Application for Review of Human Research: IRB Protocol (Biomedical Research)

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Principal Investigators: James Loughead, Ph.D.

***Study Physician*:** John Detre, M.D.

Co-Investigators: Rebecca Ashare, Ph.D.
Kristin Linn, Ph.D.

PROTOCOL TITLE

1. ***Full Title:*** Neural mechanisms associated with risk of smoking relapse

2. ***Brief Title*:** Imaging biomarkers of smoking cessation

STUDY SPONSORSHIP

1. ***Funding Sponsor:*** Center for Interdisciplinary Research on Nicotine Addiction (CIRNA)

2. ***Primary Sponsor:*** James Loughead, Ph.D.

PROTOCOL ABSTRACT

Smoking is the greatest preventable cause of mortality and a significant economic burden. Even with the best available treatments, most smokers relapse within days or weeks after a quit attempt. Nicotine replacement therapy, the most widely used pharmacotherapy, yields end of treatment quit rates of <25% suggesting that managing nicotine withdrawal is not sufficient. To improve quit rates significantly, we need a more refined mechanistic understanding of why so many smokers who attempt to quit will relapse quickly. Neuroimaging can identify mechanisms underlying behavior change beyond self-report and behavioral measures. Functional magnetic resonance imaging (fMRI) studies by our team showed that brief (e.g., 24 hr.) abstinence from smoking produces working memory deficits associated with reduced neural activity in cognitive control circuits and weakened resting state functional connectivity. Neural reactivity to smoking cues also increases risk of relapse, and psychological stress can enhance neural responses to smoking cues and increase smoking intensity. This study will examine how abstinence-induced brain changes contribute to clinical outcomes in smokers. Using our validated fMRI abstinence challenge paradigm, 200 smokers will complete two 1-hour pre-treatment fMRI scans: after smoking satiety and after 24 hours of confirmed abstinence. We will examine brain responses during performance of tasks probing working memory, cue reactivity, and stress response as well as resting state functional connectivity. Participants will then set a target quit date, receive smoking cessation counseling, and be monitored for 6 months to assess time to relapse using a validated smoking relapse protocol.

BACKGROUND – Main Study

Smoking is the greatest preventable cause of mortality and a significant economic burden [1]. Even with the best available treatments, most smokers relapse within days or weeks after a quit attempt [2-5]. Nicotine replacement therapy, the most widely used pharmacotherapy, yields end of treatment quit rates of <25% suggesting that managing nicotine withdrawal is not sufficient [6-8]. Currently available pre-treatment assessments, such as smoking measures (e.g., smoking rate, dependence, cotinine), psychological measures (attitudes, self-efficacy), and behavioral

measures (e.g., impulsivity, decision-making) account for a relatively small proportion of variance in predicting smoking relapse [9-15]. For example, measures of impulsivity predict cessation outcomes in some trials [16, 17] but not in others [18]. There are also inconsistent results for quitting motivation and self-efficacy [11, 15, 19-22]. Nicotine dependence measures are consistently related to cessation [12, 15]; however, the Fagerstrom Test for Nicotine Dependence and heaviness of smoking accounted for only ~1% of the variance in quit rates in two independent samples of smokers quitting without medication [14]. To improve quit rates significantly, we need a more refined mechanistic understanding of why so many smokers who attempt to quit will relapse quickly. Neuroimaging offers a powerful complementary tool for understanding vulnerability to relapse in central nervous system disorders, and can facilitate treatment development [23]. In the context of smoking cessation, studies of brain function can index pathological symptoms of nicotine abstinence/withdrawal and assess the relative contribution of mechanistic processes to clinical outcomes [24]. This study will investigate the interplay of multiple mechanistic pathways in early smoking relapse by examining how abstinence-induced brain changes contribute to clinical outcomes in smokers.

Functional magnetic resonance imaging (fMRI) studies by our team converge on the central role of working memory in smoking relapse. We showed that brief (e.g., 24 hr.) abstinence from smoking produces working memory deficits that are associated with reduced neural activity in cognitive control circuits and weakened resting state functional connectivity [25-29]. These altered brain responses may compromise cognitive resources needed to resist urges to smoke, thereby contributing to relapse [26, 30]. While working memory is one mechanism underlying relapse, additional neurobehavioral pathways are clearly important [31]. For example, neural reactivity to smoking cues also increases risk of relapse [31, 32]. Further, psychological stress can enhance neural responses to smoking cues [33, 34] and increase smoking intensity [35, 36]. Stress can also impair working memory [37]. The proposed study, to our knowledge, will be the first prospective study to examine the contributions of resting BOLD and BOLD signal change during working memory, cue reactivity, and psychological stress to subsequent smoking relapse. We will determine whether these mechanisms contribute to relapse beyond subjective and behavioral assessments, and explore the interactions among these processes.

Using our validated fMRI abstinence challenge paradigm [25, 27-30], 200 smokers will complete two 1-hour pre-treatment fMRI scans: after smoking satiety and after 24 hours of confirmed abstinence. We will examine neural responses during performance of tasks probing working memory, cue reactivity, and stress response as well as resting state functional connectivity. Participants will then set a target quit date, receive smoking cessation counseling, and be monitored for 6 months to assess time (days) to relapse, using a validated smoking relapse protocol [30, 38]. The primary outcome is time to relapse. Secondary outcomes include abstinence symptoms and smoking status at 30 days.

OBJECTIVES

1. Overall Objectives - (Main Study)

Aim 1: To identify brain mechanisms that increase vulnerability to relapse, using a pre-treatment abstinence challenge paradigm.
Hypothesis: Altered Blood Oxygen Level Dependent (BOLD) signal during 24-hr abstinence challenge (vs. smoking satiety) will increase the risk of faster relapse during a subsequent quit attempt.

Aim 2: To test an integrated brain-behavior model of relapse.*Hypothesis: Integration of neural and behavioral predictors will identify novel spatial patterns that distinguish quitters from relapsers at 30 days.*

BACKGROUND – Recruitment & Retention Pilot Study

Nearly one in three clinical trials closely prematurely due to under-enrollment [67]. Reports of clinical trials consistently state that initial approaches to recruitment are rarely successful, take longer and are more costly than planned, and the pool of participants is overestimated [68]. Unfortunately, many studies implement recruitment strategies without taking a systematic approach to identifying the most efficient and cost-effective approaches to enrolling subjects. With the increasing ubiquity of cell phones, text messaging (SMS) interventions have the potential to increase reach and reduce costs. In the United States, it is estimated that 85 to 91% of adults (18 and over) own a mobile phone, and these rates are observed across low- and high-income individuals [69]. SMS interventions for improving adherence to antiretroviral treatment in people living with HIV as well as smoking cessation have demonstrated efficacy [70]. However, few studies have explicitly examined strategies to optimize the use of SMS to enhance clinical trial enrollment. Behavioral economic strategies, including information provision and incentives, may represent useful approaches to overcoming barriers to clinical research and ultimately advancing science [71]. Information provision includes utilizing descriptive and injunctive norms, personalization, and reciprocity. Framing messages to shape social norms regarding research participation may increase engagement. For example, in addition to "personal medical benefit", patients cite "contributing to research that could help other people" and "giving something back in return" as the most important reasons to participate in clinical research [72]. Another common strategy for improving recruitment and retention is to offer incentives, including monetary payments or other rewards that target motivation. For instance, contingency management (CM), where tangible reinforcement is provided in close temporal proximity to a participant performing a target behavior (e.g., on-time attendance) is highly efficacious in engendering target behaviors [73-75]. Although information provision and incentives are effective strategies for behavior change, they may target different aspects of motivation: intrinsic (i.e., the behavior itself is purposive) vs. extrinsic motivation (i.e., the prospect of gaining the incentive motivates the behavior), respectively. Although numerous studies comparing intrinsic vs extrinsic strategies to enhance motivation have yielded inconsistent results, a recent meta-analysis suggested intrinsic and extrinsic factors may act synergistically [76]. Thus, we propose to employ information provision and incentive strategies independently and in combination to evaluate the optimal approach for recruiting and retaining subjects in clinical research studies.

2. Overall Objectives - (Recruitment & Retention Pilot Study)

Aim 1: To evaluate the effects of information provision and incentives, alone and in combination, on study enrollment rates.
Hypothesis: Behavioral economic interventions will (Information provision & contingency management) will produce higher rates of enrollment compared to standard recruitment.

CHARACTERISTICS OF THE STUDY POPULATION

1. Target Population

400 healthy adult smokers between the ages of 18-65 will be enrolled in order to have 200 participants complete the study.

2. Accrual

400 male or female participants will be enrolled to have 200 complete the study at the University of Pennsylvania Center for Interdisciplinary Research on Nicotine Addiction (CIRNA). Accounting for ~50% attrition (primarily participants who are found to be ineligible during the intake session), we estimate we will need to enroll 400 eligible participants (~7 smokers per month over a 50 month period) to have up to 200 participants complete the study. Participants will first be screened over the telephone and then complete an in-person Intake Visit at the Center for Interdisciplinary Research on Nicotine Addictions to confirm final eligibility.

3. Key Inclusion Criteria

Eligible participants will be:

1. Smokers between the ages of 18 and 65, reporting consumption of at least 5 cigarettes per day for at least the past 6 months;
2. Planning to live in the area for at least the next 3 months;
3. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the combined consent and HIPAA form;
4. Able to communicate fluently in English (speaking, writing, and reading).

4. Key Exclusion Criteria

Subjects who present and/or self-report with the following criteria at any point during study participation will not be eligible to participate in the study:

Smoking Behavior:

1. Use of chewing tobacco or snuff or cigars;
2. Current enrollment or plans to enroll in another smoking cessation program or research study in the next 3 months;
3. Current or anticipated (within the next 3 months) use of smoking cessation medications or nicotine replacement therapy (NRT);
4. A baseline carbon monoxide (CO) reading less than 8ppm.

