Medrio uses Transport Layer Security (TLS) encryption (SSL or HTTPS) for all transmitted internet data. All information collected within Medrio is compliant with 21 CFR 11 requirements.

10.4 Data Handling

Data of all subjects enrolled including screening failures and AEs during the study (from the time of informed consent to the end of the study of the subject) will be captured in the source documents.

11 Data Analytic Approach

Data will be inspected for outliers and if sufficiently extreme (using Chauvenet's criterion [11]) will be censored from the data analysis. An alpha criterion of 0.05 will be used in all comparisons; one-tailed testing will be conducted because there will only be interest in advancing the devaluation procedure to larger confirmatory studies if it helps, rather than hinders, complete switching to e-cigarettes. Statistical consulting will be provided by leading experts in the field, Daniel J. Bauer, Ph.D. and Patrick J. Curran, Ph.D. Statistical analyses will be organized around evaluating hypotheses for the two main Specific Aims, as follows.

11.1 Primary Outcome Measure

11.1.1 The effect of cigarette devaluation on switching from CC to the JUUL.

The primary outcome measure will be biochemically verified complete switching from CC to JUUL during weeks 9-12, i.e., self-report of no smoking confirmed by an expired air CO reading of <5 ppm. As described in Section 3.1, based on the proportion of participants who complete switching to JUUL, this reward devaluation procedure will be studied in further randomized clinical trials.

11.2 Secondary Outcome Measure

11.2.1 To correlate any changes in cigarette reward with subsequent switching behavior.

Latent curve models (LCMs; aka longitudinal mixed models, multilevel growth models) will be used to characterize changes in the two primary scales of the mCEQ questionnaire, assessing smoking satisfaction and psychological reward, over the first week of the study period. Random effects will be included for both intercepts and slopes, to allow for within-condition individual differences in initial levels and rates of reduction for these outcomes. Preliminary graphical analyses will be conducted to evaluate the tenability of linear change. If change is nonlinear, either a transformation will be used to linearize the relationship, or the model will be modified to accommodate curvature. We will evaluate the assumption of normality for the random effects and error by inspecting the distributions of the estimated values.

These LCMs will then be explored to evaluate the extent to which changes in subjective reward mediate the effect of the devaluation procedure on switching. Specifically, the individual intercepts and slopes for reward ratings will be used as predictors of switching from CC to JUUL. We predict that the cigarette devaluation procedure will lead to a decrease in reward ratings of CC, and that subjects showing the greatest decreases on these outcomes will show the highest probability of successfully switching from CC to the JUUL (i.e., greatest reduction in CC use and greatest increase in JUUL use).

12 Ethics and Regulations

12.1 IRB Approval

The protocol, informed consent document and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated. In addition, any subject recruitment materials must be approved by the IRB prior to being used.

Any change to the protocol must be submitted to the IRB for review and approval before implementation. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately provided the reviewing IRB are notified within 10 working days.

12.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki [12] and is consistent with applicable regulatory principles of ICH/GCP.

The Investigator agrees to conduct the clinical study in compliance with the protocol and approved by the IRB.

12.3 GCP and Regulatory Requirements

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and applicable regulatory requirements. The study must be conducted in accordance with the regulations of the United States Food and Drug Administration (FDA) as described in 21 CFR 50 and 56, applicable laws and the IRB requirements.

12.4 Subject Information and Consent

It is the responsibility of the investigator to provide each subject with full and adequate verbal and written information using the IRB approved informed consent document, including the objective and procedures of the study and the possible risks involved before inclusion in the study. Informed consent must be obtained prior to performing any study-related procedures.

The signed and personally dated original and completed ICF(s) must be kept by the Investigator and filed in the Investigator study file at the site or with the subject's files and a copy must be given to the subject. The subject will be informed that if they withdraw from the study, the data collected until the point of discontinuation will be maintained as part of the study data, and that all samples collected prior to withdrawal will be analyzed, unless specifically requested by the subject in writing.

12.5 Amendment to Informed Consent Form

If a protocol amendment is required, an amendment may be required to the ICF. If revision of the ICF is necessary, the Investigator or designee will ensure that the documents have been reviewed and approved by the IRB before subjects are informed and sign the amended ICF.

13 Administrative Considerations

13.1 Subject Confidentiality

All information obtained during the conduct of the study with respect to the subjects' state of health will be regarded as confidential. A statement to this effect will be written in the information provided to the subject. An agreement to disclose any such information will be obtained from the subject in writing and signed by the subject, in compliance with all local and national data protection and privacy legislation.

