# *NEURAL BASIS OF EATING BEHAVIOR IN ABSTINENT SMOKERS*

NCT #:NCT03438188
Document date: 8/4/2021

Penn Medicine
University of Pennsylvania School of Medicine

# *NEURAL BASIS OF EATING BEHAVIOR IN ABSTINENT SMOKERS*

| | |
|---|---|
| **Regulatory Sponsor:** | James Loughead, Ph.D.<br>Psychiatry- Center for Interdisciplinary Research on Nicotine Addiction (CIRNA)<br>3535 Market St.-Suite 4100<br>215-746-7279 |
| **Funding Sponsor:** | National Institutes of Health (NIH) |
| **Supplement Funding Sponsor:** | NIH |
| **IRB Protocol Number:** | 828958 |
| **Version # (Date):** | Version 15 (8.04.2021) |

# Table of Contents

# 1 Introduction

This document is a protocol for a human research study. This study is to be conducted in compliance with this research protocol, as well as according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations, and institutional research policies and procedures.

## *1.1 Background – Main Study*

Tobacco use and obesity are the two leading causes of preventable deaths. Because these two behaviors share common brain reward mechanisms, reducing one behavior often leads to increases in the other behavior. Indeed, ~80% of smokers gain weight after quitting, with an average weight gain >13 lbs. in one year (vs. ~2 lbs. in continuing smokers). Weight gain is often cited as a key reason for delaying quit attempts or relapsing, making post-cessation weight gain (PCWG) *a significant clinical problem*. While a variety of pharmacological and behavioral interventions to reduce PCWG have been tested, these tend not to be effective. To develop better treatments, we need to understand *why* people gain weight after quitting smoking.

Behavioral Economic and Incentive Salience models shed much light on this clinical problem. Smoking cessation produces reward dysregulation that can alter the motivational salience of other reinforcers, particularly food. After stopping smoking, smokers increase their between-meal snacking, especially foods high in fat and sugar. Increases in caloric intake occur within days of quitting smoking, and are clinically significant. In parallel, we have shown that smoking cessation produces working memory deficits and reduces activity in the brain's cognitive control circuits, making it even more difficult to exert self-control over temptations to eat highly rewarding foods. Thus, smokers have a double challenge: food becomes more salient and reinforcing at a time when their neurocognitive resources are compromised.

Neuroimaging can identify mechanisms underlying behavior change beyond self-report and behavioral measures. The proposed functional magnetic resonance imaging (fMRI) study breaks new ground by integrating concepts and tools from the fields of behavioral economics and cognitive neuroscience to accelerate the study of mechanisms underlying PCWG. We will use a previously validated within-subject crossover neuroimaging study design to examine changes in working memory, food salience (cue-induced craving), and food reinforcement processes in the brain after 4 days of smoking cessation (vs. smoking as usual). A non-smoker control group will provide insight into baseline differences from smokers (abstinent and satiated). Caloric intake, the primary outcome, will be assessed using 24-hr. food recalls during each study period. We will assess three parallel pathways including: working memory, food cue reactivity, and food reinforcement at the neural and behavioral levels.

## *1.2 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 Study Objectives

## 2.1 Main Study

**Aim 1:** To test three putative brain mechanisms underlying increased caloric intake during nicotine withdrawal using an abstinence challenge paradigm (within-subject).

**H1a**: Brain signal will be associated with decreased working memory (WM) in the dorsolateral prefrontal cortex (DLPFC) and reduced suppression of activity in the posterior cingulate cortex (PCC).

**H1b**: There will be increased food cue-induced activity in the insula, anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), and ventral striatum/nucleus accumbens (VS/NAC).

**H1c**: Increased food reinforcement choice-related activity in VS/NAC and ventromedial prefrontal cortex (vmPFC) will predict increased caloric intake (abstinence vs. smoking).

**Aim 2:** To evaluate the relative contribution of task-related brain signal (WM, Food Cue Response, Food Reinforcement/Choice) in prediction of nicotine abstinence-induced increase in caloric intake (within-subject).

**H2a:** Brain responses (H1a-c) will characterize abstinence challenge-induced change in caloric intake more accurately than clinical (age, sex, nicotine dependence, BMI), subjective (craving, withdrawal), and behavioral performance measures alone.

**H2b:** The relative contribution of domain-specific brain signal (WM, food cue reactivity and food reinforcement) to the prediction of abstinence challenge-induced increase in caloric intake will be evaluated (regression model).

**EXPLORATORY AIM (between group):** To provide a baseline comparison in food-related brain response between smokers and non-smokers.

This study will: (a) drive new insights about how the brain can constrain or promote the ability of smokers to prevent PCWG; and (b) lead to new theories and interventions that integrate neural and behavioral frameworks important for promoting behavior change. Support for our predictions would inform testing of novel approaches to prevent PCWG, such as computerized neurocognitive exercise training to increase DLPFC activity and shift activity away from reward sensitive brain networks.

### *2.2 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.*

# 3 Study Design

### *General Design – Main Study*

This is a within-subject cross-over neuroimaging investigation of 3 potential neural mechanisms of increased caloric intake during initial smoking cessation. Eighty smokers will be scanned on 2 occasions: (1) after 4 days of monitored abstinence (biochemically verified), and (2) after 4 days of smoking as usual (order counterbalanced) (**Figure 3**). In addition, 30 healthy non-smokers (matched for sex, age, and education) will complete one period of the study to serve as a baseline comparison group (see Exploratory Aim). As in prior studies, participants will have fasted overnight and be provided with a standard meal (BOOST® shake) when they arrive on testing days 4 and 32. Blood oxygen level dependent (BOLD) fMRI sessions will assess BOLD signal at rest and while performing tasks for food cue reactivity, food reinforcement (choice task), and working memory (N-back). Additional measures will be administered out of scanner (**Figure 3**). Caloric intake will be assessed on days 1-3 and 29-31 using a validated dietary recall procedure (days 4 and 32 are fMRI scan days and intake will be standardized). Caloric intake is the primary behavioral outcome. Task-induced BOLD signal change in hypothesized regions of interest and performance on the working memory, food cue, and food reinforcement tasks are the mechanistic variables.

Figure 3

Non-smoker Control Group (Baseline):

| Day | -7 | 1 2 3 4 |
|---|---|---|
| Activity | Intake | Period 1* |

*non-smokers complete phase 1 with identical monitoring and assessment
**order of periods (abstinence vs smoking) is counter balanced

Smoker Group (within-subject):

| Day | -7 | 1 2 3 4 | 5-28 | 29 30 31 32 | 1 Month Follow-up |
|---|---|---|---|---|---|
| Activity | Intake | Period 1 | Washout | Period 2 | Web-based Survey |
| State | Smoke | Abstain** | Smoke | Smoke | N/A |

Behavioral Outcome:
- Caloric intake (dietary recall; Days 1-3* & Days 29-32)

Intermediate Outcomes: Day 4* & Day 32
- Food reward (out of scanner)
- Working memory (fMRI)
- Food cue reactivity (fMRI)
- Food reinforcement (fMRI)

Smoking Behavior: Days 1-4* and 29-32
- Self-reported (CO-verified)

***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 "fishbowl" with a high proportion of chips with little ($1) monetary value. Participants draw from the fishbowl 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 fishbowl 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 fishbowl 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 fishbowl, 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.

### *3.1 Study Duration*

Recruitment/enrollment is anticipated to begin in January, 2018 and will continue for ~48 months. We estimate that up to 110 participants will have completed the study by January, 2022. We estimate that it will take ~8 weeks/2 months for a participant to complete the in person component of the study, with the Follow-up survey occurring 1 month after study completion. Recruitment & Retention Pilot Study will conclude when all participants have completed the in-person visits for the study.

# 4 CHARACTERISTICS OF THE STUDY POPULATION

## *4.1 Target Population*

#### 4.1.1 Smoking Sample

Participants will be 80 healthy males and females between the ages of 18-65 who have smoked at least 5 cigarettes per day for the past 6 months,

#### 4.1.2 Control Group

The non-smoking control group will consist of 30 individuals aged 18-65 reporting less than 100 lifetime cigarettes and not even a puff of a cigarette for a minimum of 2 years.

## *4.2 Accrual*

We will enroll ~375 participants (i.e. provide consent) in order to have 148 participants eligible at the in-person intake. Of the ~148 anticipated eligible participants we expect that ~40% will attend all fMRI scans and complete the study (~80 smoking & 30 non-smoking participants). We plan to achieve this goal over a 48 -month enrollment period (3-4 participants/month). Accrual estimates are based on our extensive experience conducting neuroimaging studies and specifically recruitment of fMRI subsamples from larger clinical trials.

In order to increase retention throughout the study, we will: (1) educate subjects about the benefits of participation and the knowledge gained from the study; (2) schedule sessions at times convenient for participants; (3) provide reminders; and (4) provide payment for completion of all study visits. As is the convention in smoking cessation trials, smokers who are lost to follow-up will be included in the analysis and counted as smokers.

## *4.3 Inclusion Criteria*

1. Male and female participants who are between 18 and 65 years of age.
    1. Smoking group – 80 smokers who self-report smoking at least 5 cigarettes (menthol and/or non-menthol) per day for at least the last 6 months. Smoking status will be confirmed by CO greater than or equal to 8 parts per million (ppm) at the Intake Visit.
    2. Non-smoking group - 30 individuals reporting fewer than 100 lifetime cigarettes and not even a puff of a cigarette for a minimum of 2 years. Smoking status of non-smokers will be confirmed by CO less than 5ppm. They will be matched to the smoker group on age, sex, and education.
2. Plan to live in the area for the duration of the study (i.e. ~8 weeks/2 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 (i.e. speaking, writing, and reading).

### *4.4 Exclusion Criteria*

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

Smoking Behavior

1. Regular use of nicotine-containing products other than cigarettes (e.g. chewing tobacco, snuff, snus, cigars, e-cigs, etc.). Participants agreeing to abstain from using nicotine-containing products other than cigarettes will be considered eligible.
2. Current enrollment or plans to enroll in another research and/or smoking cessation program over the duration of the study (i.e. ~8 weeks/2 months).
3. Anticipated use (within the next ~8 weeks/2 months) of any nicotine substitutes and/or smoking cessation treatments/medications unless provided through the study.
4. Provide a CO breath test reading less than 8 ppm at Intake Visit (smokers) or greater than 5ppm at intake visit (non-smokers).

Alcohol and Drug

1) History of substance abuse (other than nicotine) in the past 12 months and/or currently receiving medical treatment for substance abuse. Counseling and support groups (e.g. Alcoholics Anonymous and Narcotics Anonymous) will not be considered medical treatment for the purposes of this protocol.
2) Current alcohol consumption that exceeds 25 standard drinks/week.
3) Breath alcohol reading (BrAC) greater than .000 at the Intake Visit.
    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 (UDS) for cocaine, opiates, amphetamines, methamphetamines, phencyclidine (PCP), ecstasy (MDMA), barbiturates, benzodiazepines, methadone, and/or oxycodone at the Intake Visit.