Alcohol/Drugs:

1. Diagnosis or treatment for alcohol or drug abuse in the past two years as reported during phone screen (e.g., alcohol, opioids, cocaine, or stimulants);
2. Current alcohol consumption that exceeds 25 standard drinks/week;
3. Positive breath alcohol concentration test (BrAC greater than or equal to 0.01) at intake;
    a. Participants testing positive for breath alcohol with a reading equal to or greater than .08 (the legal driving limit) or who are visibly impaired will be instructed not to drive themselves home after the appointment. If a participant needs to use a phone to call for a safe ride home, an office telephone will be made available to the participant.
4. A positive urine drug screen for cocaine, opiates, PCP, benzodiazepines, methadone, MDMA, amphetamine, methamphetamine, tri-cyclic antidepressants and/or barbiturates at any session;

Medication:

Current use or recent discontinuation (within the past 30 days at the time of Intake) of:

1. Smoking cessation medication (e.g., Zyban, Wellbutrin, Wellbutrin SR, Chantix, NRT);
2. Anti-psychotic medications;
3. Anti-depressants (tricyclics, SSRI's, selective and nonselective MAOIs, Wellbutrin/Zyban);
4. Anti-anxiety agents;
5. Anti-obsessive agents;
6. Anti-panic agents;

7. Prescription (e.g., Provigil, Ritalin) or over-the-counter stimulants;
8. Prescription sleep aids (e.g., Ambien, Lunesta) if used more than 2x/week. If participants report use less than twice a week, they will just be asked to refrain from use during imaging portion of the study.
9. Any medication that could compromise participant safety as determined by the Principal Investigator and/or Study Physician;

Daily use of:

10. Opiate-containing medications for chronic pain.

Medical/Neuropsychiatric:

1. Women who are pregnant, planning a pregnancy, and/or breast feeding. All female subjects of childbearing potential will undergo a urine pregnancy test at Intake and both fMRI scan visits (3 urine pregnancy tests in total).
2. History of epilepsy or a seizure disorder;
3. History of stroke;
4. Self-reported brain or spinal tumor;
5. Self-reported history or current diagnosis of psychosis, bipolar disorder, schizophrenia, current major depression (subjects with a history of major depression but in remission for past 6 months are eligible), or any Axis 1 disorder;
6. Self-reported history or current diagnosis of Attention-Deficit Hyperactivity Disorder (ADHD).

fMRI-Related:

1. Self-reported history of head trauma: loss of consciousness for 3 minutes or longer, hospitalization as a result of head injury, cognitive impairment following head injury
2. Self-reported brain (or CNS) or spinal tumor;
3. Self-reported use of pacemakers, certain metallic implants, or presence of metal in the eye as contraindicated for fMRI;
4. Self-reported history of claustrophobia;
5. Being left-handed;
6. Color blindness;
7. Weight greater than 275 lbs at intake;
8. Self-reported history of gunshot wounds;
9. Any impairment preventing participants from using the response pad necessary for the cognitive testing;
10. Circumstances or conditions that may interfere with magnetic resonance imaging (MRI).

General Exclusion:

1. Any medical condition, illness, disorder, or concomitant medication that could compromise participant safety or treatment, as determined by the Principal Investigator;
2. Low or borderline intellectual functioning – determined by a score of less than 85 on the Shipley Institute of Living Scale (SILS) (administered at Intake Visit). The SILS correlates with the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Estimated IQ Test;
3. Enrollment or plans to enroll in another research study;
4. Inability to provide informed consent or complete any of the study tasks as determined by the Principal Investigator.

5. Vulnerable Populations

Children (under age 18), pregnant women or prisoners are not included in this research study.

6. Populations vulnerable to undue influence or coercion

Educationally or economically disadvantaged persons are included but not solely targeted for recruitment. Cognitively impaired persons are not included in the current study. Because of our recruitment efforts for this study, it is possible that University of Pennsylvania employees and students may be invited to participate. Status of participation in the current study will be independent of the participant's work or school activities.

7. Subject Recruitment

Participants may be recruited from TV/radio advertisements, mailings, Craigslist.org/Internet advertisements, Experiments@penn, flyers, and/or from our database of previous participants who have agreed to be re-contacted for future studies. Interested participants will complete a telephone screen to assess initial eligibility. Those who are initially eligible will be screened against our registration database to confirm that they are not currently participating in another research study at our Center and have not previously reported a condition or circumstance that would make them ineligible for the current study. Participants who are initially eligible during a telephone screening will then attend an Intake Visit during which the purpose and procedures of this study will be described to them and final eligibility will be confirmed.

Referral Bonus Program:

Participants who successfully achieve Pre-Quit Visit (PQV) will be given the opportunity to receive a small bonus for referring others to the program. If the person who is referred completes the initial eligibility phone screen, regardless of outcome, the study participant will be awarded $20 per referral, for a maximum of 3 referrals ($60). When the participant achieves their PQV they will be provided with informational flyers to give to any interested parties. These flyers will include study contact information and a unique identifying number that will help our team track the referral and properly compensate the participant. This has been successfully implemented in IRB protocols #828125 and #824504.

STUDY DESIGN

1. Phase

Not applicable

2. Design

Main Study

The proposed study is a prospective observational neuroimaging investigation utilizing a pre-treatment abstinence challenge and fMRI assessment to elucidate the mechanisms underlying smoking relapse. As shown in **Figure 1**, 200 eligible consenting smokers will be scanned on two separate occasions prior to the scheduled target quit date (week 4): once during smoking satiety and once after 24 hours of biochemically confirmed abstinence (order counter-balanced). The pre-treatment scans will both include a resting BOLD MRI scan and a BOLD fMRI scan while performing validated tasks probing working memory, cue reactivity, and stress reactivity. Participants will have an individual pre-quit counseling session (week 3), and will be counseled and monitored (with biochemical confirmation) for 6 months post target quit date, with the addition of a 12 month Follow-up survey completed remotely.

Recruitment & Retention Pilot

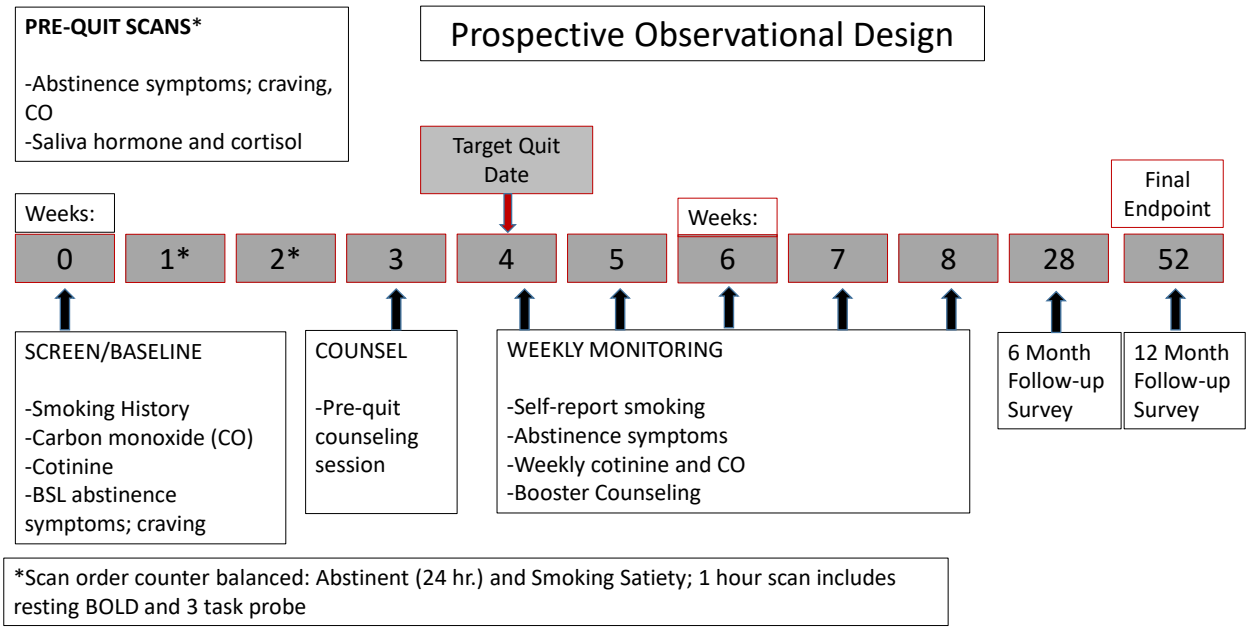
This pilot study will utilize a randomized controlled trial design to evaluate two components of behavioral economic strategies to improve recruitment and retention. To be eligible for the pilot study participants must meet all eligibility criteria for one of the four participating studies (828958, **824061**, 824860, 828125), have a phone capable of receiving SMS messages, and consent to receive SMS messages. ~576 participants will be enrolled across the four

participating research studies. All subjects will receive standard text messages and will be randomized to one of four groups (blocked within each study to ensure balanced groups): (1) Standard recruitment (SR): subjects will receive text messages ~2 days prior to their Intake visit with relevant information about the time, date, and location of the visit as well as contact information for study staff ("You have a study visit on [Date] at [Time]. Visit comp is $10. Reply Y to confirm. See http://j.mp/2222222 for reminders. Reply or appt may be canceled."); (2) SR + Information Provision (IP): Subjects will receive personalized messages designed to target injunctive norms regarding participating in research (e.g., "[Name], wondering why you should volunteer for research? Many find it a rewarding way to advance science and be a part of a community http://j.mp/2222222."); (3) SR + Contingency Management (CM): CM will be provided in the form of an opaque "lottery jar" with a high proportion of chips with little ($1) monetary value. Participants draw from the lottery jar upon completion of an objectively verified target behavior (e.g., attending an Intake visit), and bonuses are often provided for continued performance [74, 75]. This strategy has been successful in augmenting visit compliance in several treatment studies [80-82]. All text reminders will be delivered using the Way 2 Health (W2H) software platform. Upon completion of all requirements for a given visit, participants will receive 5 lottery jar draws for that visit. Attendance at all visits earns participants bonus draws upon completion of the study. Failure to attend a visit without prior approval or failure to complete all visit requirements results in no draws for that visit. The lottery jar contains 500 chips: 250 say "good job," 219 have a value of $1, 30 have a value of $5, and 1 has a value of $100. The study completion bonus will be 5 extra draws. Thus, at each visit, subjects will have the opportunity to make 5 draws from the lottery jar, for maximum possible earnings of $120; (4) SR + IP + CM (IC): In this group, subjects will receive the targeted text messages and receive CM. The design of our study allows us to examine each strategy independently as well as combined to evaluate the optimal approach.