Study records that identify subjects will be kept confidential as required by law. Except when required by law, subjects will not be identified by name, social security number, address, telephone number, or any other direct personal identifier in study records disclosed outside of Rose Research Center. For records disclosed outside of Rose Research Center, subjects will be assigned a unique code number. The key to the code will be kept separate from the locked file where the study records are stored.

13.2 Record Retention

All records of data, in any form, will be maintained by Rose Research Center as required by ICH/GCPs. Essential documents will be retained for at least 15 years after completion of the study.

Appropriate measures will be taken to prevent accidental or premature destruction of these documents.

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Appendix 1 – Medical History Form

MEDICAL HISTORY FORM

Major Medical Conditions

Have you ever had or are currently having/ being treated for any of the following conditions:

❑ Yes	❑ No	High blood pressure (Hypertension)
❑ Yes	❑ No	Heart attack, Heart Failure, OR heart disease diagnosis by cardiac angiogram
❑ Yes	❑ No	Problems with heart valves such as mitral regurgitation, stenosis, artificial valve or other
❑ Yes	❑ No	Heart rhythm problem such as atrial fibrillation, tachycardia, or pacemaker
❑ Yes	❑ No	Prior surgery on the gastrointestinal tract (e.g. colectomy, gastric by-pass, Reux-En-Y)
❑ Yes	❑ No	Skin problems
❑ Yes	❑ No	Cirrhosis of the liver
❑ Yes	❑ No	Liver problems other than cirrhosis (e.g. Hepatitis, fatty liver)
❑ Yes	❑ No	Kidney failure
❑ Yes	❑ No	Chronic Kidney Disease
❑ Yes	❑ No	Chronic Diarrhea and/or constipation such as Irritable Bowel Syndrome, Crohn's Disease, Inflammatory Bowel
❑ Yes	❑ No	Stomach/ Duodenal Ulcer (Gastrointestinal Ulcer)
❑ Yes	❑ No	Chronic Bronchitis (cough every morning)
❑ Yes	❑ No	Chronic Obstructive Pulmonary Disease (COPD) or Emphysema
❑ Yes	❑ No	Other lung disorder such as Tuberculosis, Pulmonary Fibrosis, Sarcoid
❑ Yes	❑ No	Asthma
❑ Yes	❑ No	Stroke or TIA (mini-stroke)
❑ Yes	❑ No	Seizure/ epilepsy
❑ Yes	❑ No	Migraine headaches
❑ Yes	❑ No	Unexplained fainting spells
❑ Yes	❑ No	Insomnia
❑ Yes	❑ No	Other neurologic conditions
❑ Yes	❑ No	Problems giving blood samples
❑ Yes	❑ No	Anemia requiring iron
❑ Yes	❑ No	Blood disorder
❑ Yes	❑ No	Rheumatic Disease such as Rheumatoid Arthritis, Fibromyalgia, other
❑ Yes	❑ No	Sinusitis/ Seasonal allergies
❑ Yes	❑ No	Other severe allergies
❑ Yes	❑ No	Diabetes or Pre-diabetes
❑ Yes	❑ No	Thyroid disease or condition
❑ Yes	❑ No	Cancer
❑ Yes	❑ No	Depression/ Anxiety/ Bipolar disorder
❑ Yes	❑ No	Post-traumatic stress disorder
❑ Yes	❑ No	Other Psychiatric problems (e.g., Borderline, Schizoaffective, Schizophrenia, Hypomania, AHDA)
❑ Yes	❑ No	History of Sexually Transmitted Disease (STD)
❑ Yes	❑ No	Chronic infectious syndrome such as HIV, CMV, Epstein Barr
❑ Yes	❑ No	History of drug or alcohol abuse
❑ Yes	❑ No	Intolerance to medications
❑ Yes	❑ No	Other major medical condition

Office use only:

Page 1 of 5

MEDICAL HISTORY FORM

Past Medical History

Please list any illnesses that have caused you to miss work or have interrupted your life this past year:

1. Mo/Yr:
2. Mo/Yr:
3. Mo/Yr:
4. Mo/Yr:
5. Mo/Yr:

Please list any hospitalizations. If possible, include the year:

1. Mo/Yr:
2. Mo/Yr:
3. Mo/Yr:
4. Mo/Yr:
5. Mo/Yr:

Please list any serious injuries or accidents. If possible, include the year:

