Application for Review of Human Research: IRB Protocol Summary
Biomedical Research
Section II

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PROTOCOL TITLE

1. Full Title
Understanding the Role of Cognitive Dysfunction in the Treatment of Nicotine Dependence

2. Brief Title
Cognition and Smoking Relapse

BRIEF DESCRIPTION
This study tests whether withdrawal-related cognitive deficits increase smoking relapse among HIV-infected (HIV+) vs. HIV-uninfected smokers (HIV-). Adult smokers (N=300; 150 HIV+, 150 HIV-) will complete 2 sessions to assess cognition (24h abstinence vs. smoking-as-usual; order counterbalanced; weeks 0-2). Subjects will then receive smoking cessation counseling and open label transdermal nicotine (weeks 3-12). Outcomes are: 1) cognition; and 2) abstinence rates at the end-of-treatment.

STUDY SPONSORSHIP
1. Funding Sponsor
National Institutes of Health

2. Primary Sponsor
Rebecca Ashare, Ph.D.

ClinicalTrials.gov IDENTIFIER
NCT03169101

PROTOCOL ABSTRACT

Medical advances in the treatment of HIV/AIDS have improved the life expectancy of HIV-infected individuals. Unfortunately, HIV-infected individuals are three times more likely to use tobacco than those in the general population, but little is known about the mechanisms that underlie these high smoking rates. This will be the first study to test whether the neurocognitive impairments associated with HIV-1 infection may be exacerbated during nicotine withdrawal and increase the probability of smoking relapse among HIV-infected smokers (HIV+), compared to HIV-uninfected smokers

(HIV-). To this end, adult treatment-seeking smokers (N=300; 150 HIV+ and 150 HIV-) will complete this 12-week study, which is divided into two phases: a pre-quit laboratory phase (weeks 0-2) and a treatment phase (weeks 3-12). Subjects will complete two laboratory sessions during the pre-quit phase: once following 24 hours of mandatory smoking abstinence and once while smoking-as-usual (order counterbalanced). A comprehensive cognitive task battery assessing memory, attention, and executive function will be administered during each laboratory session. During the treatment phase, all subjects will receive standard smoking cessation treatment, including counseling (weeks 3-8) and open-label transdermal nicotine (TN) patches (weeks 4-12). The primary outcomes are: 1) cognitive performance following 24-hours smoking abstinence (vs. smoking-as-usual) during the pre-quit phase; and 2) 7-day point-prevalence, biochemically-confirmed abstinence rates at the end-of-treatment (EOT) for the treatment phase.

OBJECTIVES – Main Study

1. Overall Objectives

Aim 1: To test whether HIV+ smokers experience greater abstinence-induced cognitive deficits versus HIV- smokers. *Compared to HIV- smokers, HIV+ smokers will exhibit greater deficits in verbal and working memory during abstinence (vs. smoking-as-usual).*

Aim 2: To test whether HIV+ smokers have a lower probability of quitting following standard treatment compared to HIV- smokers. *HIV+ smokers will have lower abstinence rates at EOT (vs. HIV- smokers).*

Aim 3: To test whether the association between HIV status and smoking relapse is mediated by abstinence effects on cognitive deficits. *Abstinence-induced cognitive deficits will predict relapse at EOT and will account for (mediate) differences in abstinence rates between HIV+ and HIV- smokers.*

Exploratory Aim: We will evaluate multiple cognitive domains (e.g., verbal memory, executive function, and response inhibition) to explore whether these domains uniquely predict relapse in HIV+ smokers. We will also explore potential moderators (e.g., nicotine metabolite ratio [a biomarker for rate of nicotine metabolism], nicotine dependence).

Rhythm Monitoring Sub-Study Aim(s)

Sub-study Aim 1: To evaluate the burden of atrial fibrillation and other arrhythmias among HIV-infected smokers compared with smokers without HIV infection.

Sub-study Aim 2: To assess the association between arrhythmia burden and neurocognitive performance and whether this relationship varies by HIV status.

Sub-study Aim 3: To examine the relationship between arrhythmia burden and measures of depression and whether this relationship varies by HIV status.