3. Study Duration

Enrollment will begin in June 2016. Based on the accrual projections described previously, we anticipate enrollment lasting through January 2021 (56 months). Each participant will initially required to be in the study for approximately 7 months. Recruitment & Retention Pilot Study will conclude when all participants have completed the study. For pariticpants who complete all study visits up to and including the Pre-Quit Visit, their participation will last for approximately 12 months (~52 weeks). Participants who complete up to and including the Pre-Quit Visit will complete a remote survey of their smoking and eating practices a minimum of 48 weeks after their TQD (see figure 1).

Figure 1.



DRUGS OR DEVICES

Not applicable.

STUDY PROCEDURES

1. Procedures

Telephone Screening: Potential participants will be screened by an experienced research technician to determine initial study eligibility. If the subject meets preliminary telephone eligibility criteria he/she will be invited to attend an Intake visit.

Visit Reminders: Participants will receive study visit reminders 24 – 48 hours prior to their scheduled study visits by text via the W2H software platform. Participants who cannot receive text reminders or who do not agree to receive text reminders will still be able to participate and will receive reminders via phone call or email.

Way to Health (W2H) is a software platform developed by the Penn Center for Health Incentives and Behavioral Economics (CHIBE), operated through a partnership between CHIBE and the Penn Medicine Center for Health Care Innovation and housed on Penn Medicine Academic Computing Services (PMACS) servers. W2H is an integrated, cloud-based platform that blends behavioral science with scalable digital technology to improve clinical outcomes. W2H automates many research functions necessary for conducting randomized controlled trials of healthy behavior interventions.

Intake (week 0): (Visit duration 2.5-3hrs) Participants will:

1. Hear a study description where all study procedures will be reviewed. Participant questions will be answered. Following this presentation, the combined informed consent and HIPAA form will be completed;
2. Complete a urine drug screen (at least 30ml [two tablespoons] of urine). The urine drug screen will assess the use of any study-prohibited medications/recreational drugs (See

Key Exclusionary Criteria; Alcohol/Drugs). Participants who test positive for any exclusionary medications or recreational drugs will be deemed ineligible;
3. Self-administer a CLIA-waived urine pregnancy test (female participants of childbearing potential only). Participants who believe that they may be pregnant are instructed to discontinue participation at this time;
4. Perform a BrAC assessment to control for alcohol consumption. Participants with a BrAC greater than or equal to 0.01 at Intake Visit will be ineligible;
5. Participants will be asked to perform a CO breath assessment to verify smoking status. Participants with CO readings less than 8 parts per million (ppm) will be ineligible.
6. Complete a brief medical history form with a trained staff member; for female participants, this form will include brief questions regarding menstrual cycle phase and hormonal contraception use.
7. Complete Shipley Institute of Living Scale (SILS) IQ test. Participants earning less than an estimated WAIS-R IQ score of 85 will be ineligible;
8. Complete demographics and smoking history (smoking rate, nicotine dependence, age at smoking initiation, childhood adverse events) and paper and pencil questionnaires (craving, withdrawal, mood, intention to quit smoking, impulsivity and anxiety);
9. Complete the Magnet Safety Form and Emergency Contact Form as required for scheduling fMRI scans;
10. Provide a saliva sample for baseline Nicotine Metabolite Ratio (NMR) assessment.

Participants will be asked to refrain from using any study prohibited drugs (note – participants are allowed to take prescription medicines not in the exclusion list) throughout their participation in the study.

fMRI Scanning Sessions (Weeks 1 & 2). All participants will have two imaging sessions prior to their target quit date (week 1 & week 2). Both scan sessions will be identical except for the participant smoking status. One scan will be after 24 hours of abstinence (acceptable range = 18-30 hours) and the other after smoking as usual. Visits on scanning days can be scheduled at any time of day, as long as the second scan is within a 3-hour window +/- of the first scan. Including the 1hr fMRI scan, these visits are expected to be ~4hrs in duration.

24-hour Abstinent Scan: Participants will be contacted ~48 hours prior to the scheduled abstinent scan to remind them not to smoke for 24 hours prior to the scan visit. The timing of cessation for each subject will be based on the scheduled scan time (e.g., if the scan is at 10 a.m., they will refrain from smoking after 10 a.m. on the prior day).

Smoking as Usual Scan: Participants will be contacted ~48 hours prior to the scheduled smoking-as-usual scan and instructed to smoke as usual prior to their visit. To standardize smoking across participants, they will smoke a cigarette about 30-40 minutes prior to the fMRI scan.

At both scans participants will:
1. Complete a urine drug screen (at least 30ml [two tablespoons] of urine). The urine drug screen will assess the use of any study-prohibited medications/recreational drugs (See Key Exclusionary Criteria; Alcohol/Drugs). Participants who test positive for any exclusionary medications or recreational drugs will be deemed ineligible.
2. Complete a urine pregnancy test (female participants of childbearing potential only). Self-administer a CLIA-waived urine pregnancy test (female participants only). Participants who believe that they may be pregnant are instructed to discontinue participation at this time;

3. Complete a CO breath assessment. This CO screen is to confirm that participants are in the appropriate nicotine state for that session.
    a. For the abstinent scan, participant's CO reading should be less than 8ppm or a 50% reduction from the baseline CO level (taken at the Intake Visit) to confirm that participants are compliant with the smoking requirements for this session.
    b. For the smoking session, participant's CO reading should be greater than or equal to 8ppm to confirm that participants are compliant with the smoking requirements for this session. A CO reading as low as 7ppm will be acceptable if there is a viable explanation (for example, the participant has a cold that day). If the CO readings do not meet the ranges provided here, they will be excluded from the study and forfeit future compensation.
4. Complete a BrAC assessment to control for alcohol consumption. Participants with a BrAC greater than or equal to 0.01 at either scan will be ineligible;
5. Provide a salivary cortisol sample for baseline cortisol assessment; to control for change in sex hormone levels between sessions, male and female participants will provide a saliva sample to measure levels of testosterone and estradiol.
6. Complete self-report questionnaires (mood, withdrawal, anxiety and cravings) and a magnet safety form;
7. Complete a set of abbreviated practice tasks similar to those that will be administered during the fMRI scan. Participants will be required to demonstrate understanding of the tasks, the response device, and complete one practice trial just prior to each scan;
8. Be escorted to the Center for Functional and Magnetic Resonance Imaging and Spectroscopy (CAMRIS) for the brain-scanning portion of the session;
9. Smoke one of their own cigarettes in a designated smoking area outside of the building where the fMRI scanner is located (for the smoking session only). This will be done ~30 minutes prior to the scan and will standardize the timing of cigarette exposure for all participants before they begin the fMRI scan. Upon entering the MRI facility, participants will provide a CO sample;
10. Provide second salivary cortisol sample immediately prior to getting into the scanner;
11. Undergo a resting BOLD scan followed by a BOLD fMRI scan while completing the working memory, cue reactivity and stress reactivity tasks. Total scan time, including the anatomical scan, will be under one hour (See **Table 1**).

Scanning Protocol/Data Acquisition: MRI is performed in a 1-hour session, which, in our experience, participants tolerate easily without discomfort or excessive motion. Subjects are placed supine in the scanner, wearing earplugs to muffle noise, and fitted with adjustable foam cushions to limit head motion. If a participant requires corrective lenses for vision, but does not have contact lenses, a set of plastic glasses that are approved for use in an MRI scanner will be provided to him/her. Participants will be provided with an emergency squeeze ball, so that they may interrupt the scan and/or be removed from the scanner if necessary. Head fixation will be assured through a foam-rubber device mounted on the headcoil.

TABLE 1: MRI Session

Duration (mins.)	Activity
5	Structural Scans (localizer, MPRAGE)
6	Resting State fMRI
13	Fractal N-Back Task**
2	2-item smoking urges
10	Cue Reactivity Task**
5	2-item smoking urges Pre-scan stress rating Saliva Cortisol sample #3
10	MIST (stress task)**
5	2-item smoking urges Post-scan stress rating Saliva Cortisol sample #4
56	**Total**
Total Time in Scanner: ~56m **Items presented on screen with response pad for answers	

fMRI tasks will be presented in a fixed order, starting with the working memory task and ending with the stress task. This is necessary to reduce carryover of stress effects on brain responses. Stimuli will be rear projected to the center

of the visual field using a PowerLite® 7300 Video projector system (Epson American, Inc., Long Beach, CA) and viewed through a mirror mounted on the head coil. Participants will use a fiber optic response pad (FORP™ Current Design, Inc., Philadelphia, PA) made of non-ferromagnetic components. This MR-compatible button-box is used to record task responses and reaction times. Pulse and respiration are recorded as an index of physiological arousal during the task and to statistically reduce the effects of physiological noise in the fMRI data.

Image acquisition is performed on a 3T Siemens Tim-Trio scanner with a FDA approved head coil. A T1-weighted multi-echo magnetization-prepared, rapid acquisition gradient echo (MPRAGE) structural image is acquired using standard parameters at 1mm resolution. This MPRAGE is used for functional image co-registration and transformation into standard template space. Resting BOLD fMRI will be obtained followed by the three task paradigms. Data will be exported directly to our data analysis cluster and a DVD copy of the data will be made as backup.