1. Mo/Yr:
2. Mo/Yr:
3. Mo/Yr:
4. Mo/Yr:
5. Mo/Yr:

Please list any surgeries or major procedures, along with the reason. If possible, include the year:

1. Mo/Yr:
2. Mo/Yr:
3. Mo/Yr:
4. Mo/Yr:
5. Mo/Yr:

Office use only:

MEDICAL HISTORY FORM

Family History

Has any first-degree family members (children, parents, or siblings) had any of the following illnesses:

Illness	Which family member?
Anemia or Blood disease	
Cancer	
Diabetes	
Glaucoma	
Heart disease	
High blood pressure	
Mental Illness/ Depression/ Generalized Anxiety	
Stroke	
Substance abuse (alcohol, tobacco or other)	
Other serious illness:	

Social History

Please complete the following questions:

Do you drink alcohol, beer, or wine?	❑ Yes	❑ No	If YES, how many drinks per week? _____ How many drink do you have on your heaviest drinking day of the week? _____
Do you drink coffee, tea, caffeinated soda daily?	❑ Yes	❑ No	If YES, how many cups per day? _____
Have you used a non-prescription drug such as marijuana, cocaine, heroin in the last month? Have you used prescription drugs not prescribed to you?	❑ Yes	❑ No	If YES, when and what drug/ substance and last date of use: _____

Blood Donation

Please complete the following question:

Have you received or donated blood or blood products within the last 2 months?	❑ Yes	❑ No	If YES, when and which blood product (whole blood, plasma, platelets, etc.)? _____

General Health

Please complete the following questions:

Do you use supplemental oxygen?	❑ No	❑ Yes		
Can you walk up 2 flights of stairs?	❑ No	❑ Yes, without stopping	❑ Yes, but I need to stop along the way	
How well do you walk?	❑ Independently	❑ I use a cane or walker	❑ I use a wheelchair	
Do you use CPAP machine?	❑ No	❑ Yes		

MEDICAL HISTORY FORM

General Health (Women Only)

Do you agree to use a medically acceptable form of birth control for the duration of the study? ❑ N/A ❑ Yes ❑ No

If yes, please select form of contraception you plan to use or are currently using.

❑ Tubal ligation / Hysterectomy / Bilateral oophorectomy	❑ Spouse with vasectomy
❑ Birth control pills / patches / implants / injections	❑ Not heterosexually active
❑ Condom / Diaphragm used with spermicide	❑ None
❑ Intrauterine device (IUD) / Essure	

Do you plan to become pregnant in the next 6 months? ❑ Yes ❑ No

Medications

Please list any allergies and the reaction caused by the allergy (e.g. "rash" or "tongue swelling" or "itchiness"):

Please list all medications you have used within the last month (include over-the counter drugs, vitamins/ supplements, and especially prescriptions):

Name of medication	**Dosing** (mg/tabs/pills) and **Route** (oral, topical)	**Frequency** (times per day)	Start date	Stop date	Prescribed for what problem?

MEDICAL HISTORY FORM

Smoking Cessation Products

For each of the following, mark if you have used the product, experienced any side effects, allergy or intolerance with usage or had to stop using the product due to side effects:

	Not Used	Used	Side Effects	Stopped due to Side Effects	
Nicotine Patch	❑	❑		❑ Yes	❑ No
Nicotine Gum	❑	❑		❑ Yes	❑ No
Nicotine Lozenge	❑	❑		❑ Yes	❑ No
Nicotine Inhaler	❑	❑		❑ Yes	❑ No
Nicotine Nasal Spray	❑	❑		❑ Yes	❑ No
Zyban (wellbutrin)	❑	❑		❑ Yes	❑ No
Chantix (varenicline)	❑	❑		❑ Yes	❑ No

Have you used any of these products within the past 30 days? ❑ Yes ❑ No

MD/ PA Signature

Date

Appendix 2 – Patient Health Questionnaire (PHQ-9)

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems?