Medical

1. Women who are pregnant, breast feeding, or planning a pregnancy over the duration of the study period. Women must agree to use an adequate form of contraception or abstain from sexual intercourse for the duration of the study.
2. Current treatment of cancer or diagnosed with cancer (except basal or squamous-cell carcinoma not treated with chemotherapy and/or radiation) in the past 6 months.
3. Poorly controlled, brittle, or pump-dependent Type I diabetes.
4. Current peptic ulcer bleeding.
5. Active hepatitis or poorly controlled kidney and/or liver disease.
6. Serious or unstable disease within the past 6 months. Notable diseases will be evaluated on a case-by-case basis by the Principal Investigator and/or the Study Physician.
7. Any impairment including, but not limited to, visual, physical, and/or neurological impairments preventing proper completion of the study procedures. Notable impairments will be evaluated on a case-by-case basis by the Principal Investigator and/or the Study Physician.
8. Applicable food allergies or disorders:
    - Galactosemia [a]
    - Notable milk allergy (lactose intolerant participants may proceed unless they experience severe symptoms) [b]
    - Notable soy allergy [c]
    - Peanut allergy [d]

[a,b,c] Boost® Original Very Vanilla Nutritional Shake: Contains milk and soy ingredients. Suitable for Lactose Intolerance.
[a,b,c,d] M&M's® (Milk Chocolate): Contains milk and soy ingredients (MAY CONTAIN PEANUTS)
Lay's® Classic Potato Chips (Gluten Free): Potatoes, vegetable oil, and salt

Psychiatric

1. Current diagnosis of major depression. Subjects with a history of major depression, in remission for 6 months or longer (may be stable on antidepressant medications), are eligible.
2. Lifetime history of a suicide attempt.
3. Lifetime history of schizophrenia, psychosis, and/or bipolar disorder.
4. Current diagnosis of Attention Deficit/Hyperactivity Disorder (ADHD).
5. Current diagnosis of bulimia, anorexia nervosa or binge eating.

Medication

Current use or recent discontinuation (within the last 14 days) of:

1. Smoking cessation medication (e.g., Zyban, Wellbutrin, Wellbutrin SR, Chantix).
2. Benzodiazepines and/or Barbiturates.
3. Anti-psychotic medications.
4. Prescription stimulants (e.g., Provigil, Ritalin, Adderall).
5. Systemic steroids.
6. Medications for the use of addiction treatment.

Current use of:

7. Nicotine replacement therapy (NRT).
8. Heart medications such as digoxin, quinidine, and nitroglycerin.

Daily use of:

9. Opiate-containing medications for chronic pain.
10. Inhaled corticosteroids.

Subjects will be instructed to refrain from using any study-prohibited drugs/medications (both recreational and prescription) throughout their participation in the study. After final eligibility is confirmed, subjects who report taking contraindicated medication(s) over the course of the study period may only remain eligible if the Study Physician and Principal Investigator determine that the contraindicated medication(s) do/did not significantly impact the study design, data quality, and/or subject safety and welfare. Subjects are permitted to take necessary prescription medications not included within the exclusion list during the study.

General Exclusion

1. Past, current, anticipated, or pending enrollment in another research program over the study period that could potentially impact subject safety, study data, and/or the study design as determined by the Principal Investigator and/or Study Physician.
2. Participation in a dietary program within the past 30 days.
3. Any medical condition, illness, disorder, adverse event (AE), or concomitant medication that could compromise participant safety or significantly impact study performance as determined by the Principal Investigator and/or Study Physician. Subjects may be deemed ineligible for any of the aforementioned reasons at any point throughout the study, as well as during the initial telephone screen.
4. Significant non-compliance with protocol and/or study design as determined by the Principal Investigator and/or Study Physician. Subjects may be deemed ineligible at any point throughout the study.
5. Low or borderline intellectual functioning – determined by receiving a score of less than 80 on the Shipley Institute of Living Scale (SILS), which correlates with the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Estimated IQ Test.

fMRI Exclusion Criteria

1. History of claustrophobia.
2. Lifetime history of stroke.
3. Having a cochlear implant or wearing bilateral hearing aids.
4. History of notable head trauma. Although notable head trauma is typically defined as being knocked unconscious for a period of three minutes or longer, notable head trauma will be evaluated on a case-by-case basis by the appropriate personnel prior to an eligibility decision, considering exceptions can be made based on the nature and severity of the trauma.
5. History of brain or spinal tumor.
6. Pacemakers, certain metallic implants or objects, or presence of metal in the eye as contraindicated for MRI.
7. Any circumstances (e.g., exclusionary metal implants, certain dental work, and/or physical impairments) and/or conditions that may interfere with MRI and MRI-related study visit procedures. All potential exclusionary circumstances and/or conditions will be evaluated on a case-by-case basis by the appropriate personnel prior to an eligibility decision.
8. History of gunshot wounds. Injuries from BB guns will be evaluated on a case-by-case basis by the appropriate personnel prior to an eligibility decision.
9. History of epilepsy and/or recurrent or uncontrolled seizures.
10. Weight greater than 275 lbs at Intake Visit or self-reported at phone screen. If a participant weighs less than or equal to 275 lbs at Intake, but presents with a weight greater than 275 lbs at either Scan 1 and/or Scan 2, the participant may be permitted to proceed with the scan as long as the participant's weight does not exceed 300 lbs.
11. A positive urine drug screen (UDS) for cocaine, opiates, amphetamines, methamphetamines, phencyclidine (PCP), ecstasy (MDMA), barbiturates, benzodiazepines, methadone, and/or oxycodone at intake or either Scan Visit.
12. A BrAC greater than 0.000 at intake or either Scan Visit.

### *4.5 Vulnerable Populations*

Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study. Educationally or economically disadvantaged persons are included but not solely targeted for recruitment. 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. Special protections and/or additional safeguards will be undertaken in order to protect the rights and welfare of these subject groups from coercion or undue influence as appropriate.

### *4.6 Subject Recruitment*

Participants may be recruited from television, radio, internet advertisements, newspaper, flyers, transit posters, referrals, 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. They will then attend an Intake Visit at our Center during which the purpose and procedures of this study will be described to them and final eligibility will be confirmed. Participants may complete intake session measures remotely to verify initial eligibility before an in-person visit is scheduled. All advertising materials will be submitted to the UPENN IRB for approval prior to distribution/posting.

**Referral Bonus Program**

Participants who achieve their final scans (day 4 or day 32) 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). This has been successfully implemented in IRB protocols #828125 and #824504.

### *4.7 Early Withdrawal of Subjects*

#### 4.7.1 When and How to Withdraw Subjects

Subjects are free to withdraw from the study at any time. Subjects may be deemed "ineligible" at any time per the exclusion criteria listed in section 4.5. No follow-up data collection is required for participants who withdraw or are deemed ineligible throughout the study.

## 5 Study Procedures

### *5.1 Telephone Eligibility Screen*

Individuals interested in study participation will be screened by a qualified member of the research team to determine initial study eligibility. If the participant meets preliminary eligibility, they will be invited to schedule an Intake Visit at which their final eligibility will be confirmed.

### *5.2 In-Center Visits*

In an effort to increase the safety of participant visits, while also increasing the efficiency of study procedures in light of COVID-19, study staff will be implementing electronic data collection for various study measures. Specific measures that can be collected remotely are listed below for each visit with three asterisks (***).

#### 5.2.1 Visit Reminders

Participants will typically receive study visit reminders 24 – 48 hours prior to their scheduled study visits via by text message (if applicable) 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.

#### 5.2.2 Intake Visit (~ day -14)

During the Intake Visit (Duration: ~3 hours) participants will:

1. Hear an informed consent and HIPAA presentation where all the study procedures and institutional policies will be reviewed.***
    - The combined informed consent and HIPAA form will be read verbatim. All participant questions will be answered as appropriate after which the combined informed consent and HIPAA form will be completed (signed and dated) by both the participant and a qualified member of the research team.

2. Confirm the accuracy of information (i.e. name, address, phone number, email [if applicable], date of birth, age, gender, ethnicity, and race) provided during the initial Telephone Eligibility Screen***.

Complete a UDS (at least 30ml [two tablespoons] of urine). The UDS will assess the use of any study-prohibited medications/recreational drugs (See Key Exclusionary Criteria; Alcohol and Drug).

- Participants who test positive for any exclusionary medications or recreational drugs per this protocol will be deemed ineligible.

3. Female participants only: Self-administer a CLIA-waived urine pregnancy test.
    - Female participants are informed that the participation of pregnant women in this study is prohibited and that if they believe they are pregnant they should withdraw from the study immediately.

4. Perform a BrAC assessment to control for alcohol consumption.
    - Participants with a BrAC greater than 0.000 at Intake Visit will be ineligible.
5. Perform a CO breath assessment and self-report smoking behavior over the past 24 hours to control for prior tobacco exposure.
    - Participants in the smoking group with a CO reading less than 8 ppm will be deemed ineligible.
    - Participants in the non-smoking control group with a CO reading greater than 5ppm will be deemed ineligible.
6. Complete height and weight measurements. Participants weighing over 275lbs will be excluded.
7. Complete a Medical History Form with a member of the research team to review for applicable contraindications previously listed under Inclusion and Exclusion Criteria (section 4.4 and 4.5).***
8. Complete an fMRI Medical History Form, Magnet Safety Form, and Emergency Contact Form.***
9. Complete the Shipley Institute of Living Scale IQ test.***
    - Participants earning less than an estimated WAIS-R IQ score of 80 will be deemed ineligible.
10. Complete paper and pencil questionnaires:
    - Demographics***
    - Smoking History/Nicotine Dependence (FTND)***
    - ETOH History***
    - Cigarette Brand Form (staff will record cigarette brand information)***
11. Schedule study track with a trained staff member & complete compensation paperwork.

### 5.2.3 Baseline Visit (Day -7)

Participants are asked to not consume food or caffeine for 4 hours prior to the beginning of the visit. During the Baseline Visit (Duration: ~3 hours) participants will:

1. Complete a UDS (at least 30ml [two tablespoons] of urine). The UDS will assess the use of any study-prohibited medications/recreational drugs (See Key Exclusionary Criteria; Alcohol and Drug).
    - Participants who test positive for any exclusionary medications or recreational drugs per this protocol will be deemed ineligible.