Resting State fMRI: Whole-brain functional MR images will be acquired while subjects rest with eyes closed over 39 axial, interleaving, 4-mm sections by means of a gradient-echo echo planar imaging sequence (150 volumes; echo time/repetition time, 27/2000 milliseconds; flip angle, 80°; field of view, 220 x 220 mm; image matrix, 64x64).

Task fMRI: BOLD images will be acquired using a whole-brain, single-shot gradient-echo (GE) echo-planar imaging (EPI) sequence with the following parameters: TR/TE=2000/30 ms, flip angle 90°, field of view (FOV)=192 mm, matrix = 96X96, isotropic voxel resolution 2.5 mm, slice thickness/gap=2.5/0mm, 38 slices axial-oblique parallel to AC-PC. In ongoing studies we find these parameters produce robust signal in ventral brain regions including ventral striatum and orbital/ventral prefrontal cortex with little distortion or signal loss.
Working Memory: We will use a well validated N-back task [39, 40]. The 0-back condition serves as an active baseline in the GLM analyses and working memory load is modeled parametrically. This task produces robust activation in the DLPFC (BA 9, 46), dorsal cingulate/medial prefrontal cortex (MF/CG, BA 6, 32), bilateral superior parietal lobules and deactivation in the posterior cingulate cortex (PCC) and ventral medial prefrontal cortex (vmPFC) [25, 27, 30, 39]. The primary outcomes will be left DLPFC and PCC signal change. Total task time: ~13 min.

Cue Reactivity: Subjects will view smoking-related (n = 20), neutral (n = 20), and target images (animals, n = 4) in randomized order, separated by a jittered inter-trial interval (6-14s). Participants are instructed to press a button on the response device whenever they see a target image. Subjective smoking cravings will be assessed immediately before and after the task. Total Task Time: ~10 min.

Immediately prior to the stress reactivity task participants will be asked to provide their third salivary cortisol sample.

Stress Reactivity: The Montreal Imaging Stress Task (MIST) is a well validated fMRI task [42]. The MIST visual interface presents a mental arithmetic problem, a virtual rotary dial for response selection, a feedback window (“correct,” “incorrect” or “timeout”) and two performance indicators: 1) individual subject’s overall performance and 2) average performance of all subjects. In the experimental condition (stress induction), the time allowed is calculated based on the subject’s previous performance and represented by a progress bar. For the control condition, mental arithmetic is presented at a comparable level of difficulty but without time restriction and neither the individual nor average performance are displayed. The time between tasks is varied as a function of the time limit imposed during the experimental condition, and total number of problems presented per condition is similar. A resting condition is included during which the response interface is displayed but no problems presented or response required. The task is administered in two 5-min blocks and between each block the subject is

given scripted negative feedback regarding their performance (e.g., the subject is told they must maintain a required minimum performance close to the average performance of all subjects if data are to be useful [42]). Total Task Time: ~10 min.

Following the fMRI scanning portion of the visit participants will provide another 3 salivary cortisol samples and complete the 2-item smoking urge questionnaire and stress rating 3 times in addition to a final set of questionnaires about mood, craving and withdrawal effects; immediately following the conclusion of the MIST, 15 minutes post-scan and 30 minutes post-scan. After the final salivary cortisol sample collection the session will end and participants will be free to leave.

fMRI Back-up Scheduling (week 1). Some participants may choose to be scheduled as a back-up for another participant's fMRI scan. This is done to ensure that this protocol is efficiently using the time that is reserved on the fMRI scanner. Participants who are scheduled as a back-up should prepare for their back-up scan visit in the same way that they would prepare for a primary scanning visit. On the day of the back-up, scan participants should arrive at the Center in the smoking state that they have been assigned to for their Scan 1. Upon arrival participants will go through the same visit check-in to verify eligibility for the visit.

If the primary participant for that day attends their visit and is eligible to proceed then the back-up participant will be compensated $25 for their time and will be able to leave the center and will attend their Scan 1 visit as scheduled. If the primary participant for that day becomes ineligible for any reason or does not attend their visit the back-up participant will be promoted to primary and will continue on with the appointment as their scan 1. Participants who are promoted to primary will then be compensated as per the usual Scan 1 compensation plan.

Pre-Quit Counseling (~week 3). Participants will schedule their pre-quit session after completing the second MRI scanning session. During this visit participants will have their carbon monoxide (CO) assessed and will complete paper and pencil questionnaires (PANAS, MNWS, QSU & TLFB) in addition to attending a 1-hour semi-structured individual (in person) smoking cessation counseling session. Training and quality assurance measures will be established to ensure optimal delivery of the smoking cessation protocol. We will review audiotapes of sessions for the first 2 months of the trial and randomly throughout the trial to ensure protocol adherence and to prevent intervention drift. Counselor adherence to the treatment protocol will also be facilitated by use of highly structured protocols. The counseling session begins with a discussion of reasons for quitting, the model of smoking as a learned habit, triggers for smoking, and trigger management. Participants will receive brief training in how to manage withdrawal symptoms and relapse prevention counseling (e.g., identifying high risk situations or triggers to smoke, being prepared for and coping with high risk situations, limiting access to cigarettes, managing a slip and preventing a relapse, developing a personal relapse prevention plan, and managing a complete relapse). Smokers will also receive the NCI Clearing the Air self-help smoking cessation booklet. Counseling sessions may be recorded (audio) to ensure every participant is receiving the same standard of counseling. Participants will be informed if a counseling session is being recorded. The recording will be deleted after it is reviewed.

Monitoring Visits During 30-Day Abstinence Period (~Weeks 4-8). Beginning with the target quit date (TQD) (week 4) and weekly thereafter (weeks 5, 6, 7, 8), participants will attend a brief center visits. During the first week following TQD there will be two monitoring visits to closely monitor abstinence. These visits can be scheduled any time between 8am and 7pm. The entire session will last about 45 minutes.

The target quit date session will be scheduled to occur up to 2 weeks following the pre-quit session. Prior to the booster counseling sessions, self-reported smoking will be assessed (time line follow back, CO, saliva cotinine and urinary cotinine); we will also administer self-report questionnaires (e.g., smoking urges, withdrawal and mood). Days to relapse (primary outcome) will be defined as number of consecutive days prior to 7-day relapse (7 consecutive days of smoking). Participants will then meet with a smoking cessation counselor for a 15 minute booster counseling session. Participants will receive small monetary incentives for each week of biochemically confirmed abstinence based on CO level (<=5ppm) and/or urine cotinine assessment (NicAlert, Nymox Pharmaceutical Corporation, Hasbrouck Heights, NJ) that also indicates no smoking during the past 7 days ($75/week). Participants will be paid in cash after abstinence has been verified (and will not be paid for a missed visit). There is a $50 bonus for participants who have attended at least 4 of the 5 in-person monitoring visits. Telephone assessments and counseling may be provided if participants miss a visit, at the discretion of the PI.

6 Month Follow-up (~Week 28). Participants who are biochemically verified to be quit at MV5 will be contacted 24 weeks post TQD by telephone to complete a brief survey of their smoking practices using the timeline follow-back assessment. Those who report not smoking a cigarette for at least the past 7 days prior to completing the survey will be asked to come to the Center for biochemical verification of smoking status by providing CO, saliva cotinine and a urine cotinine sample.

12 Month Follow-up (~Week 52). Participants who completed all visits up to and including the Pre-Quit visit will be contacted 48 weeks post TQD by telephone to complete a brief survey of their smoking practices and eating behavior. All measures collected at the 6 Month Follow-up will be collected with the addition two questions about readiness and intention to quit smoking (if applicable).

Table 2. Measures and Time Points

Activity	Phone Screen	Intake	fMRI Scans	Pre-Quit	TQD	MV 1-5	Follow-up	12-month Follow-up
Weeks	-1	0	1, 2	3	4	5, 6, 7, 8	28	52
Demographics		X						
Urine drug screen		X	X					
Urine pregnancy screen		X	X					
ETOH history/BrAC		X						
Height		X						
Weight		X						
Smoking behavior (FTND)		X						
Medical history form		X						
Shipley Institute of Living Scale		X						
Psychiatric hx		X						
Adverse Childhood Experiences Questionnaire		X						
Intention to quit smoking		X						
Impulsivity		X						
Anxiety			X					
Magnet safety form		X	X					
Emergency contact form		X						
Saliva NMR		X						
Salivary cortisol (nmol/l)			X					

Salivary estradiol pg/mL			X					
Salivary testosterone pg/ml			X					
fMRI								
Resting BOLD			X					
Working Memory (Fractal N-back)			X					
Cue Reactivity			X					
Stress Reactivity			X					
Primary Outcomes								
Carbon monoxide (CO)		X	X	X	X	X	X	
Urine Cotinine						X	X	
Saliva Cotinine						X	X	
Smoking rate (TLFB)		X	X	X	X	X	X	X
% Eligible at Intake (pilot)		X						
Secondary Outcomes								
Mood (PANAS)		X	X	X	X	X	X	X
Withdrawal (MNWS)		X	X	X	X	X	X	X
Smoking urges (QSU-B)		X	X	X	X	X	X	X
Attitudes toward research (pilot)	X				X		X	
Compared riskiness scale (pilot)	X	X						
Perceived coercion scale (pilot)		X						
Previous experience research studies (pilot)	X							
Prior persuasion questions (pilot)		X						
Personal financial wellbeing (pilot)	X							
Previous experience research studies (pilot)	X							
Intention and Readiness to Quit Smoking								X

Measures

Screening/Covariates:

Demographics: Standard surveys will collect demographics (e.g., age, education, race, and gender).

Urine Drug Screen: A urine sample will be collected at all study visits to conduct a urine drug screen. The urine drug screen indicates whether the subject has recently taken any of the following drugs or medications: THC, cocaine, opiates, PCP, benzodiazepines, methadone, MDMA, amphetamine, methamphetamine, tri-cyclic antidepressants, OxyContin and/or barbiturates. Participants with a positive urine drug screen for any exclusionary substance will be deemed ineligible (See Key Exclusionary Criteria; Alcohol/Drugs). In an effort to remain CLIA-compliant, results from urine drug screening will not be shared with participants. Participants will be informed that the testing is for research purposes only and that they will be informed of their eligibility status, but not of the specific testing results.