BACKGROUND – Main Study

HAART and Increased Life Expectancy among HIV-Infected Individuals. The widespread use of highly active antiretroviral therapy (HAART) has greatly improved survival rates for those diagnosed with HIV/AIDS (Brugnaro et al., 2015; Deeken et al., 2012; Palella et al., 2006). Mortality rates among HIV-infected individuals have declined from 7 deaths per 100 person-years in 1996 to 0.21 deaths per 100 person-years in 2010 (Palella et al., 2006). Despite this decrease in HIV-related mortality, rates of new HIV infections have remained constant, increasing the number of people living with HIV/AIDS four fold (2011; Hall et al., 2008; Palella et al., 1998). Although HAART enhances life expectancy and quality of life, HIV-infected individuals are increasingly vulnerable to non-AIDS-related diseases including cardiovascular disease and lung cancer (Palella et al., 2006; Rubinstein et al., 2014; Vaccher et al., 2014). Thus, addressing modifiable risk factors for disease mortality among HIV-infected individuals, including tobacco use, has become a critical priority (Nahvi and Cooperman, 2009; Pacek and Cioe, 2015).

Smoking Prevalence and Relapse Rates among HIV-Infected Individuals. The rate of smoking in the general population has decreased from >50% in 1965 to 18% today (Agaku et al., 2014). However, clinical populations of smokers, including individuals with cancer (Schnoll et al., 2003), cardiovascular disease (Rigotti et al., 2006), or major depression (Grant et al., 2004) continue to have elevated smoking rates. The persistence of smoking in certain groups of smokers, including HIV-infected individuals, may be partly due to the fact that they have been uniformly excluded from smoking cessation research (Nahvi and Cooperman, 2009; Niaura et al., 2000). Indeed, smoking rates among HIV-infected individuals are 50-74% - about three times higher than in the general population (Burkhalter et al., 2005; Collins et al., 2001; Crothers et al., 2005; Feldman et al., 2006; Webb et al., 2007). Importantly, despite the fact that the majority of HIV-infected smokers

report an interest in quitting smoking, evidence suggests that standard smoking cessation treatments have not been very effective (Pacek and Cioe, 2015). Even with transdermal nicotine (TN) – the most widely used over-the-counter treatment for nicotine dependence (Jonk et al., 2005; Pierce and Gilpin, 2002) – only 10-15% of HIV-infected smokers successfully quit smoking (Ferketich et al., 2013; Humfleet et al., 2013; Matthews et al., 2013) compared to 30% in the general population (Silagy et al., 2004). Thus, there is a clear need to identify mechanisms that underlie smoking behavior among HIV-infected individuals to guide development of population-specific smoking cessation treatments to help more HIV-infected individuals quit smoking.

Health Consequences of Smoking Specific to HIV-Infected Individuals. Recent epidemiological evidence suggests that HIV-infected smokers lose more life-years due to tobacco use than to HIV infection (Helleberg et al., 2013). Tobacco use increases the risk of developing cardiovascular and pulmonary diseases and cancer and can negate the beneficial effects of HAART among HIV-infected individuals (Feldman et al., 2006; Humfleet et al., 2009). Compared to HIV-infected non-smokers, smokers on HAART are less likely to achieve a viral or immunologic response and have a greater chance of developing a viral or immunologic failure (Feldman et al., 2006; Marshall et al., 2009). The risk of developing non-AIDS-defining cancers, including lung cancer, is two to three-fold higher among HIV-infected individuals compared to the general population (Brugnaro et al., 2015). Moreover, smoking among HIV-infected individuals can exacerbate HIV-related symptoms (e.g., respiratory problems, pulmonary pneumonia), worsen overall quality of life (Crothers et al., 2005; Cui et al., 2010; Turner et al., 2001; Webb et al., 2007), and increase the likelihood of death (Pines et al., 2011). Another consequence of smoking on HIV pathogenesis is that it can accelerate the incidence and progression of HIV-associated neurocognitive disorders (HANDs) (Purohit et al., 2013; Purohit et al., 2011).