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	❍	❍	❍	❍
2. Feeling down, depressed, or hopeless	❍	❍	❍	❍
3. Trouble falling or staying asleep, or sleeping too much	❍	❍	❍	❍
4. Feeling tired or having little energy	❍	❍	❍	❍
5. Poor appetite or overeating	❍	❍	❍	❍
6. Feeling bad about yourself- or that you are a failure or have let yourself or your family down	❍	❍	❍	❍
7. Trouble concentrating on things, such as reading the newspaper or watching television	❍	❍	❍	❍
8. Moving or speaking so slowly that other people could have noticed. Or the opposite- being so fidgety or restless that you have been moving around a lot more than usual	❍	❍	❍	❍
9. Thoughts that you would be better off dead, or of hurting yourself in some way	❍	❍	❍	❍

10. If you checked off *any* problems, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?

- ❍ Not difficult at all
- ❍ Somewhat difficult
- ❍ Very difficult
- ❍ Extremely difficult

Appendix 3 – Registration Form

REGISTRATION FORM

(Please Print)

Today's Date:			Participant Number:	
CONTACT INFORMATION				
Last Name:	First:	Middle Initial:	☐ Mr. ☐ Mrs.	☐ Miss ☐ Ms.
Street Address:				
P.O. Box:	City:	State:	ZIP Code:	
E-mail Address:			Do you have web access other than your mobile phone? ☐ Yes ☐ No	
Primary Phone Number: ( ) Cell Office Home		Other Phone Number: ( ) Cell Office Home		
Do you give Rose Research Center permission to leave a message at the above numbers? ☐ Yes ☐ No				
Emergency contact: If I cannot be reached or if there is an emergency you can leave a message with: Name of local friend or relative: Relationship: Phone no.: ( )				
_____ I understand in the event that I do not return messages and fail to come to appointments my emergency contact person may be contacted.				
DEMOGRAPHIC INFORMATION				
Birth Date: / /	Sex: ☐ M ☐ F	Marital Status (circle one): Single / Married / Divorced / Separated / Widowed		
Race: ☐ American Indian or Alaska Native ☐ Asian ☐ Black or African American ☐ Native Hawaiian or Other Pacific Islander ☐ White ☐ Other (specify) _____			Ethnicity: ☐ Hispanic or Latino ☐ Not Hispanic or Latino	
Are you a U.S. Veteran? ☐ Yes ☐No				
Are you currently employed at or have affiliation with the Rose Research Center? ☐ Yes ☐No				
Are you currently participating in another clinical trial? ☐ Yes ☐No				
Have you participated in a clinical trial in the past 3 months that included an investigational drug? ☐ Yes ☐No				
Do you own a smartphone with text message and data capabilities? ☐ Yes ☐No				

I attest that all of the information above is to the best of my knowledge and believe true, correct and complete.

_____ Participant's Signature

_____ Date

IDENTIFICATION VERIFICATION

(Office use only)

Form of ID Verified: ☐ Driver's License ☐ Photo ID ☐ Military ID ☐ Passport

_____ Research Personnel's Signature

_____ Date

Appendix 4 – Research Payment Verification Form

RESEARCH PARTICIPANT PAYMENT VERIFICATION FORM

Receipt for Payment:

In order for Rose Research Center to meet its obligations to the Internal Revenue Service we are required to obtain the following information. Payment received as compensation for participation in research is considered taxable income. You are responsible for paying any state, federal or Social Security taxes on the money you receive. If your total payment exceeds $600 in any one calendar year, we are required to report this information to the Internal Revenue Service (IRS).

The Payment Verification Form will be used in order to process your payments only. Once your information has been entered into the Greenphire payment system, this form will be destroyed. Until that time, the form will be kept in a secure and locked area at all times. Your information will not be connected to your responses to the interviews, surveys, questionnaires or with your participation in this study.

Full Name: _____

Social Security Number: _____

Permanent Home Address:

_____

_____

_____

Appendix 5 – Review of Systems

REVIEW OF SYSTEMS

Are you currently (in the last 30 days) having/ being treated for any of the following conditions:

General: *(____ none of these apply)*
- ❑ Unexplained weight loss or gain
- ❑ Fatigue/ Lack of energy
- ❑ Fever or chills
- ❑ Weakness
- ❑ Trouble Sleeping

Skin: *(____ none of these apply)*
- ❑ Rashes
- ❑ Lumps
- ❑ Itching
- ❑ Dryness
- ❑ Color changes
- ❑ Hair and nail changes

Head: *(____ none of these apply)*
- ❑ Headache
- ❑ Head Injury

Ears: *(____ none of these apply)*
- ❑ Decreased hearing
- ❑ Earache
- ❑ Ringing in ears