Urine Pregnancy Test: At the Intake and both fMRI scanning sessions female participants of childbearing potential will be supplied with a simple, CLIA-waived urine pregnancy screen and informed that pregnant women are not advised to participate in this research study. Participants will then be instructed to administer the pregnancy test independently and will inform study staff

if they would like to continue participation after they have administered the pregnancy screen. Participants will be informed that there is no penalty for discontinuing participation at this point in the visit and that they will still be provided with their preferred travel coverage.

ETOH History: ETOH history will be administered at the Intake Visit and will ask subjects about their alcohol consumption over the past 7 days.

Breath Alcohol Concentration: The BrAC assessment will be administered at all study visits. The breath alcohol monitor is a handheld device that uses a disposable mouthpiece and reports the concentration of alcohol in exhaled breath. Any reading > 0.000 indicates alcohol consumption within the last 14 hours. Participants with a BrAC greater than or equal to 0.01 at the Intake Visit will be ineligible. Participants who have a BrAC reading greater than or equal to 0.01 at Intake or either scanning visit may be ineligible to continue with the visit and will only be rescheduled/allowed to proceed with the study at the discretion of the Principal Investigator.

Smoking Behavior: At the intake visit, participants will complete the 6-item Fagerstrom Test for Nicotine Dependence (FTND) [43] and a smoking history assessment which includes age at first cigarette, age at regular (daily) smoking, and current smoking rate. Number of cigarettes smoked in past 24 hours and time of last cigarette will be recorded at each visit.

Medical: Height and weight will be measured and recorded. All participants will complete a medical history form with a trained staff member to review for all contraindications listed previously.

Shipley Institute of Living Scale: All participants will complete the Shipley Institute of Living Scale (SILS) at the Intake Visit. The scale consists of two subtests: a 40-item vocabulary test and a 20-item test of abstract thinking. The total administration time is 20 minutes (10 minutes per subtest). A trained member of the study staff will score the test. The SILS correlates with the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Estimated IQ Test; those participants earning less than an estimated WAIS-R IQ of 90 will be ineligible. The SILS is considered a highly reliable assessment tool, with a good total score internal consistency (Cronbach's alpha=.92) [44].

Psychiatric History: History or current diagnosis of psychosis, major current depression or bipolar disorder, ADHD, schizophrenia, or any other DSM-IV Axis 1 psychiatric disorder will be determined based on self-report during the medical history.

Adverse Childhood Experiences Questionnaire: The occurrence of adverse experiences during childhood will be assessed using the Adverse Childhood Experiences Questionnaire [45]. Adverse childhood events are associated with health and social problems as an adult and may influence measures collected in this study.

Intention to Quit Smoking: Intention to quit smoking in the next 3 months will be assessed using two items: "how likely to attempt" and "how likely to succeed" rated on a 4-point Likert scale (1 = "I definitely will not", 4 = "I definitely will"; Chronbach's alpha = 0.89; [46]).

Impulsivity: Impulsivity will be measured with the Barratt Impulsiveness Scale Version II [47]. This reliable measure has been shown to be a better predictor of ability to abstain from smoking than other similar measures [48].

Magnet Safety Form: A standard assessment form created by the Department of Radiology at the Hospital of the University of Pennsylvania will be completed by the participant at the Intake

visit and before entering the scanner at each fMRI scan session. It assesses history of specific prosthesis, surgical implants, and other MRI contraindications.

Emergency Contact Form: A form used to collect emergency contact information in the event of an emergency at the fMRI scanner.

Saliva NMR: Saliva samples will be collected at intake and analyzed for levels of nicotine metabolites (cotinine and 3'-hydroxycotinine). The ratio of 3'-hydroxycotinine to continine (nicotine metabolite ratio, or NMR) provides an estimate of the individual rate of nicotine metabolism, and has been associated with quit outcomes [30] and individual differences in neural responses during abstinence [49].

Salivary cortisol: Salivary cortisol will be used to confirm that the MIST produced a stress response [33, 50, 51]. Cortisol (nmol/l) will be collected at multiple time points during the scan visit: baseline (~45 min before scan), immediately before entering the scanner, immediately before the MIST, immediately following the MIST, and 2 additional post-scan recovery time points (15 min and 30 min post-scan; [52]). Approximately 1.5-2 mls of saliva will be collected at each time point using a cotton swab which subjects will be instructed to place between their tongue and cheek for approximately 2-3 minutes until the swab is completely saturated (Salivette, Sarstedt Inc.). The saliva swab will then be placed in a plastic tube and stored at –20°C. Saliva samples will be assayed using salivary high sensitivity cortisol enzyme immunoassay (EIA) kits (Salimetrics LLC, State College, PA, USA). Salivary cortisol is highly correlated with plasma cortisol [53].

Salivary estradiol: Salivary estradiol will be used to control for between-session differences that may occur due to change in estradiol levels in male and female female participants. Estradiol (pg/ml) will be collected at the start of the scan session. Approximately 2 mls of saliva will be collected using a passive drool method and saliva collection aid (Salivette LLC, State College, PA, USA). The saliva will be stored in plastic vials at –20°C. Saliva samples will be assayed using 17-β estradiol EIA kits (Salimetrics LLC, State Collect, PA, USA). Salivary estradiol is highly correlated with plasma estradiol [54].

Salivary testosterone: Salivary testosterone will be used to control for between-session differences that may occur due to change in testosterone levels in male and female participants. Testosterone (pg/ml) will be collected at the start of the scan session. Approximately 2 ml of saliva will be collected using a passive drool method and saliva collection aid (Salivette LLC, State College, PA, USA). The saliva will be stored in plastic vials at –20°C. Saliva samples will be assayed using testosterone EIA kits (Salimetrics LLC, State Collect, PA, USA). Salivary testosterone is highly correlated with plasma testosterone [55].

fMRI Measures: See fMRI Scanning Sessions above.

Primary Outcomes (Main Study): Multiple measures of abstinence will be measured for this study. The primary outcome will be the number of days to relapse following the target quit date. Relapse will be confirmed using a conventional SRNT guideline criterion of either a positive biochemical verification of smoking [3, 56] or 7 consecutive days of smoking based on self-report (it is very unlikely that a subject would meet the latter criterion without also meeting the former, given the long half-life of cotinine). The days to relapse will be based upon time from target quit date to the first day of the relapse period. Self-reported daily smoking data will be collected using a validated timeline follow-back method [57]. Self-reported abstinence will be biochemically verified on a weekly basis using urine cotinine (<100ng/ml) [56] and a CO reading

of ≤5PPM. Drop-outs will be considered relapsers following the last date of abstinence data provided [7, 58]. Secondary outcomes will include days to first "slip", and cross-sectional measures of 7-day and 30-day point prevalence (biochemically verified weekly with cotinine, which provides an assessment of smoking in the last 7 days).

Carbon Monoxide (CO): The CO monitor is a handheld device that uses a disposable mouthpiece, reports CO in parts per million (ppm), and takes about 5 minutes to administer. Carbon monoxide measurements will be collected from smokers at each visit as a biochemical verification of smoking exposure.

Urine Cotinine: Smoking status will be assessed with NicAlert™ urine dipsticks from Nymox Pharmaceutical Corporation. A midstream urine sample of approximately 25mL will be used to test for the presence of cotinine. Results will appear in one of seven category levels of usage. Level 0 indicates no detectable tobacco use; levels 1-2 indicate presence of cotinine, but as a non-user, and levels 3-6 indicate cotinine consistent with tobacco use. Participants with results in levels 3-6 will be considered smokers. Urine cotinine will be assessed at all Monitoring Visits 2-5, if participant has reported weekly abstinence.

Saliva Cotinine: Saliva cotinine will be collected to biochemically verify smoking status. Saliva samples will be collected at monitoring visits 2-5 from participants who report smoking abstinence and have a CO value of less than or equal to 5ppm.

Primary Outcomes (Recruitment & Retention Pilot Study):

Meeting Eligibility Criteria: The primary outcome is the percentage of subjects who meet final eligibility criteria (i.e., enrollment). We chose this as the outcome based on our data suggesting that subjects who meet these criteria are highly likely to reach ITT status.

Secondary Subjective Outcomes (Main Study):

Mood: Positive and Negative Affect: The Positive and Negative Affect Schedule (PANAS) [59], a 20-item Likert-format self-report measure, will be used to assess Positive Affect (PA; 10 items, e.g., enthusiastic, strong) and Negative Affect (NA; 10 items, e.g., distressed, upset), two dominant and generally orthogonal dimensions of affect.

Nicotine Withdrawal: The Revised Minnesota Nicotine Withdrawal Scale (MNWS-R) [60] is a fifteen-item self-report measure where participants rate their feelings of withdrawal on a scale of 0 (none) to 4 (severe). This measure will be administered at all study visits.

Smoking Urges/Craving: The 10-item brief QSU-B questionnaire on smoking urges [61] will be administered at the same time points to assess cravings to smoke. The QSU-B contains 2 subscales (anticipation of reward, relief from negative affect). During the fMRI scans (prior to and following the cue reactivity task), participants will also be asked to rate the severity of their urges to smoke using two 4-point Likert scale items: "cravings for a cigarette" and "urges to smoke at this time" (0=not present, 3=severe). These 2 items have been related to smoking cessation outcomes [62] and resting cerebral blood flow in our prior study [63], and are feasible to assess as a brief measure in the MRI scanner.

Stress/Anxiety: Anxiety will be measured at both fMRI scanning sessions using the State-Trait Anxiety Index [64], which has been used as a covariate in fMRI studies of stress response [52].

Participants will be asked to rate "how stressed do you feel right now" on a scale from 0-100 immediately before and after the MIST.