HIV-Associated Neurocognitive Disorders (HANDs) Impair Quality of Life. HANDs are classified into three categories: HIV-associated dementia (HAD), HIV-associated mild neurocognitive disorder (MND), and HIV-associated asymptomatic neurocognitive impairment (ANI) (Antinori et al., 2007; Robertson and Yosief, 2014). These deficits have been attributed to chronic neuroinflammation as a result of HIV-1 infection (Ballester et al., 2012; del Palacio et al., 2012) and the consequent neuronal damage and degradation via neurobiological mechanisms including neurotoxins that damage synaptic transmission of neurotransmitters [32,46]. Since the advent of HAART, the incidence of HAD – the most severe form of HAND – has substantially decreased from approximately 16% to more recent estimates of 5% (Heaton et al., 2010; Heaton et al., 2011). Nevertheless, milder forms of neurocognitive impairment persist, despite HAART. Indeed, 39%-69% of HIV-infected individuals exhibit deficits in multiple cognitive domains including memory, attention, processing speed, verbal fluency, and executive function (Devlin et al., 2012; Heaton et al., 2011). Importantly, these mild cognitive deficits are associated with functional disabilities including unemployment, difficulty driving, and poor adherence to HAART (Doyle et al., 2013; Schouten et al., 2011; Thames et al., 2013).

HIV-Associated Neurocognitive Disorders may be Exacerbated by Smoking. Abundant evidence suggests that, in the general population, chronic smoking increases the risk of neurocognitive dysfunction and increases levels of global cognitive impairment (Durazzo et al., 2012; Paul et al., 2006; Weiser et al., 2010). Similarly, HIV-infected smokers exhibit clinically significant deficits in learning, memory, and global cognitive function relative to HIV-infected non-smokers (Bryant et al., 2013; Durazzo et al., 2007). Although the mechanism by which smoking contributes to increased risk of HANDs is unknown, several theories have been proposed. For instance, *in vitro* evidence suggests that nicotine and HIV work together to alter synaptic plasticity and neuronal cells (Atluri et al., 2014). Chronic nicotine exposure may also compromise the integrity of the blood-brain barrier and increase the likelihood of exposure to HIV-infected monocytes and/or tobacco constituents, which, in turn, enhances the risk for neurodegeneration (Manda et al., 2010). Thus, in order to better understand why HIV-infected individuals have more difficulty quitting smoking, it will be essential to understand the relationship among HIV infection, smoking, and cognitive function.

Smoking and Cognition: Deficits Produced during Abstinence and the Relationship to Relapse. The nicotine withdrawal syndrome is complex as the time course and nature of symptoms vary across smokers (Hughes, 2007b; Shiffman et al., 2006). In addition to the physiological and psychological symptoms of nicotine withdrawal, cognitive impairment is common, reported by nearly 50% of smokers (Hughes, 2007c). These abstinence-induced cognitive impairments peak during the first few days after a quit attempt (Hendricks et al., 2006; Hughes, 2007c; Shiffman et al., 2006) and can be measured objectively in animals and humans. Data across species support the reversal of these effects following administration of nicotine or medications efficacious for smoking cessation (Davis et al., 2005; Patterson et al., 2009; Portugal and Gould, 2007). Interestingly, the domains of cognitive function impaired during abstinence are qualitatively similar to those observed in HANDs (Antinori et al., 2007; McArthur et al., 2010; Robertson and Yosief, 2014; Woods et al., 2004) and include attention (Myers et al., 2005), working memory (Jacobsen et al., 2005; Mendrek et al., 2006), and response inhibition (Ashare and Hawk, 2012; Harrison et al., 2009). The clinical relevance of abstinence-induced cognitive deficits is supported by the high prevalence in treatment seeking smokers (Covey et al., 2008; Hughes, 2007b; Rukstalis et

al., 2005) and the predictive validity for smoking relapse (Culhane et al., 2008; Krishnan-Sarin et al., 2007b; Patterson et al., 2010; Powell et al., 2004). Indeed, abstinence-induced cognitive impairment predicts relapse to smoking, perhaps in an effort to alleviate these symptoms and restore functioning to pre-cessation levels (Culhane et al., 2008; Kassel et al., 2007; Krishnan-Sarin et al., 2007a; Patterson et al., 2010). Evidence supporting the importance of higher order cognitive control in maintaining goal-directed behavior (Hare et al., 2009; Kouneiher et al., 2009) may provide a theoretical framework for explaining why cognitive deficits may be associated with relapse. Indeed, cognitive deficits are gaining attention as a core dependence phenotype and a target for treatment development efforts (Ashare and Schmidt, 2014; Lerman et al., 2007; McClernon et al., 2015; Sofuoglu, 2010). Therefore, the neurocognitive impairments associated with HIV-1 infection and those observed during smoking abstinence may act synergistically to produce greater abstinence-induced cognitive impairments among HIV-infected smokers compared to HIV-uninfected smokers, making quitting smoking particularly difficult for HIV-infected smokers.