2. Perform a BrAC assessment to control for alcohol consumption.
    - Participants with a BrAC greater than 0.000 at Baseline Visit will be ineligible to proceed with the visit. The Principal Investigator may permit the participant to reschedule the visit to another day.
3. Perform a CO breath assessment & daily smoking rate (timeline follow back [TLFB]) (smokers only).
4. Self-report smoking behavior over the past 24 hours to control for prior tobacco exposure and provide their daily smoking rate (timeline follow back [TLFB]) (smokers only).
5. Have weight measured.
6. Complete paper and pencil questionnaires:
    - Withdrawal Symptoms (MNWS)***
    - Smoking Urges/Craving (QSU-B)***
    - Depression Symptoms (CES-D)***
    - Positive & Negative Affect (PANAS)***
    - Eating Behavior (DEBQ)***
    - Eating Inventory-Disinhibition (EI-D)***
    - Weight Concerns***
7. Immediately prior to the laboratory tasks, participants will be asked to rate, “How hungry are you right now?” using a scale from 0 “not at all” to 10 “extremely.”***
8. Participants will be provided with a Boost® Nutritional Drink to consume prior to completing the laboratory tasks.
9. Complete the Individualized Food (Pre-FCQ-S) task. Foods rated least appetizing (n=20) and foods rated most appetizing (n=20) will be selected to create personalized food cue stimuli for the Food Cue-Induced Craving (FCQ-S) task administered over the course of the study.
10. Select either the salty (Lay’s® Classic Potato Chips) or sweet (M&M's® [Milk Chocolate]) snack food as the snack to “work for” (Pre-RRVF) in the Relative Reinforcing Value of Food (RRVF) task over the course of the study.
11. Complete computerized laboratory tasks:
    - Food reward
    - Working memory (N-back)
12. Immediately after the laboratory tasks, participants will be asked to rate, “How hungry are you right now?” using a scale from 0 “not at all” to 10 “extremely.”***

### 5.2.4 Mandatory Abstinence Period for Smoking Group (~days 1-3 or 29-31)

Participants will be randomized with respect to the order of the study periods; one-half of participants will have their mandatory abstinence period on days 1-4 and one-half will have this period on days 29-32. On the evening prior to the mandatory abstinence period, participants will receive a 20-minute structured telephone counseling session from a trained smoking cessation counselor to prepare for the upcoming 4-day abstinence period. Quit strategies include identifying triggers and alternative behaviors to smoking, deep breathing, and stimulus control methods. The abstinence periods will be framed as “practice quit attempts” unaided by nicotine replacement therapy or other medication.

On study days 1-3 (period 1) and 29-31 (period 2), participants will come to the Center and complete measures that may include a CO reading, breath alcohol test (BrAC), and questionnaires (smoking behavior, urges, mood, withdrawal, eating). Please see measures

table for specific time points. To verify smoking abstinence participants must have a CO reading of <10ppm or >50% reduction from their intake CO value on day 1 (or 29) and a CO reading of <5ppm on days 2, 3, or 4 (or 30, 31 & 32). Participants that do not meet CO criteria, have a BrAC greater than 0.000, or a positive urine drug screen will be withdrawn from the study, unless the Principal Investigator permits the participant to reschedule the visit to a later date.

Day 1/Day 29 Back-up Scheduling: Some participants may choose to be scheduled as a back-up for another participant's Day 1 or Day 29 visit. This is done to ensure that this protocol is efficiently using the time that is reserved on the fMRI scanner days at Days 4 and 32. Participants who are scheduled as a back-up should prepare for their back-up Day1/Day 29 in the same way that they would prepare for a primary visit. On the day of the back-up, participants should arrive at the Center in the smoking state that they have been assigned to for their respective Day 1/Day 29. 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 Day 1/Day 29 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 Day 1/Day 29 session. Participants who are promoted to primary will then be compensated as per the usual Day 1/Day29 compensation plan.

### 5.2.5 Smoking as Usual Period for Smoking Group (~days 1-3 or 29-31)

Participants will be instructed to smoke as usual during this period. They will make the same visits to the Center and complete the same measures during the mandatory abstinence period. As in our prior studies, to minimize deprivation and standardize exposure on the scanning day (day 4 or 32), participants will be instructed to smoke immediately prior to entering the scanner building (accompanied by a research technician). There will be ~45 minutes between this cigarette smoked and the beginning of the imaging session in the smoking as usual period.

### 5.2.6 24-Hour Dietary Recalls:

On days 2-4 and 30-32, a trained member of the research staff will use a multi-pass method with an interactive computerized software program, the ASA24® (Automated Self-Administered 24-hour Recall), to determine total kcal/day. If participants are unable to complete a scheduled recall over the telephone or are onsite for a scheduled visit, participants may be asked to complete a 24-hour dietary recall with the research staff in-Center.

### 5.2.7 Washout Period for Smoking Group (~days 5-28)

Between study periods there is a "washout period" (days 5-28) when participants will smoke as usual. No study visits will occur during this time.

### 5.2.8 fMRI Scan Visits 1 & 2 (~days 4 and 32)

Prior to each scan, participants will be instructed to fast overnight (beginning at ~10pm) until after the completion of their fMRI scanning visit the following day. The fast period will include a Boost® Nutritional Drink (Vanilla) that will be provided during the scanning visit to standardize prior food intake and remove deprivation to increase sensitivity to changes in food reward. Since participants are asked to fast overnight, all scanning sessions will be scheduled to occur in the morning. However, a scan may be completed in the afternoon at the discretion of the Principal Investigator due to extenuating circumstances. Additionally, participants will be instructed not to consume caffeine for 4 hours prior to the beginning of the visit in order standardize satiety. Including the 1-hour fMRI scan, scanning visits are expected to last ~4 hours in duration. If a scanner hardware/software malfunction occurs and data is unable to be collected, an fMRI scan(s) may be rescheduled at the discretion of the Principal Investigator.

At both scanning visits 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 study-prohibited medications/recreational drugs will be deemed ineligible for the study at the discretion of the Principal Investigator.
2. Self-administer a CLIA-waived urine pregnancy test (female participants only). Participants who believe that they may be pregnant are instructed to discontinue participation in the study at this time.
3. Perform a BrAC assessment to control for alcohol consumption.
    - Participants with a BrAC greater than 0.000 will be ineligible to complete the study unless the Principal Investigator permits the participant to reschedule the neuroimaging scan to another day.
4. Perform a CO breath assessment
5. Self-report smoking behavior over the past 24 hours to control for prior tobacco exposure and provide their daily smoking rate (timeline follow back [TLFB]) (smokers only).
6. Have weight measured.
7. Complete a magnet safety form***.
8. Complete paper and pencil questionnaires (craving, withdrawal, mood, eating)***.
9. Complete a set of abbreviated practice tasks similar to those that will be administered during the fMRI scan. Participants will be expected to demonstrate an understanding of the tasks and the response device prior to the fMRI scan.
10. Be provided with a Boost® Nutritional Drink and water.
11. Be escorted to the imaging facility at either the Hospital of the University of Pennsylvania or the Stellar Chance building for the brain-scanning portion of the session.
12. **SMOKING SCAN ONLY**: Participants will smoke one of their own cigarettes (~45 min. before initiating fMRI) in a designated smoking area outside of the building where the fMRI scanner is located in order to standardize the timing of cigarette exposure for all participants.
13. Undergo a 1-hour fMRI scan adhering to the procedures and Table 1 below:

Scanning Protocol/Data Acquisition: MRI is performed in a 1-hour session, which, in our experience, participants tolerate easily without discomfort or excessive motion. Prior to entering the scanning area, an approved MRI Technician or MRI User will review the participant's magnet safety form and will confirm that the participant has removed all metal and/or objects containing magnetic strips from their persons. Once the participant is approved to enter the scanning area, the participant will be 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.

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.

**TABLE 1: fMRI Session**

| ~Duration (mins.) | Activity |
|---|---|
| 5 | Structural Scans (localizer, MPRAGE) |
| 10 | Resting State BOLD fMRI |
| 15 | Food Reinforcement/Choice [a] |
| 12 | Working Memory [a,b] |
| 10 | Food Cue Reactivity [a] |
| 2 | B0 Map **if time permits** |

Total Time in Scanner: ~54 minutes
[a] fMRI tasks will be presented in a fixed order
[b] Stimuli (Form A/B) will be counterbalanced within subject

Task 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.

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.

Food Cue Reactivity: The task will present (5 sec) 20 pictures of food rated (at Intake) as most appetizing and 20 pictures of food rated (at Intake) least appetizing, and 20 pictures of a water glass. Participants will be instructed to imagine tasting and eating the pictured food for as long as the food is presented. Order of presentation is randomized and the task consists of 60 events separated by an inter-stimuli interval (fixation point) ranging from 2-11 sec (mean 5.5 sec). As a secondary measure, food craving will be assessed prior to and after completion of the scan. The food craving assessment is the 3-item "desire" subscale of the reliable and valid state version of the Food Craving Questionnaire (FCQ-S). Total task time: ~10 minutes.

Food Reinforcement/Choice: Participants choose between a standard low effort monetary reward and either (on separate trials) a food or monetary reward of higher value and effort. Each trial presents a choice between a standard reward (27 button clicks for $0.25) or exerting greater effort to earn a larger reward. In half of the trials, larger rewards will be $0.50 (2 x standard value). In the remaining trials the larger reward will be double the calibrated snack portion (e.g., 20 M&Ms). Effort for more valuable rewards will vary from 27 to 775 responses in 25 log10 steps. Pairs of visual stimuli depicting the two options appear for 4.5 sec followed by a 3-14 sec inter-trial interval. Each pairing is presented twice, making 50 trials for each class. Left/right position of stimuli is randomized, as is trial type (monetary vs. food; effort levels). To increase motivation to choose food and monetary reward, participants are told they will complete the work and receive the outcome of 4 randomly selected food and monetary (maximum $2.00) trials. Total task time: ~15 minutes.

Working Memory: We will use a 12-minute visual N-back task validated for fMRI studies of smokers. A total of 20 fractals (target-foil ratio 1:3) are presented for each condition (i.e., 0-back, 2-back, 3-back), and each condition (60 sec block) is repeated 3 times in pseudo-

random block design experiment. Each fractal is displayed for 500ms followed by 2500ms inter stimuli interval. Total task time: ~12 minutes.

14. When all scans are completed, participants will be removed from the MRI scanner and be asked to complete a brief ~5-minute "work" task (i.e. clicking on a target a certain amount of times) based on their selections during the in-scanner Food Reinforcement/Choice task on a laptop computer.
15. Participants will receive the appropriate reward(s) (food and/or monetary) per the post-scan work task, as well as receive compensation for time and their preferred travel compensation per the study compensation schedule. At the end of the session, participants will be escorted to the exit of the imaging facility where they will be free to leave.

**5.2.8 End of Recruitment and Retention Pilot Debriefing Call** (After Scan 2 or last visit completed). After the participant has completed their final visit (Scan 2 or their last completed session after withdrawal or ineligibility), study staff will reach out to all participants enrolled in the recruitment and retention pilot to provide additional details about their participation in the pilot.

### 5.2.9 Optional Quit Smoking Session (1-2 weeks following study completion)

After completing Scan 2, participants will be given the opportunity to obtain additional quit resources. Participants may opt to attend an in-person session or complete a call with one of our trained quit smoking counselors. During the call or in-person session there will be 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. This session is completely optional and is for the sole purpose of providing participants who are interested in quitting an opportunity to gain helpful tools to aid them in potential quit attempts. There is no data collection or compensation associated with this session.

### 5.2.10 1-Month Follow-up Survey

Smokers who complete all study in-person study visits will be contacted at minimum 4 weeks after their last study visit (Period 2 Session 4) by phone to complete a brief survey of their smoking and eating behaviors. Participants will complete the Smoking Related Eating and Episodes Test (SWEET)*** and two questions relating to readiness and intention to quit smoking in addition previously collected questions about withdrawal symptoms (MNWS)***, Positive and Negative Affect (PANAS)***, and smoking urges/craving (QSU-B)***. Participants who are classified as study completers as of 4/14/2020 (N = 15) will be re-contacted by phone to completed re-consent before the survey administration.