Readiness/Intention to Quit Smoking: two questions will be asked at the 12-month follow-up survey to assess readiness to quit smoking and intention to quit smoking. The readiness questions is asks on a Likert scale from 1 – 9 the participant's current thinking about smoking (1 = taking action to quit, 9 = no though of quitting). The intention to quit smoking questions asks how likely the participant is to try to quit in the next 30 days on a Likert scale from 1 -- 4 (1 = very unlikely, 4 = very likely). The two questions will be asked regardless of study-quit status.

Secondary Subjective Outcomes (Recruitment & Retention Pilot Study):

Impressions of Research: Attitudes towards research; motivations for participation; perceived risks/benefits of research; personal financial wellbeing and perceptions of influence or coercion will be assessed via text survey at baseline (following phone screen), mid-way through participation and at study completion. Study staff will attempt to contact subjects who withdraw or are lost-to-follow up to identify reasons for withdrawal. We will assess overall satisfaction with the study, acceptability of the frequency and content of messages (IP and IC groups only). For all models, a term will be included for individual study as well as other relevant covariates (e.g., sex, age, income).

2. Statistical Analysis

Data Screening*:* Prior to performing analyses, standard data screening/cleaning procedures will be applied. These procedures will (a) screen the data for data-entry errors, (b) check for outliers, (c) assess the extent and pattern of missing data, (d) create all summary scores needed for analysis, and (e) check that appropriate distributional assumptions are met. Assumptions will be examined using standardized residuals, influence diagnostics, and graphical displays. We will employ image quality assessment procedures to examine global and ROI-based raw and processed temporal signal-to-noise ratio, absolute and relative motion, and signal spike count. Subjects with potential outliers (>2 SDs above mean) will be flagged to determine if the time-series is valid, and if so it will remain. Otherwise it will be corrected or removed from the analysis. The final sample will be examined in a similar fashion to determine whether any subjects warrant data cleaning or exclusion from the final analysis. All analyses will be conducted using Stata software (STATA Corporation, College Station, Texas).

Missing Values: We will examine the characteristics of those subjects who drop out to identify any associations between dropout and baseline measures. These analyses will be descriptive, as we expect few dropouts. Items missing at random on survey measures will be imputed prior to calculating final scores using conditional means, estimated with a version of Buck's method [65]. The analyses will also be repeated using only complete observations to assure that parameter estimates are not impacted by imputation.

Task fMRI: fMRI preprocessing will use standard algorithms in FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl) including distortion correction, slice-time correction, motion correction, spatial smoothing, high-pass filtering (120s) and co-registration to the MPRAGE. fMRI preprocessing will also include removal of physiological noise related to in-scanner pulse and respiration measures using RETROICOR. After preprocessing, basic subject-level BOLD time series analysis will be carried out using the general linear model (GLM) in FSL, using a canonical double-gamma hemodynamic response function (HRF) for convolution, and linear contrasts to estimate task-specific BOLD responses for each individual. Temporal derivative and extended motion parameters will be included in models when appropriate. For the block-design

N-back task, analysis will focus on the parametric effect of increasing working memory load across four levels (linearly modeled [-3 -1 1 3]). For the cue reactivity task, the primary contrast will be smoking cues>neutral cues. For the stress task, the primary contrast will be stress > control blocks.

Subject-level statistical image maps will be transformed into a common anatomic space (Montreal Neurological Institute, MNI) for group-level analysis. Session (abstinence vs. smoking) whole brain, voxelwise analyses will test abstinence effects in brain regions specified above. The peak voxel in each significant cluster will be used to assign appropriate anatomical labels. Percent signal change within significant clusters will utilized in regression models described below. Age, self-reported ethnicity, nicotine dependence severity (FTND), and withdrawal symptom severity will be included as covariates in the relevant statistical models. For all tests, significance will be determined using cluster $p<.05$ and voxel-height $Z>2.33$.

Aim 1: Modeling of Days to Relapse:
The outcome associated with Aim 1 is censored time to event and the predictors are continuous measures (difference scores) extracted from ROIs associated with each neurobehavioral domain. We will test this hypothesis within each domain (working memory, cue reactivity, and stress) using Cox regression; the test statistic will be the z-score corresponding to the hazard ratio, with significance corrected for the total (8) cross domain ROIs. We will also test baseline clinical predictors and abstinence challenge-related performance measures (difference scores) for entry into each of the domain specific models.

Aim 2: Integrated Brain-Behavior Model:
We anticipate that abstinence-induced deficits in working memory in the Left DLPFC will predict time to relapse, as will brain responses to cues and to stress. We predict that the effect of brain responses to cues (two regions) and to stress (three regions) on days to relapse is moderated by abstinence-induced deficits in left DLPFC activity. Provided that left DLPFC deficit shows some importance in Aim 1 ($p<0.2$), we will enter the main effect into the cue and the stress models of relapse. Further, we will test interactions of left DLPFC working memory deficit with ROIs in the cue and stress models that have also shown promise in Aim 1 ($p<0.2$). Interactions will be tested at alpha=0.05 using the z-score corresponding to the ratio of hazard ratios (HRR).

Power and Sample Size Considerations:
Power analyses were conducted using PASS v 13.0 (Power and Sample Size, NCSS, Kaysville, UT). For Aim 1 we considered three neurobehavioral domains containing a total of 8 ROIs (predictors). We expect that predictors will be correlated, and therefore pure Bonferroni correction is too conservative [66]. In our preliminary data, within domain (e.g. working memory) correlation falls between 0.5 and 0.6 but between domains (e.g. working memory, cue reactivity) the correlation is weaker. Accounting for this weak inter-correlation, we will set alpha at $p<0.0085$. A sample of 200 participants provides 80% power to detect a one-sample effect size of 0.25, or a hazard ratio of 1.32. Effect sizes (Cohen's d for a one-sample test) observed in our prior study [30] ranged from 0.245-0.297.

Recruitment & Retention Pilot Study:
Power is provided for our primary aim. The analysis will compare the enrollment rates between the four intervention arms, and examine main and interaction effects. For SR arm, we expect a 28% of subjects who schedule an Intake will be eligible and enroll (based on existing data across the four studies). With the proposed sample of 576, we have >80% power ($\alpha=.05$) to detect a difference between the SR arm and the IP and CM arms of 12%, corresponding to an OR of 1.75. For the interaction term, we have 80% power ($\alpha=.05$) to detect a departure from additivity of the main effects corresponding to a ratio of odds ratios (ORR) of 5.5.

3. Confidentiality

Confidentiality of the data generated in this study shall be maintained in the following ways:

1. All participant information will be kept in a secure filing cabinet that is accessible only to authorized study personnel.
2. All databases containing participant information will be password protected, and again, accessible only to authorized study personnel.
3. Any study communications made by e-mail will use ID numbers only and never include names or any other personal information.
4. All data sets will use ID numbers only. A separate data set subject map table linking names with ID numbers will be accessible only by authorized personnel.
5. Audio and/or video recordings will be transcribed and then destroyed to eliminate audible identification of subjects.
6. Participant electronic re-consent for the 12 month Follow-up Survey will be stored on REDCap along with all measures collected for the 12-month Follow Up Survey. These measures are identical to the measures collected during the 6-month Follow Up Survey (See Table 2 above) with the addition of the two quitting related questions (see secondary objective outcomes above).

Since self-report and biological data will be collected and stored as part of this study, it is possible that subject privacy or confidentiality can be threatened. To address this concern, the data management system has set up several safeguards to prevent unauthorized access to participant data. In the subject map table, an automatically generated index number is assigned to a subject's study identification number. A linked subject identification table is created to store subject name, address, and telephone contact information. This table uses the automatically generated index number rather than the study identification number. The master subject map and subject identification information are maintained in separate locations. Using this method, no identifying subject information is directly linked to bio-samples or results. Any publication of data will not identify participants by name or with an identifier that could be used to reveal identity.

All biological samples will be labeled with study ID only. All subject data that can be linked to the study ID will be stored in the secure data management system, which has limited, password-required access. The aforementioned precautions and procedures will be applied to protecting subject privacy and the protected health information detailed in Section 4 below.

The PMACS will be the hub for the hardware and database infrastructure that will support the project and is where the W2H web portal is based. W2H uses a role-based access control (RBAC) approach to assure that participant confidentially and study integrity is preserved. The PMACS provides a secure computing environment for a large volume of highly sensitive data.

4. Subject Privacy/Protected Health Information

The following protected health information (PHI) may be collected as part of this study:

1. Name
2. Street address, city, county, zip code
3. All elements of dates (except year) for dates directly related to an individual and all ages over 89
4. Date of birth
5. Social Security Number
6. Telephone number, email address
7. Results from all questionnaires, tests, and procedures
8. Saliva samples for NMR assessment, cortisol assessment, estradiol assessment, and testosterone assessment

9. Any other unique identifying number, characteristic, or code

Potential participants will be contacted over the phone after responding to recruitment efforts. Only individuals who have responded to recruitment efforts or who have agreed to be contacted regarding research studies at our Center will be contacted. If an individual cannot be reached immediately, staff members will identify themselves only as calling from the University of Pennsylvania; no mention will be made of the inquiry regarding study participation. Participants will undergo an initial phone screening where preliminary eligibility for the research study will be determined. Only if a participant is initially eligible, will they attend an in-person Intake Visit to confirm eligibility. All data collected over the phone and during in-person visits will be collected by research staff that have completed the CITI Protection of Human Subjects Research Training as well as HIPAA Compliance Training. Any study communications made by e-mail will use ID numbers, only and never include names or other personal information. In all data sets we will use ID numbers only. A separate list of names with ID numbers will be accessible only by authorized personnel. All testing, medical and psychiatric interviews will be conducted individually in dedicated testing and evaluation rooms to protect participant privacy. All records will be kept in locked filing cabinets to maintain confidentiality. Results will not be communicated to other personnel or to the subjects. Data will be accessible to the Study Investigators, Study Physician, study staff, UPenn IRB, Office of Clinical Research and authorized UPenn staff (e.g. accounting and billing matters, provide treatment, etc.).