Cognitive Deficits may Underlie Smoking Persistence among HIV-Infected Individuals. Convergent evidence suggests that the combination of cognitive deficits associated with HIV-1 infection and cognitive deficits that occur during smoking abstinence may create a dual challenge for HIV-infected smokers during a quit attempt. Specifically, the cognitive deficits observed in HIV-infected individuals may be exacerbated during early nicotine withdrawal, relative to HIV-uninfected individuals (**Aim 1**). Indeed, smokers with comorbid disorders associated with deficits in cognition, such as depression and schizophrenia, may be more likely to experience abstinence-induced cognitive deficits (Ashare et al., 2014; George et al., 2002; Sacco et al., 2005). We theorize that the presence of HANDs coupled with a further decrease in cognitive function during abstinence promotes persistence of smoking. We propose that, following standard treatment, HIV-infected smokers will have more difficulty maintaining abstinence compared to HIV- smokers (**Aim 2**) and this difference will be explained (mediated) by abstinence-induced cognitive deficits (**Aim 3**). It is also possible that HIV-infected smokers experience abstinence-induced deficits in specific cognitive domains that are not observed in HIV-uninfected smokers (**Exploratory Aim**). For example, HANDs is associated with deficits in verbal memory (Devlin et al., 2012; Heaton et al., 2011), but verbal memory is not always impaired during smoking abstinence (Dawkins et al., 2007; Powell et al., 2002). Therefore, we will explore whether specific cognitive domains (e.g., verbal memory) are particularly important in explaining the relationship between HIV status and relapse, relative to other cognitive domains (e.g., executive function). The proposed study is uniquely positioned to identify a primary mechanism that may underlie smoking persistence among HIV-infected individuals with the goal of developing treatment approaches that target cognitive function.

BACKGROUND - Rhythm Monitoring Sub-study

People living with HIV (PLWH) are at a higher risk for developing cardiovascular disease including arrhythmic disorders such as atrial fibrillation (AF) (Hsu et al., 2013). Common HIV-related comorbidities are also associated with greater risk of AF including tobacco use (Heeringa et al., 2008) and hypertension. In pooled analyses of over 30,000 patients without a history of stroke, atrial fibrillation was associated with a 40% increased risk of cognitive impairment (Kalantarian et al., 2013). Importantly, modifiable risk factors such as quitting smoking may reduce the incidence of AF (Chamberlain et al., 2011). This sub-study aims to provide a better understanding of a) the burden of AF and other clinical arrhythmias such as sinus bradycardia, premature ventricular contractions, and non-sustained ventricular tachycardia in HIV-infected smokers compared with uninfected smokers and b) the impact of arrhythmia burden on cognitive and psychiatric measures in HIV infected individuals compared with uninfected persons.

BACKGROUND – Recruitment & Retention Pilot Study

Nearly one in three clinical trials closes prematurely due to under-enrollment. 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. 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. SMS interventions for improving adherence to antiretroviral treatment in people living with HIV as well as smoking cessation have demonstrated efficacy. 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. 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. 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. 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. 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.

OBJECTIVES - Recruitment & Retention Pilot Study

Aim 1: To evaluate the effects of information provision and incentives, alone and in combination, on study enrollment rates.

Hypothesis: Behavioral economic interventions will (Information provision & contingency management) will produce higher rates of enrollment compared to standard recruitment.

CHARACTERISTICS OF THE STUDY POPULATION

1. Target Population

Three hundred (150 HIV+ and 150 HIV-) adult male and female smokers 18 years of age or older who smoke at least 5 cigarettes per day and are interested in quitting smoking will complete the study. HIV-infected smokers will have been diagnosed with HIV/AIDS (identified through the UPENN CFAR Clinical Core, UPHS PennChart reviews and community-based HIV/AIDS organizations and events; see specific criteria below) and HIV-uninfected smokers will have no diagnosis of HIV, confirmed either via blood test (see recruitment strategy below) or self-report. Participants in the HIV+ and HIV- groups will be matched according to key demographic and smoking characteristics (see Accrual below).

At PENN, a previous nicotine patch trial recruited a sample comprised of 45% women and 16% racial/ethnic minorities (Schnoll et al., 2010b). A separate PENN smoking cessation trial that used targeted efforts to recruit minority smokers had a sample comprised of 55% women and 52% racial/ethnic minorities (Schnoll et al., 2011). The UPENN CFAR Clinical Core population is 78% African American and 4% Hispanic American.