Eyes: *(____ none of these apply)*
- ❑ Vision problems
- ❑ Specks
- ❑ Blurry or double vision
- ❑ Flashing lights
- ❑ Redness
- ❑ Pain

Nose: *(____ none of these apply)*
- ❑ Stuffiness
- ❑ Discharge
- ❑ Itching
- ❑ Sinus pain
- ❑ Nose Bleeds

Throat: *(____ none of these apply)*
- ❑ Teeth/gum problems
- ❑ Dentures
- ❑ Hoarseness
- ❑ Sore tongue
- ❑ Dry mouth
- ❑ Sore throat
- ❑ Thrush
- ❑ Non-healing sores
- ❑ Difficulty swallowing

Neck: *(____ none of these apply)*
- ❑ Lumps
- ❑ Stiffness
- ❑ Pain
- ❑ Swollen glands

Respiratory: *(____ none of these apply)*
- ❑ Cough (dry or wet, productive)
- ❑ Shortness of breath
- ❑ Coughing up blood
- ❑ Painful breathing
- ❑ Wheezing

Cardiovascular: *(____ none of these apply)*
- ❑ Chest pain or discomfort
- ❑ Tightness
- ❑ Heart pounding/ Fluttering/ Palpitations
- ❑ Difficulty breathing lying down
- ❑ Swelling
- ❑ Shortness of breath with activity
- ❑ Suddenly awaking from sleep with shortness of breath

Gastrointestinal: *(____ none of these apply)*
- ❑ Swallowing difficulties
- ❑ Heartburn
- ❑ Constipation
- ❑ Vomiting
- ❑ Change in bowel habits
- ❑ Rectal bleeding
- ❑ Diarrhea
- ❑ Stomach pain
- ❑ Yellow eyes or skin
- ❑ Change in appetite
- ❑ Nausea

Urinary: *(____ none of these apply)*
- ❑ Frequency
- ❑ Urgency
- ❑ Blood in urine
- ❑ Pain with urination
- ❑ Change in urinary strength
- ❑ Incontinence

REVIEW OF SYSTEMS

Vascular: *(____ none of these apply)*
- ❑ Calf pain with walking
- ❑ Leg cramping
- ❑ Leg pains

Musculoskeletal: *(____ none of these apply)*
- ❑ Muscle or joint pain
- ❑ Stiffness
- ❑ Back pain
- ❑ Redness of joints
- ❑ Swelling of joints
- ❑ Trauma

Neurologic: *(____ none of these apply)*
- ❑ Dizziness
- ❑ Fainting
- ❑ Tingling
- ❑ Weakness
- ❑ Numbness
- ❑ Tremor
- ❑ Shaking episodes

Hematologic: *(____ none of these apply)*
- ❑ Bruise easily
- ❑ Bleed easily

Endocrine: *(____ none of these apply)*
- ❑ Heat or cold intolerance
- ❑ Sweating
- ❑ Frequent urination
- ❑ Thirst
- ❑ Change in appetite

Psychiatric: *(____ none of these apply)*
- ❑ Nervousness
- ❑ Memory loss
- ❑ Feeling down

Females only: *(____ none of these apply)*
- ❑ Pregnant or currently breast feeding

Office use only:

_____ MD/ PA Signature

_____ Date

Appendix 6 – Session Payment Form

For your time and inconvenience related to your participation in this study, you will be paid up to a total of $915 if you complete this study. If you do not complete the study, for any reason, you will be paid for the study visits you do complete according to the following schedule:

- You will receive $25 for completing Study Visit 1.
- You will receive $75 for completing Study Visit 2 through Study Visit 7 ($450 total)
- You will receive $5 for responding to each text message during the study (once per day for approximately 84 - 88 days = approximately $440). In order to receive compensation for each message, you will need to answer all of questions before you receive your next text message.

SESSION PAYMENT LOG

SESSION	DATE ATTENDED	AMOUNT ELIGIBLE VISIT	AMOUNT ELIGIBLE SMS	AMOUNT TO BE PAID	RRC INITIALS	PARTICIPANT INITIALS	DATE PROCESSED
Visit 1-Screen		$25	$0				
Visit 2		$75	$0				
Visit 3		$75					
SMS			☐ x $5				
Visit 4		$75					
SMS			☐ x $5				
Visit 5		$75					
SMS			☐ x $5				
Visit 6		$75					
SMS			☐ x $5				
Visit 7		$75					
SMS			☐ x $5				
TOTAL		$475					

I certify that the payment eligibility process has been fully explained to me and I agree with and accept all conditions of the payment eligibility process.