5. Tissue Specimens

Urine: A urine sample will be required at the Intake Visit and every scan session for drug and pregnancy screenings. Additional urine samples will be required for Monitoring visits for biochemical verification of smoking status (cotinine). These samples will be disposed of following the conclusion of every study visit.

Saliva NMR: ~2ml saliva samples will be collected at Intake for NMR assessment.

Saliva Cortisol: Additional ~2ml saliva samples will be collected at both fMRI scanning visits to assess for cortisol levels at 6 points throughout the visit.

Saliva estradiol and testosterone: Additional ~2ml saliva sample will be collected at both fMRI scanning visits to assess estradiol and testosterone level.

6. Genetic Testing

Not Applicable.

RISK/BENEFIT ASSESSMENT

1. Potential Study Risks

The potential risks to participants, and their likelihood and seriousness, are described below. Participants can choose, as an alternative, to not enroll in this study. Overall, there is minimal risk for serious adverse reactions as a consequence of enrolling in this study. Adverse reactions will be assessed and reported as required by Federal law and UPenn regulations.

Withdrawal Syndrome: Many individuals who abstain from smoking exhibit a pattern of symptoms related to withdrawal from tobacco use. These symptoms include: sadness and anxiety, irritability, anger, difficulty concentrating, appetite change and weight gain, insomnia, and decreased heart rate. Eliminating the risk for these would not be possible, although in most cases these events are short-lived and have low intensity. Study staff will be trained to

recognize these symptoms and educate the participants about them (e.g., their duration, methods for reducing them).

fMRI: The known MRI-related risks associated with this study are minimal. All sequences and RF coils will be approved by CAMRIS prior to utilization. Because of the strong magnetic field, people with pacemakers, certain metallic implants, or metal in the eye cannot participate in this study. These exclusions will be reviewed carefully with the study staff prior to scanning.

The greatest risk with MRI is a metallic object flying through the air toward the magnet and hitting the participant. To reduce this risk we require that all people involved with the study remove all metal from their clothing and all metal objects from their pockets. No metal objects are allowed in the magnet room at any time. In addition, once the participant is in the magnet, the door to the room will be closed so that no one inadvertently walks into the magnetic field. Although there are no known risks of MRI on pregnant women or a fetus, there is a possibility of yet undiscovered pregnancy related risks. Since there is no direct benefit from participating in this protocol for a pregnant woman, women of child bearing potential will be supplied with a simple, CLIA-waived urine pregnancy screen to self-administer at each scan visit, and will be advised that we recommend that pregnant women do not participate in the study. They will then be instructed to administer the pregnancy test independently and will inform study staff if they would like to continue participation after they have administered the pregnancy screen. Participants will be informed that there is no penalty for discontinuing participation at this point in the visit and that they will still be provided with their preferred travel coverage.

There is no known health risk associated with exposure to magnetic fields during an MRI. There are minimal risks from the loud noise associated with the MRI scanner and from the discomfort of lying on a hard surface. Participants will be provided with protective earplugs as necessary and every attempt will be made to ensure comfort with blankets, etc. during the scan.

The levels of energy used to make magnetic resonance measurements are far less than are used in a single X-ray, and many patients have been safely studied using magnetic resonance techniques. However, some people become uncomfortable or claustrophobic while inside the magnet. If participants become uncomfortable, they may withdraw immediately from the fMRI portion of the study. During some of the MRI scans, participants have occasionally reported “tingling” or “twitching” sensations in their arms or legs, especially when their hands are clasped together. To prevent this, all participants will be instructed to keep arms and legs apart.
The imaging component of this study is part of a research protocol, and is not intended to provide a comprehensive clinical fMRI examination of the brain. In the event that a significant brain abnormality is observed while processing subject brain images for the research study, the images will be reviewed by a radiologist. There will be no charge to the subject for this examination of their images. A report will be filed in the subject’s chart at the Center. The subject will be contacted and Center staff will arrange for the radiologist’s report and structural images to be sent to the subject and/or their physician. Subjects will also be offered a consult with the study physician. These possible finding(s) may or may not be significant and may lead to anxiety about the subject’s condition and to further work-up by the subject’s physician.

Assessments: The MIST task has the potential to induce mild stress; however, in our preliminary study of 40 participants no adverse psychological consequences were reported. Nonetheless, we will take several steps to minimize this risk after each scanning session. To maintain fidelity of the manipulation between repeated sessions, subjects will not be fully debriefed until after the second fMRI scan. However, on each scan day the research staff will assess the participant’s current stress level immediately after the fMRI scan and just before they

leave the appointment. Anyone reporting elevated stress at the end of the visit will be evaluated by study PI and, if necessary, debriefed regarding their MIST performance. Following completion of the second fMRI scan, participants will be debriefed regarding all aspects of the MIST. They will be told that the task designed so the problems would be difficult for them and that the task did not assess their actual mathematical ability. Subjects will also be told that the feedback they received from the experimenter was scripted and also not reflective of their true ability. In addition, subjects will be asked not to share this information with others who may participate in the study.

Email Communications: In this research study participants may prefer to receive appointment reminders via email or submit questions related participation via email. Email is not a secure means of communication. Email messages travel across the Internet passing through multiple computers before reaching their final destination. It is not possible to know whether an email a participant sends will be viewed along the way. Additionally, if sent messages are not deleted, an email provider may have an archive of everything that is sent. If someone gets access to an email account (for example, a participant's family member), they could see archived messages. There are many other ways in which emails are not secure—these are only selected examples. To manage this risk the informed consent form will include specific language to educate research participants on the privacy risks involved in email communications. Participants will also be explicitly instructed to only use email communications for routine matters and never for personal or confidential messages or questions.

Threats to Privacy/Confidentiality: See description in Section 3 (Confidentiality) and 4 (Subject Privacy/Protected Health Information) above.

2. Potential Study Benefits

Participants will be provided with smoking cessation counseling as part of the study protocol and will have the opportunity to reduce or quit smoking.

3. Alternatives to Participation

The alternative to participation is to decide not to enroll in this study.

4. Data and Safety Monitoring

During the course of the study, data and safety monitoring will be performed on an ongoing basis by the Principal Investigator, project staff, and the IRB. The project staff are responsible for collecting and recording all clinical data. This includes ensuring that all source documents exist for the data on the case report forms, ensuring all fields are completed appropriately, and all corrections are done according to Good Clinical Practice (GCP's). Any inconsistencies/deviations will be documented. Project staff will perform regular chart reviews to verify data integrity. Project staff will meet on a regular basis to reconcile data queries. The IRB will review the trial on an on-going basis.

Unanticipated Problems, AE, and SAE Definitions.

Unanticipated Problems Involving Risk to Subjects or Others:

Any incident, experience, or outcome that meets all of the following criteria will be considered an unanticipated problem in the current study:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, FDA approved labeling, etc)

- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event:
An ***adverse event*** (AE) is a subcategory of the broader category of "Unanticipated problems Posing Risk to Participants or Others" and is defined as any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:
- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Any event that could be characterized by the definitions above is an AE **whether or not considered related to the study.**

Serious Adverse Event:
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:
- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but based upon appropriate medical judgment may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious. All adverse events that do not meet any of the criteria for serious will be regarded as ***non-serious adverse events***.

Collection and Recording of AEs and SAEs.
Adverse Events and SAEs will be collected by spontaneous self-report.

Research staff are trained to inquire (time of onset, nature of issue reported, possible relation to study, review of previously reported side effects or concerns, concomitant medications, severity/intensity, etc.) about any notable side effects or medical concern reported by participants. Side effects will be rated by participants utilizing the following severity scale: 0 (None=No Concerns), 1 (Mild=Side Effect or event does not interfere with usual daily activities), 2 (Moderate= Side effect does interfere with some activities), and 3 (Severe=No normal activities are possible). Any severe (or a pattern of modern) side effects or notable medical concerns will be reported to the Project Manager, Study Physician, and Principal Investigator to determine a course of action and relationship (causality) to the study procedures. This

consultation, including all relevant information will be documented via email. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

Information surrounding AEs and SAEs are recorded and secured within the appropriate source documents (i.e. subject chart), Case Report Forms (e.g. SEC form, etc.) when applicable, an AE note or SAE report, and the AE/SAE log within the Study Administrative File.

Documentation of AEs will include the following information:

- Protocol name
- Subject identifier
- Description of the event
- Date and time of onset and outcome
- Intensity/Severity
- Action taken
- Relationship (causality) to the study
- Outcome

Documentation of SAEs will include the following information:

- Protocol name
- Subject identifier
- Description of the event
- Date and time of onset
- Current status
- The reason why the event is classified as serious
- Action taken
- Investigator assessment of the association between the event and study treatment
- Welfare of subjects/Outcome
- Follow-Up Plan (if applicable)

Management of SAEs or Other Study Risks.
The Study Physician will oversee the management of all SAEs and other study risks. SAEs will be monitored closely until the event has been stabilized and/or the subject has been referred to the care of their primary care physician. The Study Physician will also review data collected during the medical history portion of the Intake Visit for all subjects who experience a SAE and, when required, will provide follow-up consultation with the participant. All instances of consultation will be recorded.

AE, SAE, and Unanticipated Problems Reporting.
The procedures for unanticipated problem, adverse event, and serious adverse event reporting are consistent with NIH and UPenn-specific guidelines and are as follows:

1. Alert the IRB of any and all reports of unanticipated problems involving risk to subjects or others, AEs, and SAEs when appropriate (i.e. within 10 business days, summary at continuing review, etc.). AEs and SAEs meeting reportable event/unanticipated problem guidelines (unexpected and related) will be submitted to the appropriate IRB within 10 business days of occurrence using the on-line system. If an AE/SAE involved a death and indicates that participants and others are at an increased risk of harm, the event will be reported to the IRB within 3 days.
2. Inform applicable members of the study team of any and all reports of adverse events.