**Table 2. Study Measures and Time Points**

| Days | Phone Screen | Intake | Baseline | Period 1 | | | | Wash-out | Period 2 | | | | De-brief Call | Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | -15 | -14 | -7 | 1 | 2 | 3 | 4 | 5-28 | 29 | 30 | 31 | 32 | ~32 | ~59 |
| **SCREENING/COVARIATES** | | | | | | | | | | | | | | |
| Urine Drug Screen | | x | x | | | | x | | | | | x | | |
| Urine Pregnancy Screen (if applicable) | | x | | | | | x | | | | | x | | |
| Breath Alcohol (BrAC) | | x | x | | | | x | | | | | x | | |
| Height | | x | | | | | | | | | | | | |
| Weight | | x | x | x | | | x | | x | | | x | | |
| Medical History Form*** | | x | | | | | | | | | | | | |
| fMRI Medical Hx. Form*** | | x | | | | | | | | | | | | |
| Magnet Safety Form*** | | x | | | | | x | | | | | x | | |
| Emergency Contact Form*** | | x | | | | | | | | | | | | |
| Demographics*** | | x | | | | | | | | | | | | |
| ETOH History*** | | x | | | | | | | | | | | | |
| Smoking History/Nicotine Dependence (FTND)*** | | X* | | | | | | | | | | | | |
| Smoking Rate (TLFB) | | | x* | x* | x* | x* | x* | | x* | x* | x* | x* | | |
| Cigarette Brand Form*** | | X* | | | | | | | | | | | | |
| Shipley Institute of Living Scale (SILS)*** | | x | | | | | | | | | | | | |
| Carbon Monoxide (CO) | | x | x* | x* | x* | x* | x* | | x* | x* | x* | x* | | |
| Eating Behavior (DEBQ)*** | | | x | | | | x | | | | | x | | |
| Eating Inventory-Disinhibition (EI-D)*** | | | X | | | | x | | | | | x | | |
| Depression Symptoms (CES-D)*** | | | x | | | | | | | | | | | |
| Smoking Urges/Craving (QSU-B)*** | | | x | x* | x* | x* | x* | | x* | x* | x* | x* | | X |
| Weight Concerns*** | | | x | | | | | | | | | | | |
| Debriefing Phone Call | | | | | | | | | | | | | X | |
| **MECHANISMS** | | | | | | | | | | | | | | |
| Working Memory | | | x | | | | x** | | | | | x** | | |
| Food Reward | | | x | | | | | | | | | | | |
| Preferred Snack Choice (Pre-RRVF) | | | x | | | | | | | | | | | |
| Food Reinforcement (RRVF) | | | | | | | x** | | | | | x** | | |
| Pre-FCQ-S | | | x | | | | | | | | | | | |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Food Cue-Induced Craving (FCQ-S) | | | | | | | x** | | | | | x** | | |
| Withdrawal Symptoms (MNWS)* *** | | | x | x | x | x | x | | x | x | x | x | | X |
| Positive and Negative Affect Schedule (PANAS)*** | | | x | x | x | x | x | | x | x | x | x | | X |
| Readiness/Intention to Quit Smoking*** | | | | | | | | | | | | | | X |
| Smoking-Related Eating and Episodes test (SWEET)*** | | | | | | | | | | | | | | X |
| **PRIMARY OUTCOMES** | | | | | | | | | | | | | | |
| Caloric Intake (Dietary Recalls) | | | | | x | x | x | | | x | x | x | | |
| % Eligible at Intake (pilot) | | X | | | | | | | | | | | | |
| **SECONDARY OUTCOMES** | | | | | | | | | | | | | | |
| Attitudes towards research (pilot) | X | | | | | | | | | | | | | |

***Smokers only***

****Assessed in fMRI***

*****Denotes measures that can and will be collected remotely using REDcap.***

## *5.4 Description of Study Measures*

Similar to Section 5.2 In-Center Study Visits and Table 2 above, measures that can be collected remotely using REDcap are denoted with three astericks (***).

### 5.3.1 Screening/Covariates

Urine Drug Screen: A urine sample (~30ml) will be collected at the Intake Visit and both neuroimaging scans to conduct a urine drug screen. The urine drug screen indicates whether the subject has recently taken any of the following recreational drugs or medications: THC, cocaine, opiates, amphetamines, methamphetamines, phencyclidine (PCP), ecstasy (MDMA), barbiturates, benzodiazepines, methadone, tricyclic antidepressants, and/or oxycodone. Participants with a positive urine drug screen for any substance listed above other than THC or tricyclic antidepressants at the Intake visit will be deemed ineligible. A urine sample that doesn't register a temperature reading of at least 90 degrees Fahrenheit will not be considered a valid sample. In an effort to remain CLIA-compliant, results from urine drug screen 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. In order to document inclusion/exclusion criteria for regulatory purposes, results of the urine drug screens (test cup) will be retained in research charts and in an electronic research record within our local data management system (Access). These results are not and will not be entered into a participant's electronic medical record.

Participants who test positive for any study-prohibited medications/recreational drugs at either neuroimaging scan will be deemed ineligible.

Urine Pregnancy Test: At the Intake Visit and both neuroimaging scans, female participants will be supplied with a simple, CLIA-waived hCG pregnancy test strip and a urine sample cup

(participants may use the urine drug screen cup if desired). Participants will then be instructed to self-administer the pregnancy test and be told that if they are (or believe they may be) pregnant they should not participate in the research study. The participants will inform the study staff if they are able to continue participation after they have reviewed the results of the pregnancy test. 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 their preferred travel coverage for the visit.

Breath Alcohol Concentration (BrAC): Participants will complete a BrAC assessment at the Intake Visit and both neuroimaging scans. Participants will be made aware of the BrAC assessment prior to all applicable visits and asked to avoid alcohol and alcohol-based products (e.g. mouthwash, breath spray, etc.) the evening and morning before the Intake Visit and both neuroimaging scans. The BrAC monitor is a handheld device that uses a disposable mouthpiece and reports the concentration of alcohol in exhaled breath. Any reading greater than 0.000 indicates alcohol consumption within the last 14 hours. Participants with a BrAC greater than 0.000 at the Intake Visit will be deemed ineligible. Participants with a BrAC greater than 0.000 at either neuroimaging scan will be deemed ineligible unless the Principal Investigator permits the participant to reschedule the neuroimaging scan to another day.

Height: Research staff will collect and document participant height utilizing a mounted stadiometer at the Intake Visit.

Weight: Weight will be measured by a physician's scale (pounds) at the intake visit. Participants will be wearing light clothing without shoes. Participants weighing over 275 pounds at intake will be deemed ineligible.

Medical History Form***: A medical history form (led by the research staff) will be completed to review for applicable contraindications previously listed under Key Inclusion/Exclusion Criteria at the Intake Visit.

fMRI Medical History Form***: Participants who met the initial fMRI eligibility criteria at phone screen will be asked to complete a separate fMRI medical history form to review for applicable contraindications previously listed under Key Inclusion/Exclusion Criteria.

Magnet Safety Form***: Participants will complete a standard magnet safety form provided by the Department of Radiology at the Hospital of the University of Pennsylvania at the Intake visit and before entering the scanner at each fMRI scan. The magnet safety form assesses a history of specific prosthesis, surgical implants, and a variety of other MRI contraindications.

Emergency Contact Form***: Participants will provide emergency contact information in the event of an emergency at the fMRI scanner.

Demographics, Smoking History, Cigarette Brand, and Nicotine Dependence (FTND)***: Standard questionnaires will be administered at the Intake Visit to collect the following data: demographics, age at smoking initiation, current smoking rate, previous quit attempts, and own cigarette brand information (Cigarette Brand Form). The Fagerstrom Test for Nicotine Dependence (FTND) will also be administered. The FTND is a 6-item, self-report measure of nicotine dependence derived from the Fagerstrom Tolerance Questionnaire. The FTND scale has satisfactory internal consistency (Cronbach's alpha = .64) and high test-retest reliability ($r$ =.88).

Smoking Rate Timeline Follow Back (TLFB): A reliable and valid timeline follow-back method will be used to assess daily smoking (presence and rate) at every visit post Intake.

ETOH History***: An ETOH history questionnaire will be administered at the Intake Visit and will assess alcohol consumption over the past 7 days.

Shipley Institute of Living Scale (SILS)***: All participants will complete the SILS at the Intake Visit. The SILS is a self-administered test designed to assess general intellectual functioning in adults and adolescents and to aid in identifying cognitive impairments. 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 85 will be ineligible. The SILS is considered a highly reliable assessment tool with good total score internal consistency (Cronbach's alpha= .92).

Hunger Scale***: Immediately prior to and after completion of computerized laboratory tasks, participants will be asked to rate, "How hungry are you right now?" using a scale from 0 "not at all" to 10 "extremely."

Eating Behavior (DEBQ)***: The Dutch Eating Behavior Questionnaire will assess *restrained eating* (10 items, tendency to restrict food intake), *external eating* (10 items, tendency to eat in response to food related cues) and *emotional eating* (13 items, tendency to eat in response to emotions). These scales are associated with food craving and response to food cues. Participants indicate on a Likert-style scale how often each item is applicable to them (0= not relevant; 1 = never to 5=very often).

Eating Inventory-Disinhibition (EI-D)***: Disinhibition will be measured with a subscale (16 items) of the Eating Inventory that is thought to reflect responsivity to environmental food cues, and internal cues, and linked to food reinforcement and weight change.

Carbon Monoxide (CO): CO will be measured at the Intake Visit for all participants and at all subsequent in-person visits to confirm smoking status of the smoking group. The CO monitor is a handheld device that uses a disposable mouthpiece, reports CO in parts per million (ppm), and takes about 3-5 minutes to administer.

Depression Symptoms (CES-D)***: The Center for Epidemiologic Studies Depression Scale is a 20-item Likert-style scale used to assess depressive symptomatology. This scale has high internal consistency (r=.85-.90) and has been shown to correlate with clinical ratings of the severity of depression. In our previous research, CES-D scores have correlated significantly with self-medication smoking and nicotine dependence.

Smoking Urges/Craving (QSU-B)***: The well-validated and reliable 10-item brief Questionnaire of Smoking Urges will assess *craving* for cigarettes. The QSU-B utilizes a "right now" frame of reference.

Weight Concerns***: Weight concerns associated with quitting smoking will be measured with a reliable (α=.87) and valid 6–item scale. Responses to the 6 items range from 1 (not at all) to 10 (very much). Scores are the average of responses to all items.

### 5.3.2 Mechanisms

Individualized Food (Pre-FCQ-S): In preparation for the food cue-induced craving task, participants will rate how appetizing they find pictures of food (e.g., cupcakes, fruits, vegetables) at the Intake Visit. Foods rated least appetizing (n=20) and foods rated most appetizing (n=20)

will be selected to create personalized food cue stimuli. This task will be administered during the baseline visit.