2. Accrual

For this trial, we project that we will screen about 1200 smokers over 63 months (allowing six months to complete follow-up). Based on our varenicline trial with HIV-infected smokers (IRB Protocol #815435) and the present inclusion/exclusion criteria, we expect about one-third of these smokers to be eligible for the trial (n = approximately 415). To be conservative, given the possible health problems evident in this population of smokers, we will project less than 25% of participants will withdraw from the trial and more than 75% of subjects will complete follow-ups to have 300 complete the study. As is advised in smoking cessation trials (Hughes et al., 2003), intent-to-treat will be used for primary analyses, with missing outcome data coded as smokers.

Accrual - Cardio Monitoring Sub-study

Eligible participants enrolled in the parent study will have the opportunity to participate in the cardio monitoring sub-study. We estimate that in order to achieve a sample of 50 smokers (25 HIV+ and 25 HIV-) with usable data, we will need to enroll 60 participants into the sub-study. Recruitment for the cardio monitoring sub-study ended as of March 2020.

3. Key Inclusion Criteria

Eligible subjects will be males and females:

1. 18 years of age or older who self-report smoking at least 5 cigarettes (menthol and non-menthol) per day, on average.
2. **HIV status**
    a) HIV-infected smokers: diagnosed with HIV infection and exhibiting viral load of less than or equal to 1000 copies/mL and CD4+ counts of greater than or equal to 200 cells/mm^3 within 12 months prior to enrollment.
    b) HIV-uninfected smokers: negative HIV status will be confirmed by an on-site rapid HIV blood test.
3. Able to use transdermal nicotine (TN) safely, based on a medical evaluation.
4. Residing in the geographic area for at least 4 months.
5. Women of childbearing potential (based on medical history) must consent to use a medically accepted method of birth control (e.g., condoms and spermicide, oral contraceptive, Depo-Provera injection, contraceptive patch, tubal ligation) or abstain from sexual intercourse during the time they are in the study and using transdermal nicotine.
6. If current or past diagnosis of bipolar disorder, eligible if:
    a. No psychotic features
    b. MADRS: total score less than 8 (past 4 weeks), suicidal item score less than 1 (past 4 weeks)
    c. Y-MRS: total score less than 8 (past 4 weeks), irritability, speech content, disruptive or aggressive behavior items score less than 3 (past 4 weeks)
    d. No psychiatric hospitalization or Emergency Room visits for psychiatric issues in the past 6 months
    e. No aggressive or violent acts or behavior in the past 6 months
7. Able to communicate fluently in English.
8. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the combined consent/HIPAA form.

4. Key Exclusion Criteria

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

<u>Smoking Behavior</u>

1. Current enrollment or plans to enroll in another smoking cessation program in the next 4 months.
2. Regular (daily) use of electronic cigarettes, chewing tobacco, snuff, snus, cigars, cigarillos, or pipes.
3. Current use or plans to use nicotine substitutes (gum, patch, lozenge, e-cigarette) or smoking cessation treatments in the next 4 months.

<u>Alcohol/Drug Exclusion Criteria</u>

1. Current untreated and unstable diagnosis of substance dependence (eligible if past use and if receiving treatment and stable for at least 30 days). Current untreated and unstable diagnosis of substance abuse requires Study Physician approval.
2. A positive urine drug screen for cocaine, methamphetamines, PCP, barbiturates, ecstasy (MDMA) at Intake (see Measures and Table 1 for details). At Lab 1 and Lab 2, positive urine drug screens will be reviewed on a case-by-case basis. The PI will determine if the participant will be excluded or allowed to reschedule the visit, at which time they must provide a negative drug screen to continue with the study. Participants believed to have a false-positive result on the drug screen may continue in the study, with investigator approval.

<u>Medication Exclusion Criteria</u>

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

1. Other smoking cessation medications (e.g. Zyban, Wellbutrin, Wellbutrin SR, Chantix)
    a. Note: Once participants are found eligible for the study, they are instructed to only use the NRT provided to them by the study staff. If a subject reports using a non-study smoking cessation medication (including

other forms of NRT), the study physician and PI will evaluate the situation and determine if it is safe for the subject to continue participation.