_____ _____

Participant Signature Date

_____ _____

Research Personnel's Signature Date

Appendix 7 – Smoking History

SMOKING HISTORY

What brand of cigarettes do you smoke? _____

Color of cigarette pack? _____

Size: ❍ Kings ❍ Regulars ❍ 72's ❍ 100's ❍ 120's

Flavor: ❍ Menthol ❍ Non-menthol

Pack type: ❍ Hard pack ❍ Soft pack

Filtered? ❍ Filtered ❍ Unfiltered

1. How many cigarettes do you smoke a day? _____cigs per day

2. On average, how many days per week do you smoke? _____days per week

2. How old were you when you first smoked a cigarette? _____ years old

3. How old were you when you became a regular smoker? _____ years old

4. How many years have you been a regular smoker? _____ years

5. Have you been a regular smoker for the past year?
❍ Yes ❍ No

6. How many times have you tried to seriously quit smoking (for at least 1 day)? _____ attempts

7. Since you first started smoking, what was the longest period of time that you were able to stay off cigarettes? (If less than 1 day, do not include time sleeping) _____
❍ Hours ❍ Days ❍ Weeks ❍ Months ❍ Years

8. Have you participated in a smoking study in the past?
❍ Yes ❍ No

If YES, when? _____ Where? _____

9. Do you intend to quit smoking in the next 90 days?
❍ Yes ❍ No

10. Does someone you live with smoke cigarettes?
❍ Yes ❍ No

11. Have you smoked cigar in the past 14 days?
    O Yes O No

    If YES, specify? _____

12. Have you smoked a pipe, hookah or an e-cigarette in the past 14 days?
    O Yes O No

13. Have you used snuff or chewing tobacco in the past 14 days?
    O Yes O No

14. Have you used experimental or investigational drugs in the past 30 days?
    O Yes O No

15. Do you wake in the middle of the night to smoke?
    O Yes O No

16. Are you willing to learn how to operate and willing to use e-cigarettes during this study?
    O Yes O No

Appendix 8 – modified Cigarette Evaluation Questionnaire (mCEQ)

Rose Research Center, LLC

Participant Number:	
Participant Initials:	
Study:	
Visit:	
Date:	

CIGARETTE EVALUATION QUESTIONNAIRE - modified

Have you smoked any cigarettes since your last visit?

- ❍ No: Skip questionnaire
- ❍ Yes: Please answer the following questions based on the **FIRST** cigarette you smoked on the last day you smoked.

	Not at all	Very little	A little	Moderately	A lot	Quite a lot	Extremely
1. Was it satisfying?	❍	❍	❍	❍	❍	❍	❍
2. Did it taste good?	❍	❍	❍	❍	❍	❍	❍
3. Did it make you dizzy?	❍	❍	❍	❍	❍	❍	❍
4. Did it calm you down?	❍	❍	❍	❍	❍	❍	❍
5. Did it help you concentrate?	❍	❍	❍	❍	❍	❍	❍
6. Did it make you feel more awake?	❍	❍	❍	❍	❍	❍	❍
7. Did it reduce your hunger for food?	❍	❍	❍	❍	❍	❍	❍
8. Did it make you nauseated?	❍	❍	❍	❍	❍	❍	❍
9. Did it make you feel less irritable?	❍	❍	❍	❍	❍	❍	❍
10. Did you enjoy the sensations of the smoke in your throat and chest?	❍	❍	❍	❍	❍	❍	❍
11. Did it immediately reduce your craving for cigarettes?	❍	❍	❍	❍	❍	❍	❍
12. Did you enjoy smoking?	❍	❍	❍	❍	❍	❍	❍

Appendix 9 – Assessment of Behavioral OUTcomes (ABOUT)

ASSESSMENT of BEHAVIORAL OUTcomes (ABOUT)

Related to Tobacco and nicotine products

The next questions ask about your experience with tobacco and nicotine products. Please answer all questions. Please think about all the tobacco and nicotine products that you use as you answer all of the following questions.