Preferred Snack Choice (Pre-RRVF): Participants will select either the salty (Lay's® Classic potato chips) or sweet (M&M's®) snack food as the snack to "work for" when completing the RRVF task over the remainder of the study. This determination will be made at the baseline visit.

Food Cue-Induced Craving (FCQ-S): Food cue-induced craving will be assessed using a personalized food cue exposure paradigm, whereby pictures of foods rated least appetizing (L, n=20), most appetizing (M, n=20), and a picture of a glass of water (W, n=20) will be presented to participants seated at a computer screen. Participants will be instructed to imagine tasting and eating the pictured food for as long as the image is presented. The images will be presented in six blocks. Each block consists of image presentation (10 images, 8 sec duration) and craving assessment. The M, L, and W food cues will be presented in one of two sequences (i.e., MWLMWL or LWMLWM) counterbalanced across participants. Before the task and after each block, participants will complete the state version of the Food Craving Questionnaire, Desire Subscale (FCQ-S). The 3 items (desire to eat, craving, urge to eat) will be tailored to ask about the M, L, and W images on a 5-point scale (strongly disagree to strongly agree). Personalized cues can maximize craving induction and produce greater increases in subjective craving and objective indices of cue reactivity than standard cues. Reactivity to palatable food images is associated with body mass and weight gain. The Food Cue-Induced Craving task will be administered at scan 1 (Day 4), and scan 2 (Day 32) Visits.

Food Reward: Food reward will be assessed by exposing participants to 16 computer-based images of common snack foods spanning caloric content and macronutrient composition (low/high fat sweet, low/high fat savory). After each 5-second snack food exposure, participants will provide ratings of how much they like the food and how pleasant it would be to eat this food right now. Ratings will be made on visual analog scales anchored by 0 (not at all) to 100 (extremely). The food reward task will be administered at baseline.

Food Reinforcement (RRVF): The Relative Reinforcing Value of Food will be assessed via a validated behavioral choice task, permitting the evaluation of the preference for food over other alternatives. Participants will be asked to move a computer mouse to hit targets on one of two sides of a split-screen monitor, to earn points toward either food or money. Participants selected the snack food (salty or sweet) that they wanted to consume for the assessment at the Intake Visit. Using a concurrent schedule, participants will be told that they can switch from working on one side of the screen to the other as often as they wish. Adapted from previous research, participants will be instructed to move the computer mouse to have the cursor hit the targets (either a $ or food). Consistent with relative reinforcement paradigms, the reinforcement schedule in the money-earning screen will remain constant at a fixed ratio FR-25 (25 targets achieved to earn a point) while the reinforcement schedule for food will increase (require more effort) with a progressive ratio schedule of PR-25x over 10 trials, such that 25, 50, 75, 100, 125, 150, 175, 200, 225, and 250 targets will have to be achieved to earn a point. The computer task will be performed until a participant completes 10 trials and accumulates a total of 10 points from which they will earn either $0.10 for each point (i.e., up to $2.00 paid at the end of the task) or a standardized amount (grams) of their chosen snack food for each point. Food earned is consumed at the end of the task to prevent satiation from influencing responding in subsequent trials. Per convention, the RRVF outcome is defined by a breakpoint (maximum amount of responding) for food vs money across the trials. The Relative Reinforcing Value of Food behavioral choice task will be administered at scan 1 (Day 4), and scan 2 (Day 32) visits.

Positive and Negative Affect (PANAS)***: The Positive and Negative Affect Schedule (1-week frame of reference), a 20-item Likert-format self-report questionnaire, will be used to measure positive mood and negative mood. The two subscales have 10 items each, are internally consistent in both nonpsychiatric and psychiatric samples (α = .79 to 91), and exhibit good convergent and discriminant validity.

Withdrawal Symptoms (MNWS)***: The Minnesota Nicotine Withdrawal Scale - Revised version (MNWS-R) will measure *withdrawal symptoms* (n=15) associated with quitting smoking. Participants will rate the intensity of their symptoms on the following scale: 0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = severe and a summary score will be calculated. The MNWS with a 1-week frame of reference will be utilized throughout the trial.

Self-Report Eating Related to Smoking (SWEET)***: The Smoking-Related Eating and Episodes Test asses 4 content domains related to eating and smoking (Huger, Craving, Overeating, Body Images) using a 5-point Likert scale (1 = never, 2 = rarely, 3 = sometimes, 4 = often, 5 = always) and how these domains are related to other study measures. The SWEET is collected at the 1 Month Follow-up survey time point to assess smoking to moderate eating, and eating to moderate smoking in a self –report assessment.

Readiness/Intention to Quit Smoking***: Readiness to Quit Smoking will be assessed using the prompt “Please indicate your current thinking about smoking. Responses are on a 9 point Likert Scale (1 = Taking action to quit, 3 = starting to think about how to change my smoking patterns, 5 = I think I should quit but not quite ready, 7 = I think I need to consider quitting someday, 9 = No thought of quitting). Intention to quit smoking will be assessed using the prompt “How likely do you think it is that you will try to quit smoking within the next 30 days?” with responses ranging on a 4 point Likert scale (1 = very unlikely, 4 = very likely). Both of these questions are asked on the 1 Month Follow-up survey only.

### 5.4.3 Primary Outcomes – Main Study

Food Intake (24-Hour Dietary Recalls): Food intake (secondary outcome) will be assessed via 6 telephone-administered, 24-hour dietary recalls on days 1-3 and 29-31. A trained member of the research staff will use a multi-pass method with an interactive computerized software program, the ASA24® (Automated Self-Administered 24-hour Recall), to determine total kcal/day (outcome variable). The ASA24® was created by investigators at the NCI. Three recalls are considered optimal for assessing dietary intake, especially when weekend and weekdays are assessed, as we propose to do when possible. If participants are unable to complete a scheduled recall over the telephone or are onsite for a scheduled visit, participants may be asked to complete a 24-hour dietary recall with the research staff in-Center. Comparable accuracy can be achieved when administered in-person and over the telephone. Food recalls are widely used, reliable, and valid, assessing kcals/day within 10% of actual dietary intake measured under laboratory observation and by doubly labeled water.

fMRI Tasks: See section 5.2.8: fMRI Scanning Visits for the complete descriptions of the in-scanner tasks.

*Food Cue-Induced Craving*. The key outcome for this variable is BOLD signal change for most appetizing foods (versus water, and versus least appetizing foods as an active control). Primary regions of interest for the BOLD fMRI analysis are insula, caudate, OFC and ACC. As a secondary measure, food craving will be assessed prior to and after completion of the scan. The food craving assessment is the 3-item “desire” subscale of the reliable and valid state version of the Food Craving Questionnaire (FCQ-S).

*Relative Reinforcing Value of Food (via Food Reward Reinforcement/Choice task).* The primary behavioral outcome will be the amount of additional effort subjects are willing to

expend in order to obtain food. The primary regions of interest for the BOLD fMRI analysis are VS and vmPFC. Within these regions, the food choices (all 50 trials where food is an option) vs. fixation will be the primary contrast. Selection of this primary contrast will ensure the same stimuli will be analyzed across participants and conditions and maximize statistical power for detecting food-related activation.

*Working Memory N-Back Task.* Based on our prior work, the primary performance measure will be correct reaction time, and the secondary measure will be number correct; the primary regions of interest for the BOLD analysis will be DLPFC and medial/frontal cingulate gyrus.

**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 (Recruitment & Retention Pilot Study):**
Impressions of Research: Attitudes towards research; motivations for participation; perceived risks/benefits of research; 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. All secondary outcomes will be delivered via the W2H platform and imported into REDCap. 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).

### *5.4 Tissue Specimens*

Urine: A urine sample will be required at the Intake Visit and both fMRI Scan Visits for drug (~30ml) and pregnancy screenings. These samples will be disposed of following the conclusion of the study visit.

### *5.5 Sample Size Determination*

We plan to test hypotheses at a global 5% Type I error (alpha) for each family of hypotheses, and have chosen a completed sample (N=110) that will achieve at least 80% power using 2-sided tests. Our analysis of power was based on “effect size” (standardized difference). Effect sizes were calculated from our own preliminary data, from published data summaries, and from published estimates of effects (e.g., t statistics, coefficients, p-values) using validated summary methods. We have several hypotheses and more than one outcome measure for some (e.g., different brain regions). We will control error in a family-wise manner, adjusting alpha (Bonferroni Aims 1 and 2, Hochberg step-up procedure for Aim 3) for the number of tests within each hypothesis family. Bonferroni corrections will also be adjusted for the correlations among multiple outcomes.

**Aim 1** includes 2 hypotheses (**H1a&b**) regarding treatment effects on neural responses, including 5 ROIs responding to food-related tasks. We test at $p<0.02$ because of the high correlation among ROIs within subjects (rho=0.54). Estimates of effect size from our center data (d=0.36) indicate that we have 80% power to detect the effects. Aim 1 also tests hypothesis **H1c** for cessation effects. At the Bonferroni corrected threshold of p=0.0167, we have 80% power to detect small to medium effect sizes (d=0.37).

**Aim 2** (**H2a&b**) essentially tests for mediation. The hypothesis that cessation increases food intake will be tested at 0.05, with power for effect sizes ~d=0.32. For Aim 2b (ROIs predicting food intake), we expect a weaker correlation than H1a (rho=0.4), and our adjusted threshold for significance is p<0.01. Expected effect sizes are approximately 0.5, and we expect 96% power to detect the effects.

**Aim 3** begins with the model in Aim 2b above, and tests interacting effects of working memory-related BOLD signal and food reinforcement (or food cue reactivity) on food intake. We will reduce the complexity of this analysis by using difference scores (pre minus post) to model a 2-way interaction between working memory and food reinforcement on food intake. We will only test for brain ROIs found to be sensitive to treatment in Aim 1; the number of tests for interaction is uncertain. We anticipate that these effects will be positively correlated and will use the Hochberg step-up procedure, which is robust to correlations among outcomes in the range we expect. For purposes of power calculation, we assumed a correlation of 0.5, which resulted in a corrected p-value of 0.02 for 5 tests. Keeping the independent variables continuous, we can detect an interaction term (one-sample per subject, standardized) of d=0.36 with 80% power. Literature estimates for similar interactions were 0.65, 0.66, and 0.35. The lowest estimate gives 77% power, and the average (0.55) yields 98% power.

**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 (α=.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 (α=.05) to detect a departure from additivity of the main effects corresponding to a ratio of odds ratios (ORR) of 5.5.

### *5.6 Statistical Methods*

*Image Preprocessing*. 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, 6mm spatial smoothing, high-pass filtering (120s), and co-registration to the structural MRI. Quality assessment (QA) procedures will examine global and ROI-based temporal signal-to-noise ratio (tSNR), absolute and relative motion, and signal spike count. To enhance sensitivity and reliability, potential motion artifact will be reduced using time-point censorship of high motion volumes, which has demonstrated advantages in fMRI.

*Subject-level Image Analysis*. Following preprocessing, subject-level BOLD timeseries analysis is carried out using the general linear model (GLM) as implemented in FSL, with a canonical double-gamma hemodynamic response function (HRF) for convolution, and linear contrasts to estimate task-specific BOLD responses for each individual session.