In addition to unanticipated problems (including applicable AEs and SAEs), the following events will be promptly reported to the IRB within 10 business days:

1. Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).
2. Any adverse event that would modify the protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.
3. Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
   - An interim analysis indicates that subjects have a lower rate of response to treatment than initially expected.
   - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
   - A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
4. Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
5. Breach of confidentiality.
6. Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
7. Incarceration of a subject when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
8. Complaint of a subject when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
9. Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more subjects at increased risk, or affects the rights or welfare of subjects.

5. Management of Information for Multi-center Research where a Penn Investigator is the Lead Investigator of a multi- center study, or Penn is the lead site in a multi-site study.
Not applicable.

6. Risk/Benefit Assessment
Research staff will monitor subjects closely during their participation. Thus, the risk to benefit ratio for this project is perceived to be low and justifies its implementation.

SUBJECT COMPENSATION

Participants will be compensated for the time and effort required to complete study procedures. Participants will be given the means to travel to and from their appointments at no cost to them. Participants will be given two options for travel coverage: 1) participants may elect to receive a flat rate of $10/day to cover their travel expenses to and from the center or 2) participants may elect to use a round-trip ride service (i.e. Lyft.) which will be arranged and paid for in full by the research study. If participants choose to use the ride service, they will not receive $10 for their travel reimbursement.

Participants will be eligible for compensation only if they complete the visits/assessments listed below (Table 3). Participants who are found ineligible for any reason during Study Visits will only be provided $10 for their time, in addition to their preferred travel coverage for that session. Participants who withdraw partway through a session (other than the Intake session) may receive prorated compensation for that session. Through participation in this research study participants are estimated to earn up to $810 in visit compensation. If the participant elects to use the ride service, all travel will be paid for by the research study. If the participant elects to travel to and from their appointments independently, they will be reimbursed $10/visit ($120 over the course of the study) to put towards their travel expenses.

Recruitment and Retention Pilot: Upon completion of all requirements for a given visit, participants randomized to CM will receive 5 lottery jar draws for that visit. Attendance at all visits earns participants bonus draws upon completion of the study. Failure to attend a visit without prior approval or failure to complete all visit requirements results in no draws for that visit. The lottery jar contains 500 chips: 250 say "good job," 219 have a value of $1, 30 have a value of $5, and 1 has a value of $100. The study completion bonus will be 5 extra draws. Thus, at each visit, subjects will have the opportunity to make 5 draws from the lottery jar, for maximum possible earnings of $120 per visit.

Participants will be paid in cash for intake visits. At the baseline visit participants will be issued a Greenphire ClinCard, which is a reloadable, pre-paid card for the purposes of compensation. Compensation will be loaded onto the ClinCard at the end of successfully completed visits. Participants may opt to receive a text message alert when a payment has been loaded onto the Clincard.

TRAVELING VIA THE RIDE SERVICE

Participants may elect to use "Roundtrip", which is a ride service that partners with Lyft to coordinate roundtrip rides to appointments. Study staff will schedule each ride by using the participant's first and last name, and phone number via Roundtrip's HIPAA compliant platform. Participants will receive a reminder 24-48 hours prior to their appointment to confirm their appointment. Participants will receive a second reminder call to notify them of their pickup time, and to confirm important details pertaining to their round-trip ride. If the study staff cannot reach the participant by 5pm the day prior to their appointment, their ride may be cancelled. If the participant confirms their appointment after 5pm the day prior to their appointment, they will still be permitted to attend the visit and will receive $10 to cover their travel expenses if they attend. If a participant needs to cancel a previously confirmed ride, they must do so by contacting the study staff directly, preferably by 5pm the day prior to their appointment. Participants who fail to notify the study staff within this timeframe may no longer be permitted to utilize the ride service at future study visits

Table 3. Study Compensation

Time Point	Study Week	Session Length	Visit Compensation	Quit Incentives[2]	Completion Bonus	Total Estimated[6]	Travel Reimbursement[5]	Lottery Jar[7]
Intake	0	~3hrs	$10	N/A	N/A	$10	$10	5 draws
Scan 1	1	~4hrs	$90	N/A	N/A	$90	$10	5 draws
Scan 2	2	~4hrs	$90	N/A	N/A	$90	$10	5 draws
Back-up Scan[1]	1	~45min	$15	N/A	N/A	($15[1])	$10	5 draws

Pre-Quit Visit	3	~1.5hrs	$20	N/A	$70[2]	$90	$10	5 draws
Target Quit Date	4	~45min	$20	N/A	N/A	$20	$10	5 draws
Monitoring Visit 1	5	~45min	$10	$35[3]	N/A	$45	$10	5 draws
Monitoring Visit 2	5	~45min	$10	$40[3]	N/A	$50	$10	5 draws
Monitoring Visit 3	6	~45min	$10	$75[3]	N/A	$85	$10	5 draws
Monitoring Visit 4	7	~45min	$10	$75[3]	N/A	$85	$10	5 draws
Monitoring Visit 5	8	~45min	$10	$75[3]	$50[4]	$135	$10	Up to 10 draws
6-Month Follow-up Phone Call	28	~15min	$35	N/A	N/A	$35	N/A	
Abstinence Verification	28	~30min	$35	N/A	N/A	$35	$10	
12-Month Follow-up Phone call	52	~15min	$25	N/A	N/A	$25	N/A	
TOTALS			$390	$300	$120	**$810**	$120	

[1] Some participants may be double booked for visits including an fMRI. This will ensure that valuable time on the scanner is not wasted. Participants that are booked as back up participants will be fully aware of their status as the backup and will have agreed to be available in the event that the primary participant does not attend the visit. If the participant is not needed for a scan on the day that they are signed up as a backup, they will earn $25 for their time and availability- and will be scheduled as a primary candidate for the next available scanning session.
[2] Participants who complete both fMRI scan visits will receive a $70 bonus at their Pre-Quit visit.
[3] In order to receive quit incentives participants must have a CO less than or equal to 5PPM at all monitoring visits and/or a NicAlert value of less than or equal to level 2 (non-user of tobacco products) MV2-MV5, depending on prior monitoring visit quit status.
[4] To earn this bonus, participants must have achieved at least 4 out of 5 monitoring visits.
[4] Participants who attend at least 4 out of 5 monitoring visits will receive a $50 completion bonus at their Monitoring Visit 5.
[5] Only applicable to participants who opt to receive $10 travel reimbursement for that visit.
[6] Maximum total compensation estimated if participant opts to utilize ride service for transportation coverage. If a participant is deemed ineligible during a study visit, they will only receive $10 for their time in addition to their preferred travel coverage.
[7] Participants will be given 5 draws from our lottery jar for the chance to earn additional monetary incentives. As a bonus for completing the study, participants will get an additional 5 draws from the lottery jar during their final visit.

INFORMED CONSENT

1. Consent Process

Participants will complete an initial eligibility assessment by phone, reducing the likelihood that participants attend an Intake Visit only to learn that they are ineligible. The phone screen poses no more than minimal risk and involves no procedures for which written consent is normally required outside of the research context. All participants who are contacted for the phone screen will have responded to an advertisement for the research study, and have therefore requested the initial phone screening call. Those interested/eligible at phone screen will be scheduled for an in-person Intake Visit (Week 0). At this Intake Visit, participants will provide written study consent and HIPAA documents (combined) before completing additional survey measures and undergoing any study related activities. Participants will receive a copy of the combined consent/HIPAA form. Hard copies of Intake Visit data and a copy of the signed

combined consent/HIPAA forms will be stored in a subject's study folder. The original signed combined consents/HIPAA will be centrally stored in Regulatory Consent Binders.

2. Electronic Re-consent for the 12-month Follow-up Survey via REDcap
Participants who previously signed a consent version prior to version 15 for the lottery condition and version 16 for the standard condition, who are classified as study completers (defined as completed all visits up to an including the Pre-Quit Visit), will be contacted at least 48 weeks after their target quit day (TQD) to complete the 12-month follow-up survey. Since the visit is a new addition to the study protocol (in V19 only), participants will be re-consented prior to administering the 12-month follow up survey. Due to the COVID-19 pandemic, seeking participant re-consent via RedCap will be utilized prior to administering measures. Current UPenn IRB guidance (revised 4/8/2020) indicates utilizing REDcap for obtaining remote consent is acceptable.

2. Waiver of Authorization.
Not applicable

RESOURCES NECESSARY FOR HUMAN RESEARCH PROTECTION

1. Research Staff
The following research staff will be directly involved with the implementation and execution of the current study:

- James Loughead, Ph.D., Principal Investigator
- John Detre, M.D., Study Physician
- Rebecca Ashare, Ph.D., Co-Investigator
- Kristin Linn, Ph.D., Co-Investigator
- Susan Ware, B.S., Database Manager
- Paul Sanborn, M.A., Samples Manager
- Wen Cao, Support Staff
- Dominique Spence, Support Staff
- Thaine Smith, Support Staff
- Cecelia Tannous-Taylor, Support Staff
- Brianna Soreth, Support Staff
- James Padley, Support Staff

2. Staff Training
Dr. Loughead and the Project Managers will oversee the development of protocols for laboratory related tasks and training of staff in these protocols. Dr. Loughead and/or the Project Managers will be responsible for the development of procedures pertaining to all study visits and implementing and monitoring ongoing staff training procedures accordingly. An initial, intensive training period will be implemented followed by periodic in-service trainings that will be coordinated by the Project Managers. They will also oversee study progress as part of regular study meetings. All research staff will undergo training on research practices involving human subjects, including the protection of subject confidentiality, and will maintain current certification in patient oriented research.

3. Study Facilities
This project will be conducted at and through the Center for Interdisciplinary Research on Nicotine Addiction (CIRNA) at the University of Pennsylvania. The above mentioned center has numerous similar protocols and well-developed procedures for staff training, data collection and

storage, and study completion. The facilities available for this project include a large conference room, individual consulting rooms with computer/internet access, storage rooms, office space for study personnel, and data management facilities.The Magnetic Resonance Imaging Center in the University of Pennsylvania Medical Center provides all the necessary equipment and staff to conduct an fMRI investigation.

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