1. Over the **past 7 days**, on average, how soon after you woke up did you use your first product?

0 to 5 minutes	☐
6 to 15 minutes	☐
16 to 30 minutes	☐
31 to 60 minutes	☐
More than 1 hour to 3 hours	☐
More than 3 hours	☐

2. Over the **past 7 days**, on average, how long before going to sleep did you use your last product?

0 to 5 minutes	☐
6 to 15 minutes	☐
16 to 30 minutes	☐
31 to 60 minutes	☐
More than 1 hour to 3 hours	☐
More than 3 hours	☐

ASSESSMENT of BEHAVIORAL OUTcomes (ABOUT)

Related to Tobacco and nicotine products

3. Currently…	Not at all	A little	Moderately	Very Much	Extremely
a. How much do you feel you need your product(s) to function "normally"?	❍	❍	❍	❍	❍
b. How difficult do you think it would be for you to completely quit your product(s)?	❍	❍	❍	❍	❍

4. Over the past 7 days, how often did you…	Never	Rarely	Sometimes	Most of the time	All the time
a. Have a strong desire to use your product(s)?	❍	❍	❍	❍	❍
b. Use more of your product(s) than you intend to?	❍	❍	❍	❍	❍
c. Feel that you "HAD to have one"?	❍	❍	❍	❍	❍
d. Use your product(s) in a situation where you weren't supposed to?	❍	❍	❍	❍	❍
e. Find it hard to control the need or urge to use your product(s)?	❍	❍	❍	❍	❍
f. Sneak off to use your product(s)?	❍	❍	❍	❍	❍
g. Avoid an activity because you couldn't use your product(s)?	❍	❍	❍	❍	❍
h. Stop what you were doing to use your product(s)?	❍	❍	❍	❍	❍

Appendix 10 – Employment History

EMPLOYMENT HISTORY

1. What is the highest degree you have completed?

   - ○ High school diploma or G.E.D.
   - ○ Technical degree
   - ○ Two-year associate degree (e.g. A.A.)
   - ○ Four-year undergraduate degree (e.g. B.A., B.S.)
   - ○ Professional degree (e.g. P.A., R.N.)
   - ○ Master's degree (e.g. M.A., M.S., M.B.A.)
   - ○ Doctorate (e.g. Ph. D., M.D., J.D.)
   - ○ Other_____

2. How many years of formal education have you completed: (Include grade school and higher) _____

3. What is your current employment status?

   - ○ Not employed (please answer question 4)
   - ○ Part-Time work
   - ○ Full-time work

4. If not employed is selected, please specify your answer:

   - ○ Education (Full-time student)
   - ○ Retired
   - ○ Medical leave
   - ○ Homemaker
   - ○ Laid off
   - ○ Other _____

5. What is your current job title; if no longer employed, in what position were you last employed?

_____

6. How physically demanding is your current employment?

- ○ Not employed
- ○ Not demanding at all
- ○ Very little demanding
- ○ A little demanding
- ○ Somewhat demanding
- ○ Moderately demanding
- ○ Very demanding
- ○ Extremely demanding

7. How mentally or emotionally stressful is your current employment?

- ○ Not employed
- ○ Not stressful at all
- ○ Very little stress
- ○ A little stressful
- ○ Somewhat stressful
- ○ Moderately stressful
- ○ Very stressful
- ○ Extremely stressful

8. What is your gross (before taxes) annual household income?

- ○ < $16,000
- ○ $16,001- $32,000
- ○ $32,001- $48,000
- ○ $48,001- $64,000
- ○ $64,001- $80,000
- ○ $80,001- $96,000
- ○ >$96,000

9. What are your estimated total assets? (Include house, automobiles, stocks, savings, furniture, etc.).

- ○ <$50,000
- ○ $50,001- $100,000
- ○ $100,001- $200,000
- ○ $200,001- $300,000
- ○ $300,001- $400,000
- ○ $400,001- $500,000
- ○ $500,001- $750,000
- ○ >$750,001

10. How many people live in your household? _____

Appendix 11 – Fagerström Test for Nicotine Dependence (FTND)

FAGERSTRÖM TEST FOR NICOTINE DEPENDENCE

INSTRUCTIONS: Please mark the answer that most accurately answers each question.

1. How soon after you wake up do you smoke your first cigarette?

   ○ Within 5 Minutes ○ 6-30 Minutes ○ 31-60 Minutes ○ After 60 Minutes

2. Did you find it difficult to refrain from smoking in places where it is forbidden, e.g., in church, at the library, in the cinema, etc.?