*Group-level Image Analysis*. Subject-level statistical image maps (abstinence vs. smoking as usual) will be transformed into a common anatomic space (Montreal Neurological Institute, MNI) for group-level image analysis. A priori region of interest (ROI) analyses will focus on specific regions for each task. For the n-back, primary ROIs will be MF/CG, and bilateral DLPFC. For the cue and reinforcement tasks, primary ROIs will be VS and vmPFC; secondary ROIs will include MF/CG, amygdala, OFC, and insula. Percent signal change and activation extent within these ROIs will be used for statistical tests of key hypotheses. In addition, we will use exploratory voxel-wise random effects analysis in FSL to test for the same effects outside of predicted regions. These exploratory voxel-wise analyses will be cluster-corrected using Z>3.09 (p<.001) and cluster probability (family-wise error) p<0.001.

*Connectivity Analysis.* We will also conduct functional connectivity (FC) analysis to characterize functional interactions between ROI "seed" timeseries (VS and DLPFC) and whole brain. To explore wholebrain patterns of connectivity, we will examine graphical network topology in resting BOLD data. In task data, we will perform psychophysiological interaction (PPI) analyses to investigate task modulation of ROI functional connectivity.

*Hypothesis Testing.* The hypotheses in this proposal will test mean percent signal change extracted from *a priori* ROIs and exported for off-line hypothesis testing using Stata (StataCorp, Texas).

**Aim 1** will examine the relationship of changes in brain responses. These comparisons are all within-subject, and will be analyzed as abstinent minus smoking difference scores using multiple linear regression (regress, StataCorp, Texas). The hypotheses will be tested using the t-score corresponding to the main effect of BOLD difference on caloric intake. Covariates can be included in the model to control error (sex, BMI, nicotine dependence, age, weight concerns), although we do not expect to make large gains for adding subject-level controlling variables in a model of difference scores.

**Aim 2** seeks to determine the additional explanatory value of brain signal over and above models using only clinical, subjective, and behavioral performance measures **(H2a)**. The use of difference scores reduces a complex longitudinal analysis of mediation to an analysis of a single (non-repeated) measure. Our analyses will test for incremental change in $R_2$ when models incorporate brain data. We will also examine the correlations among our predictors and identify potential for collinearity via variance inflation. We will then construct models of ΔkCal admitting blocks of variables hierarchically, and testing for improvement in fit by Wald test, starting with clinical variables (age, sex, FTND, BMI), behavioral performance, and subjective responses to abstinence challenge (N-back, MNWS, QSU-B, food reinforcement task breakpoint). Finally, we will add the difference scores from imaging, and estimate overall improvement **(H2a)** in $R_2$. At each stage, we will allow highly redundant variables to drop out if variance inflation factor (VIF) is greater than 5. We will then return to the clinical plus behavior model and test the addition of each brain domain separately, again using the incremental improvement in $R_2$ by domain **(H2b)**. Finally, we will explore data reduction methods (Principle Component Regression, Partial Least Squares) for entering correlated imaging variables in order to minimize the confounding effects of correlated predictors.

Our Exploratory Aim is a between-group analysis to provide a baseline comparison in food-related brain response between smokers and non-smokers. The analysis will include 30 non-smokers who will take part in a single non-smoking phase of the study and will include each of the predictor measures in H1. The analysis will utilize one-way ANOVA methods, fitted with GEE regression (Gaussian family), with a 3-level design code representing non-smoker, smoker sated, and smoker abstaining (non-smokers will have only one entry per subject, smokers will have two). Non-smokers will be treated as the reference group. Comparisons of interest,
non-smoker versus sated smoker, and non-smoker versus abstaining smoker, will be tested using the z-score corresponding to the regression coefficient. A small number of covariates may be included in the model to control error.

*Missing Values*. As with most studies, we expect to have some degree of missing data. We will assess the extent and type of missing data and select the most appropriate method for dealing with missing data (e.g., multiple imputation). For example, for items missing at random on survey measures, missing items can be imputed prior to calculating final scores using conditional means, estimated with an iterated version of Buck's method. A less common but

more important cause of missing data is differential dropout, which can cause imbalances in the randomization. We will examine the characteristics of those subjects who drop out, paying particular attention to whether there is an association between dropout and abstinence sequence. These analyses will be descriptive, as we expect few dropouts.

# 6 Risks / Benefits

## *6.1 Potential Study Risks*

The potential risks to participants, their likelihood and seriousness, and strategies to mitigate risks 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/AEs will be collected, assessed, and reported as per the study protocol (see section 8: Safety and Adverse Events), federal law, and University of Pennsylvania regulations.

Withdrawal Syndrome: Many individuals who abstain from smoking exhibit a pattern of symptoms related to withdrawal from tobacco use. These symptoms include: anger, irritability, frustration, anxiousness or nervousness, depressed mood or sadness, cravings for nicotine, difficulty concentrating, appetite change and weight gain, insomnia or other sleep problems, restlessness, impatience, constipation, dizziness, coughing, nightmares, nausea, sore throat, headache, muscular pain, or fatigue. Eliminating the risk for these would not be possible, although in most cases these events are short-lived and have low intensity. The study personnel will be trained to recognize these symptoms and educate the participants about them (e.g., duration and methods for reducing them).

Food Allergies: Participants will be provided with nutritional shakes and potato chips or milk chocolate as part of their participation in this research trial. The risk of a participant experiencing an allergic reaction to any of the ingredients in these commercially available food products will be mitigated by prospectively excluding those with the applicable food allergies. In addition, the research staff will reconfirm that the participant doesn't have any of the applicable food allergies prior to distribution of the aforementioned food products at the Baseline Visit.

Psychological Distress: Participants may experience emotional distress during smoking cessation counseling and assessments from discussing feelings and attitudes about smoking or from learning about the risks from smoking. These events happen very rarely and in almost all cases are short-lived and of low intensity, lasting for 1-2 weeks. Study personnel will be alerted to expect this from a small number of subjects and will be trained to make referrals for mental health services as needed. Personnel will be trained to query for adverse emotional reactions during counseling and assessments and will be trained to deal with such reactions and to provide additional referrals if needed.

Urine Sample Collection: Participants may experience mild discomfort from providing urine samples. All samples will be collected by trained member of the research staff.

Email Communications: In this research study participants may prefer to receive appointment reminders via email or submit questions related to 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.

fMRI: The known MRI-related risks associated with this study are minimal. All sequences and RF coils will be approved by the Center for Magnetic Resonance Imaging and Spectroscopy (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 childbearing potential will be supplied with a simple, CLIA-waived urine pregnancy screen to self-administer at each scan visit, and will be told that pregnant women may 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 their preferred travel coverage for the visit.

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 the radiologist affiliated with this protocol in conjunction with the Study Physician. 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 and/or radiologist if appropriate. 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.

Confidentiality and Loss of Privacy: See section 8.6.1 and 8.6.2 for methods in which Confidentiality and Subject Privacy/Protected Health Information will be secured and maintained.

### *6.2 Potential Study Benefits*

Participants who enroll in this trial will benefit from the knowledge that they are contributing in an important way to potentially furthering scientific knowledge concerning ways to improve treatment for smokers, and prevent PCWG. Weight gain can precipitate smoking relapse and contribute to other health issues.

### *6.3 Risk/Benefit Assessment*

There is minimal risk for serious adverse events by enrolling in this research study. The procedures used in this study have been shown to be relatively safe. 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.

## 7 Safety and Adverse Events

### *7.1 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 (SAE)*** 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***.

Adverse Event Reporting Period:
The study period during which AEs/SAEs will be reported is from the initiation of any study procedures until the end of the study. Any event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in the study after the final time point will be assessed and reported as appropriate.
Preexisting Condition:
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

Post-study Adverse Event:
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Hospitalization, Prolonged Hospitalization, or Surgery:
Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as a SAE unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an AE if the condition meets the criteria for an AE.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

## *7.2 Collection and Recording of Adverse Events*

### 7.2.1 AE Collection Methods

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.

### 7.2.2 AE/SAE Documentation and Internal Reporting Procedures

AE/SAE Documentation: 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. All applicable AEs and SAEs will then be documented on a cumulative AE and SAE log maintained within the regulatory binder.

Completed documentation of applicable AEs will include the following information:

- Protocol Title and IRB#
- Subject Identifier
- Event Title
- Date Site Notified
- Event Start Date and Time
- Event Stop Date and Time
- Description of Event/Course (including sequelae)
- Severity:
    - None = No concerns
    - Mild = Side effect or issue does not interfere with usual daily activities
    - Moderate = Side effect or issue interferes with some activities
    - Severe = No normal activities are possible
- Relatedness to the study procedures (PI and/or Study Physician):
    - Unrelated = Definitely not related
    - Unlikely = Doubtfully related
    - Possibly = May be related
    - Probably = Likely related
    - Definitely = Related
- Expectedness per protocol and/or consent
    - Expected/Anticipated
    - Unexpected/Unanticipated
- Action(s) taken (if appropriate)
- Outcome (if appropriate)

Documentation of SAEs will include the following information on a standardized SAE Form:

- Protocol name and number

- Subject identifiers
- Demographic data
- TN Lot number, expiration date, and other descriptive information (if appropriate)
- Date Site Notified
- Date and time of SAE onset
- Date and time of SAE resolution, if available
- Course/Description of Event (including sequelae)
- Action Taken
- Outcome
- Follow-up plan
- Serious Status (What makes the event an SAE)
- Severity of the event
    - None = No concerns
    - Mild = Side effect or issue does not interfere with usual daily activities
    - Moderate = Side effect or issue interferes with some activities
    - Severe = No normal activities are possible
- Relatedness to the study procedures (PI and/or Study Physician):
    - Unrelated = Definitely not related
    - Unlikely = Doubtfully related
    - Possibly = May be related
    - Probably = Likely related
    - Definitely = Related
- Clinical assessment of subject conducted at time of SAE (if appropriate)
- Results of any laboratory tests and/or diagnostic procedures (if appropriate)
- Autopsy findings (if appropriate)
- Concomitant medications and therapies (excluding treatment of event)
- Relevant Medical History (if appropriate)

Internal Reporting Procedures: All relevant follow-up information outlined above (see AE/SAE documentation) concerning applicable AEs will be reported to the Study Coordinator (or other senior personnel), Principal Investigator, and Study Physician to determine a course of action, relatedness (causality) to the study, and expectedness (if not already established). This consult 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 (or unlikely) to be the cause.

## *7.3 Reporting of Serious Adverse Events and Unanticipated Problems*

The procedures for unanticipated problem, adverse event, and serious adverse event reporting are consistent with NIH and UPenn-specific guidelines and are as follows:

### 7.3.1 Investigator reporting: notifying the Penn IRB

This section describes the requirements for safety reporting by investigators who are Penn faculty, affiliated with a Penn research site, or otherwise responsible for safety reporting to the Penn IRB. The University of Pennsylvania IRB (Penn IRB) requires expedited reporting of those events related to study participation that are unforeseen and indicate that participants or others are at increased risk of harm. The Penn IRB will not acknowledge safety reports or bulk adverse event submissions that do not meet the criteria outlined below. The Penn IRB requires

researchers to submit reports of the following problems within 10 working days from the time the investigator becomes aware of the event:

- Any AE (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the Principal Investigator and Study Physician is:

  Unexpected (An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts).

  **AND**

  Related to the research procedures (According to the Penn IRB standard operating procedures [SOPs], an event is "related to the research procedures" if the event is deemed **probably or definitely related** to the procedures.")

Reporting Process:
Unanticipated problems posing risks to subjects or others as noted above will be reported to the Penn IRB using the form: "Unanticipated Problems Posing Risks to Subjects or Others Including Reportable Adverse Events" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

Reporting Deaths (more rapid reporting requirements):
Deaths that occur during the course of a research study and that are:

- Unexpected; AND
- Related to the research study; AND
- When other participants are believed to be at an increased risk of harm

Must be reported to the IRB within 3 days from the time the investigator becomes aware of the death.

Other Reportable events:
The following events are also reportable to the Penn IRB:

- 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).
- 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.
- 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 participants 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.

- Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant 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.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk, or affects the rights or welfare of subjects.

### *7.4 Medical Monitoring*

It is the responsibility of the Principal Investigator and Study Physician to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of AEs/SAEs as noted above, as well as adherence to the study data and safety monitoring plan outlined in sections 8 and 10.

## 8 Data Management

The CIRNA Data Management Team has developed a data management system (DMS) that will facilitate the operational facets of this study, including determination of entry eligibility, production of lists of subjects for telephone contacts for scheduling, and data entry. The DMS uses the relational database product Microsoft Access as the primary software platform for data entry and validation, storage, retrieval, modification, and security. The DMS ensures data integrity through range and validity checks during the data entry process. Daily backups are performed to protect data against accidental destruction or corruption.

### *8.1 Data Management System Development*

The CIRNA Data Manager will work closely with the trial investigators to develop an understanding of the data collection, storage, and quality assessment needs for the trial. This includes the design and development of the trial data collection forms and any additional administrative Case Report Forms (CRF) to ensure that standardized, uniform data collection and data management procedures are implemented and sustained throughout the trial. The data collection forms will serve as templates for designing the data entry screens. The Data Manager will work closely with trial investigators and senior personnel to design, develop, and test an appropriate database structure to support the requirements of the DMS and to promote data security and integrity. Electronic audit trails of changes to database contents are incorporated into the design and will capture and record those changes automatically. In addition to the trial database where actual results will be maintained, a development database will be created. The development database is a working environment that facilitates the development, testing, troubleshooting, enhancement, and training for the DMS without adversely affecting the integrity of the collected project data.

Prior to deployment and use by the research staff, the database and DMS will be subjected to extensive functional testing. This testing is conducted according to a written test plan and is intended to verify the proper functioning of all components of the DMS. Any components that do not function as they were intended will be identified and evaluated by the development team to determine appropriate corrective action. Testing will also include an evaluation by user representatives for adherence to the requirements established by the intended users for the DMS. Successful completion of these user acceptance tests will mark the end of development

and predicate the deployment of the DMS for use in storing and managing active trial data. Any modifications made to the DMS will be conducted in accordance with change control procedures.

### *8.2 Data Security*

All research data for the trial will be stored in an electronic Access database that is managed by the Data Manger. The database will be hosted on a secure computing server and will be restricted to only those individuals who are authorized to work on the trial. Individual user accounts with passwords will be used to restrict access to the database. Specific privilege assignments within the database will also be employed to limit the types of functions that authorized users can perform to those functions that are appropriate for their role in the trial. Additional measures to prevent unauthorized external access to the database environment will be employed using network firewall technologies. The Data Manager will maintain the database in an appropriate manner for the retention period required by regulation. Database administration includes user account maintenance, database security, performance monitoring, and database change management.

Storage and archiving for imaging data will be stored on The Center for Functional Neuroimaging (CfN) secure computer cluster.

### *8.3 Data Processing*

The data entry screens will resemble the data collection forms as closely as possible to allow visual referencing during data entry. This data entry module will be configured for single data entry. Participant data will be collected by research staff, recorded on study-specific CRFs, and scanned in or entered directly into the appropriate DMS module. Data entry checks will be included in the entry screen designs where appropriate to limit the opportunity for erroneous entries due to mistyping. Such data entry checks would include value range comparisons, valid data type checks, required value checks, and/or skip pattern enforcement. Following telephone eligibility screening, research staff will perform subject registration. Following the Intake Visit, research staff will randomize eligible subjects. The randomization module will allow the research staff to randomize subjects into one of the two trial arms. At the randomization attempt, the DMS will check the eligibility data to confirm that randomization is valid. A randomization assignment will then be provided.

### *8.4 Data Quality Assurance*

A data quality module will be developed to assess data entered into the database in relation to a set of rules that describe expectations for those data items. This set of data validation rules will be defined by the data manager, working closely with trial investigators, to identify data items that may have been collected incorrectly or entered into the database inaccurately. The module will run automatically to inspect all newly entered or modified data. The research staff will review the results of the data validation and take any required corrective action for invalid data. Queries will be recorded and tracked in the data quality module. Corrections identified for individual data items will be managed by the research staff. All changes made will be recorded in an electronic audit trail and documented using change control procedures.

Monitoring of trial progress will be accomplished, in part, through the use of standard reports. The Data Manager will program a set of standard enrollment, tracking, quality review, and safety monitoring reports. Data audits will occur after the first few participants are enrolled and periodically during the trial to detect errors in data entry. Eligible participants will have 100% of their source document information compared with the data entered in the database. Any errors will be investigated and resolved, and a plan will be implemented to prevent further errors should concerning patterns emerge.

## *8.5 Subject and Specimen Tracking*

The Data Manager will develop a module to assist research staff in recruitment and retention tracking for trial subjects. This module will accept and store contact information for potential subjects and will include data items to indicate the completion status of significant events. The tracking module will include information about contact and visit schedules to assist in preparing communications to potential subjects and trial participants concerning scheduled events. The module will also allow for incentive-related inventory management. When obtaining saliva specimens, the research staff will complete a specimen registration CRF and scan/enter the data into the DMS. A unique specimen identifier will be assigned and recorded on the CRF. Labeled specimens and applicable information will be transferred to the lab for analysis as required for analysis.

## *8.6 Data Handling and Record Keeping*

### 8.6.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI. Note that in the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization.

Confidentially of study data will be maintained in the following manner:

- Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study.
- Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords. All data will be stored on the Penn network server.
- Prior to access to any study-related information, personnel will be required to review and sign statements agreeing to protect the security and confidentiality of identifiable information.
- Whenever feasible, identifiers will be removed from study-related information.
- Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys.
- Measures collected remotely will be stored using REDcap, a HIPPA compliant platform for managing protected health information (PHI)

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 9.6.2 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. The PMACS provides a secure computing environment for a large volume of highly sensitive data.

### 8.6.2 Subject Privacy/Protected Health Information

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

1. Name, Street address, city, county, zip code
2. All elements of dates (except year) for dates directly related to an individual and all ages over 89
3. Date of birth
4. Social Security Number
5. Personal and family medical history
6. Some personal information that may be considered sensitive, such as drug and alcohol use history, etc.
7. Emergency contact name, contact number, and relationship
8. Telephone number, email address
9. Results from all questionnaires, tests, and procedures

Potential participants will be contacted over the phone after responding to recruitment efforts or having agreed to be contacted for future studies. 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 telephone screening where preliminary eligibility for the research study will be determined. Only if a participant is initially eligible, will they be asked to 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. Once enrolled, information will never be recorded with identifiers other than study ID. A separate list of names with ID numbers will be accessible only by authorized personnel. All records will be kept in locked filing cabinets to maintain confidentiality. All analyses will be conducted on de-identified data.

Data will be accessible only to the Study Investigators, Study Physician and Study Radiologist, study staff, applicable Center staff, UPenn IRB, Office of Clinical Research, CAMRIS, authorized UPENN and staff (e.g. accounting and billing matters, provide treatment, oversee MRI scans [MRI Technicians], etc.), National Cancer Institute, and the FDA.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify a subject directly. At most, the website will include a summary of the results. Subjects may search this website at any time.

# 9 Data and Safety Monitoring

## *9.1 Research Roles*

During the course of the study, data and safety monitoring will be performed on an ongoing basis by the Principal Investigator, Study Physician, research staff, and the IRB. The research

staff are responsible for collecting and recording all clinical data. This includes ensuring that all source documents exist for the data on the CRFs, ensuring all fields are completed appropriately, and all error corrections are done according to GCPs. Any inconsistencies/deviations will be documented and addressed as appropriate. The research staff will perform regular chart reviews to verify data integrity. The Study Coordinator (or senior personnel) and Principal Investigator will maintain the study regulatory binder/essential documents per Good Clinical Practice (GCP). The Study Physician will be available to review medical issues related to participation for each participant on an ongoing basis as outlined in this protocol. Research staff will meet and communicate on a regular basis to reconcile data queries and safety concerns. The IRB will review the trial on an on-going basis per institutional and federal regulations until the study is formally closed-out.

CAMRIS will be responsible for the regulatory oversight of all MRI related activities within this protocol, including initial review and approval of the study.

## *9.2 Staff Training*

Staff training will consist of an initial explanation and review of the protocol, informed consent form, CRFs and laboratory tasks, sample collection protocols, data management system, adverse event collection and reporting, and all study-specific SOPs. In addition, during a standardized training period, the duties of each staff member will be clearly outlined and all applicable regulations will be reviewed. Training interactions will be documented in a training log, which will be maintained within the regulatory binder. Senior personnel will supervise junior staff and provide re-training as needed.

Dr. Loughead and senior staff will oversee the development of protocols for activities and training of staff in these protocols. Dr. Loughead and/or the Project Coordinator will also be responsible for the development of procedures pertaining to all study visits and implementing and monitoring ongoing staff training procedures accordingly.

All personnel working on this project will complete required training in the protection of human subjects and the protection of personal identifiable information (i.e. HIPAA) before interacting with study data or research participants. All human subject and privacy protections certifications will be maintained in the regulatory binder.

## *9.3 Monitoring Activities*

### 9.3.1 AE/SAE Monitoring

Monitoring and management of AEs/SAEs will be conducted in real-time by the Principal Investigator, Study Physician, and the research team at regular time points as per the methods and procedures detailed in section 8: Safety and Adverse Events.

### 9.3.2 Initial Assessment (Intake) Monitoring

The study staff will conduct a manual review of source documents and CRFs for all subjects determined to be eligible at telephone screen and again prior to the Intake Visit. Eligibility data will be reviewed in real-time at the Intake Visit by the research staff. In addition, The Study Coordinator (or senior personnel) will verify that all data have been collected and, when applicable, meet the eligibility criteria on a “Final Eligibility Checklist.” The Final Eligibility Checklist will be signed and dated by the Study Coordinator (or senior personnel) to formally document review. If the Study Coordinator (or senior personnel) notes a pattern of improper data collection or deviations, additional trainings will occur.