   ○ Yes
   ○ No

3. Which cigarette would you hate most to give up?

   ○ The first one in the morning
   ○ Any other

4. How many cigarettes per day do you smoke?

   ○ 31 or more ○ 21-30 ○ 11-20 ○ 10 or less

5. Do you smoke more frequently during the first hours of waking than during the rest of the day?

   ○ Yes
   ○ No

6. Do you smoke if you are so ill that you were in bed most of the day?

   ○ Yes
   ○ No

Appendix 12 – Reasons to Smoke

REASONS TO SMOKE

INSTRUCTIONS: Listed below are thirteen common reasons why people like to smoke. Using the scale on the right, fill in the bubble for each statement which most closely describes how important that reason is to you.

	Least Important	Hardly Important	Not Really Important	A Little Important	More Important	Really Important	Most Important
1. It calms me down	❍	❍	❍	❍	❍	❍	❍
2. It gives me something to do with my hands	❍	❍	❍	❍	❍	❍	❍
3. I like the taste and smell	❍	❍	❍	❍	❍	❍	❍
4. I like the sensations deep in my throat or chest	❍	❍	❍	❍	❍	❍	❍
5. It wakes me up when I am drowsy	❍	❍	❍	❍	❍	❍	❍
6. I like to watch the smoke	❍	❍	❍	❍	❍	❍	❍
7. It makes relaxing seem even better	❍	❍	❍	❍	❍	❍	❍
8. It satisfies my craving	❍	❍	❍	❍	❍	❍	❍
9. It gives me a rush	❍	❍	❍	❍	❍	❍	❍
10. It gives me more confidence around other people	❍	❍	❍	❍	❍	❍	❍
11. It helps me control my weight	❍	❍	❍	❍	❍	❍	❍
12. It's is like a friend	❍	❍	❍	❍	❍	❍	❍
13. It helps me concentrate	❍	❍	❍	❍	❍	❍	❍

Page 1 of 1

Appendix 13– SMS Daily Survey

* 1. How soon after you woke up did you take your first puff? (e-cigarette or cigarette)

- ◯ Within 5 Minutes
- ◯ 6-30 Minutes
- ◯ 31-60 Minutes
- ◯ After 60 Minutes

* 2. Have you smoked any cigarettes today?

- ◯ Yes
- ◯ No

* 3. How many cigarettes have you smoked today?

* 4. How satisfying were the cigarettes you smoked today?

- ◯ Not at all
- ◯ Very little
- ◯ A little
- ◯ Moderately
- ◯ A lot
- ◯ Quite a lot
- ◯ Extremely

* 5. Did you use your e-cigarette before smoking your first cigarette of the day?

- ◯ Yes
- ◯ No

* 6. How many times did you use your **e-cigarette** today?

* 7. Of those {{Q6}} times you used your e-cigarette, how many of those were right before a cigarette?

* 8. How satisfying was the **e-cigarette** you used today?

- ◯ Not at all
- ◯ Very little
- ◯ A little
- ◯ Moderately
- ◯ A lot
- ◯ Quite a lot
- ◯ Extremely

* 9. How much did you crave cigarettes today?

- ◯ Not at all
- ◯ Very little
- ◯ A little
- ◯ Moderately
- ◯ A lot
- ◯ Quite a lot
- ◯ Extremely

* 10. How much did you crave e-cigarettes today?

- ◯ Not at all
- ◯ Very little
- ◯ A little
- ◯ Moderately
- ◯ A lot
- ◯ Quite a lot
- ◯ Extremely

Appendix 14 – JUUL Flavor Assessment Questionnaire

Rose Research Center, LLC

Participant Number:	
Participant Initials:	
Study:	
Visit:	
Date:	

Juul Flavor Assessment Questionnaire

Now that you have tried the two flavors of JUUL, are you willing to switch to either of these JUUL flavors?

(CHECK ONE RESPONSE ONLY)

YES_____ No_____

_____

Participant's Signature and Date

Appendix 15 – 6 Month Follow up Survey

* 1. Hello
Have you smoke a combustible cigarette since your last visit?

- Yes
- No

* 2. If yes, are you still smoking combustible cigarettes right now?

- Yes
- No

* 3. How many combustible cigarettes do you smoke per day on average?

* 4. Have you used an e-cigarette since your last visit?

- Yes
- No

* 5. If yes, are you still using an e-cigarette?

- Yes
- No

* 6. How often do you use an e-cigarette?

7. Are you using any other nicotine containing products? (Nicotine Patch, Nicotine Gum, Nicotine Lozenge, etc.)

- Yes
- No