#### 9.3.3 Protocol Monitoring

Protocol monitoring includes a survey of those activities that are associated with protocol adherence such as identifying, reporting, and rectifying protocols deviations, reviewing for violations of inclusion/exclusion criteria, and ensuring the adherence to study-specific SOPs, GCP, and other federal and institutional regulations. Protocol monitoring will be performed on an ongoing basis through the following methods:

1. Checklists will be utilized at all time points to ensure all data is collected per protocol and procedures are followed as appropriate.
2. A Final Eligibility Checklist will be completed after the Intake Visit for all participants who enroll (i.e. sign consent) in the study.

#### 9.3.4 Database Auditing

As outlined in section 9: Data Management, the study DMS will be equipped with internal validation checks to ensure data is entered within reasonable ranges. Error messages will be displayed in real-time if data appears inaccurate. Staff will have to respond to these error messages before data can be saved. In addition, The Study Coordinator (or senior personnel) will perform regular milestone quality assurance checks.

#### 9.3.5 Data Security

As outlined in section 9: Data Management, study data will be secured through controlled user access and accessible to authorized personnel only. Source documents will be secured in locked filing cabinets.

### *9.4 Frequency of Data and Safety Monitoring*

Data will be reviewed internally on a regular basis. Specifically:

1. At data capture, the research staff will review data for completeness and integrity.
2. At data entry, the DMS will include multiple internal validity checks which will prompt the staff if an entry was made that is out of range or in an unacceptable format.
3. Eligibility data will be reviewed in real-time at the Intake Visit. In addition, the Study Coordinator (or senior personnel) will review and verify that all data have been collected and, when applicable, meets the eligibility criteria on a “Final Eligibility Checklist.”
4. On a regular basis, the project staff will review data through an internal chart review procedure supported by the DMS.
5. All CRFs for eligible subjects are 100% source-data verified through an internal data management system (Data Entry/Quality Assurance) on an ongoing basis.
6. The study statistician will review data prior to analysis to ensure integrity and validity.

### *9.5 Auditing and Inspecting*

The Principal Investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data, etc.). The Principal Investigator will ensure the capability for inspections of applicable study-related facilities. Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

## 10 Ethical Considerations

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations, and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

### *10.1 Informed Consent*

A fully trained staff member will obtain informed consent using the combined consent and HIPAA form approved by the IRB (UPENN). The consent process will take place prior to the initiation of any study procedures. The consent process will occur in-person at the CIRNA and will involve a discussion of the study requirements and procedures. The combined consent and HIPAA form will be read verbatim to participants. Participants will have an opportunity to ask any questions and/or express concerns. Participants can elect not to participate and may withdraw at any time without penalty. Participants will receive a copy of the combined consent and HIPAA form for their records. The consent process will take place in English, there will be no waiting period, no coercion to participate, and all participants will be considered competent to provide informed consent (i.e., they will be asked if they understand what they are consenting for). The consent form must be signed and dated by the participant and the investigator-designated research professional obtaining the consent. The original signed combined consent and HIPAA form will be centrally stored in regulatory binders (consent).

### *10.2 Electronic Re-consent prior to 1 Month Follow-up Survey*

Study staff will contact all study completers prior to 4/17/2020 (N = 15) by phone to obtain informed consent prior to administering the 1 Month Follow-up survey. Staff will be available to answer questions by phone while the participants completed the informed consent via REDcap. Due to the COVID-19 pandemic, current IRB guidance (issued 4/8/2020) states that obtaining consent via REDcap is an acceptable way consent subjects. Study re-consents and all data collected for this time point will be stored in REDcap.

### *10.3 Electronic Consent for Newly Enrolling Subjects (6/22/2020)*

In an effort to maintain social distancing initiatives (due to COVID-19) as in-person new participant enrollment resumes (6/22/2020), all newly enrolling participants will be consented electronically in REDcap prior to an on-site visit. Participants will complete a phone call with research staff in which the research staff will explain verbatim the consent document. Participants will have questions answered, and provide an electronic signature. Study staff will also sign off on completion of the consent form. Electronic copies of the consent will be stored in REDcap, and physical copies will be printed and stored in study regulatory consent binders. This procedure is consistent with current IRB guidance on remote consenting of subjects (5/22/2020).

## 11 RESOURCES NECESSARY FOR HUMAN RESEARCH PROTECTION

### *11.1 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
- Susan Ware, Database Developer/Manager
- Paul Sanborn, Research Staff
- Wen Cao, Imaging analyst
- Dominique Spence, Research Staff

- Thaine Smith, Research Staff
- Brianna Soreth, Research Staff

### *11.2 Study Facilities*

This project will be conducted at and through the CIRNA. The CIRNA has successfully conducted similar protocols and has well-developed procedures for staff training, data collection and storage, and study completion. The facilities available for this project include a large and small conference room, individual consulting rooms with computer/internet access, storage rooms, office space for study personnel, and data management facilities. In addition, CIRNA houses two freezers for sample storage. A -80°C freezer is used for long-term sample storage, while a -30°C freezer is utilized for daily access of current sample boxes. These freezers contain temperature and power monitoring sensors which are connected to a Sensaphone alarm system that will contact specific biospecimen staff in the event of an emergency.

If participants require referral for psychological services, information about such programs at 3535 Market Street and/or the Philadelphia area will be provided; we have a form with specific information about such programs already in use in other CIRNA studies.

The Center for Functional Neuroimaging (CfN) provides infrastructure support for functional neuroimaging and is comprised of investigators and staff with a broad range of experience including regulatory affairs pertaining to neuroimaging, MRI methods development, MRI physics and pulse programming, instrumentation, experimental design, computing, and image analysis procedures. The center provides support for technical aspects of neuroimaging using MRI, including experimental design, data acquisition, and image analysis, and interfaces with several other complementary programs in brain, behavior and imaging. The CfN currently has a computing cluster of over 600 computing cores at 3.1 GHz on a 10GbE network linked to public terminals by a high speed network along with 100TB of RAID storage and tape backup. This cluster runs Matlab, IDL, AFNI, and a variety of customized software environments. The CfN is supported by an NINDS P30 Center Core. The CfN also manages access to neuroscience MRI scanning on research dedicated systems to be used in this trial: A 3 Tesla Siemens Trio whole-body MRI system located in the Hospital of the University of Pennsylvania and a Siemens Prisma 3 Tesla whole-body MRI with a 64-channel head/neck array located in the basement of the Stellar Chance Building.

## 12 Study Finances

### *12.1 Funding Source*

This study is financed through a grant from the U.S. National Institutes of Health.

### *12.2 Conflict of Interest*

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All University of Pennsylvania investigators will follow the University conflict of interest policy.

### *12.3 Subject Compensation*

Participants will be compensated in cash at each in-person visit they attend and can receive up to $394 (for visit and task compensation) and up to $504.00 (with travel reimbursement) for successfully completing all study requirements in their entirety as per the Study Compensation

table (Table 3) below. If the participant elects to use the ride service, all travel will be paid for by the research study. 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. If the participant elects to travel to and from their appointments independently, they will be reimbursed $10/visit ($110 over the course of the study) to put towards their travel expenses.

No compensation will be provided if a participant fails to complete any of the 24-hour dietary recalls at each of the assigned time points. Compensation that is earned for completing the 24-hour dietary recall assessments will be distributed in-person or via ClinCard at the participant's discretion. Participants can earn up to an additional $2.00 during the completion of the RRVF task. Participants who successfully complete the first study period, that optionally refer others to the program (i.e., person referred to program completes initial phone screen) will be awarded $20 per referral, for a maximum of 3 referrals. Participants who are found ineligible for any reason during any visits will only receive travel reimbursement ($10.00). No study compensation will be distributed to participants who complete visit activities over the telephone. Participants will be asked to complete a W-9 tax form at the conclusion of the Intake Visit because the University of Pennsylvania is required to report to the Internal Revenue Service (IRS) any cumulative payments for participation in research studies at the University of Pennsylvania that exceed a total of $600.00 in a calendar year. A W-9 will aid the Center in tracking and reporting those who participate in multiple projects at the Center and accrue over $600.00 in a calendar year.

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 (and a maximum of $145 at the final visit if participants have earned the additional 5 draws).

Participants will be paid in cash for intake visits and task compensation. 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.

## 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 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 Day | Session Length | Visit Compensation | Task Compensation | Total Estimated[5] | Lottery Jar[7] |
|---|---|---|---|---|---|---|
| Intake | -7 | 3 hrs | $10 | $10 | $20 | 5 Draws |
| Baseline | -- | 1.5 hrs | $10 | | $10 | 5 Draws |
| Back-up Session[1] | 1 or 29 | ~1hr | $15 | | $15 | 5 Draws |
| Session 1 | 1 | 30 mins | $15 | | $15 | 5 Draws |
| Session 2 | 2 | 30 mins | $15 | | $15 | 5 Draws |
| Session 3 | 3 | 30 mins | $15 | | $15 | 5 Draws |
| Session 4 | 4 | 4hrs | $90 | Up to $2[2] | Up to $92 | 5 Draws |
| 24hr Dietary Recalls (3)[3] | 1-3 | | $30 | | $30 | |
| Session 5 | 29 | 30 mins | $15 | | $15 | 5 Draws |
| Session 6 | 30 | 30 mins | $15 | | $15 | 5 Draws |
| Session 7 | 31 | 30 mins | $15 | | $15 | 5 Draws |
| Session 8 | 32 | 4hrs | $90 | Up to $2[2] | Up to $92 | Up to 10 draws |
| 24hr Dietary Recalls (3)[2] | 29-31 | | $30 | | $30 | |
| 1 Month Follow-up Survey | ~59-61 | ~15 mins | $25 | | $25 | |
| **TOTALS** | | | **$390** | Up to $14 | **Up to $ 404** | |
| Travel Reimbursement[5] | | | **$10** | | **Up to $110** | |
| **TOTALS (with Travel Reimbursement)** | | | | | **Up to $ 514[6]** | |
| Referral Bonus Program[4] | | | $20 | | Up To $60 | |
| **TOTALS (with Referrals)** | | | | | **Up to $ 574** | |

[1] Some participants choose to be optional back-up and be double booked for Session 1 or Session 5 visit. This will ensure that valuable time on the scanner (day 4/32) 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 the session 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 session, respectively.

[2]The value noted in the table is the possible monetary value that a participant might receive based upon choices made while completing the Food Choice Task. Not all participants will receive this amount of money; some may receive a portion of snack food instead. At the end of the task, up to 4trials are selected in a pseudo-random manner and participants complete the work and receive the reward they chose on those trials. Please see primary outcomes for a detailed description of the Food Choice Task.

[3]Participants must complete all three 24-hour dietary recall assessments to receive compensation ($30.00) at each assigned time point.

[4]Participants who successfully complete the first study period may refer others to the program (i.e., person referred to program completes initial phone screen) and will be awarded $20 per referral, for a maximum of 3 referrals.

[5] Only applicable to participants who opt to receive $10 travel reimbursement for each visit.

[6] Maximum total compensation estimated if participant opts to utilize ride service for transportation coverage. If a participant is deemed ineligible during intake visit only, 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.

---

# 13 References

See the NIH grant proposal for references.

Recruitment pilot references available upon request.