2. Anti-psychotic medications (if used to treat psychotic symptoms. Other uses may be eligible pending physician approval).
3. Daily use of opiate-containing medications for chronic pain (Duragesic/fentanyl patches, Percocet, Oxycontin). Smokers who report taking opiate-containing medications on an "as-needed" basis will be instructed to refrain from use until their study participation is over and that they will be tested to ensure they have complied with this requirement.
4. Asthma medications/corticosteroids (require physician approval)
5. Anti-depressants (require physician approval)

Medical Exclusion Criteria

1. Females who self-report current pregnancy, planning a pregnancy during the study, or currently breastfeeding/lactating.
2. Current diagnosis of unstable and untreated major depression, as determined by self-report & MINI (eligible if stable for at least 30 days).
3. Current or past diagnosis of psychotic disorder, as determined by self-report or MINI.
4. History of heart disease, stroke or MI, unstable angina, or tachycardia (if stable, requires Study Physician approval).
5. Uncontrolled hypertension (SBP greater than 160 or DBP greater than 100) present at Intake.
    a. Note: If a participant presents with blood pressure greater than 160/100 at sessions occurring on Week 3 (Pre-Quit) or at any other point during the treatment period, they will not be provided with/able to continue on TN unless the study physician grants approval.
6. Previous allergic reaction to TN.
7. History of diabetes (requires Study Physician approval)
8. History of seizures (requires Study Physician approval)
9. History of stomach ulcers (requires Study Physician approval)

Suicide History Exclusion Criteria

1. Suicide risk as indicated by at least one of the following on the Columbia Suicide Severity Rating Scale (the PI &/or PM will be consulted to assess safety and determine eligibility in cases close to the eligibility cutoffs):
    a. Current suicidal ideation (within 30 days of enrollment)
    b. Two or more lifetime suicide attempts
    c. Any suicide attempt within 2 years of enrollment

General Exclusion Criteria

1. Any medical condition or concomitant medication that could compromise subject safety or treatment, as determined by the Principal Investigator and/or Study Physician.
2. Color blindness.
3. Any impairment (physical and/or neurological) including visual or other impairment preventing cognitive task performance.
4. Inability to provide informed consent or complete any of the study tasks as determined by the Principal Investigator and/or Study Physician.

Rhythm Monitoring Sub-Study Exclusion Criteria.

1. Skin sensitivity to monitoring devices (potential subjects will be screened prior to enrollment)

5. Vulnerable Populations

Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study.

6. Populations vulnerable to undue influence or coercion

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

7. Subject Recruitment

Participants will be recruited from the Infectious Disease practices at the Hospital of the UPENN, Presbyterian Hospital, and Pennsylvania Hospital. Dr. Frank will oversee the integration of this study into the clinics, ensuring access to participants, collection of medical data (through UPHS PennChart medical record reviews and laboratory result requests), and access to private consulting rooms for screening at the CFAR clinics. These practices see over 500 patients monthly and more than 200 new patients each year.

After obtaining the necessary training and clinic clearances to access PennChart for participating UPHS clinics, Research Assistants (RAs) will review the electronic medical records to identify potential subjects on a weekly basis (each site has patient smoking status indicated on the record). Individual medical records will be evaluated for eligibility based on the inclusion and exclusion criteria for this study. Daily clinic schedules will be ascertained and RAs will approach patients prior to or after consultation or treatment at the clinic. In addition to in-clinic recruitment, RAs will contact potentially eligible patients (after EMR review) by telephone based on their clinic provider's specified research contact preference. Providers may choose one of the following contact options: 1) all patients identified as initially eligible may be contacted 2) all patient records identified as initially eligible will be sent to the provider via PennChart for review and approval prior to contact 3) all patient records identified as initially eligible may be sent to the provider, who assumes full responsibility and discretion regarding the research contact (no contact may be made by the research staff). Those patients deemed eligible for contact will be contacted by telephone. RAs will introduce the research study and the collaboration between the researchers, infectious disease clinic, and the patient's provider. After assessing the patient's interest, HIV status, and smoking status, the patient will then be provided with additional study information and an opportunity to assess his/her intake eligibility based on a screening questionnaire.

If our accrual rate is lower than anticipated based on our feasibility data, Dr. Metzger and the CFAR CAB will use their connections, or we will attempt to make contact, with community-based organizations that provide services to people living with HIV and/or provide HIV testing services in the greater Delaware and Lehigh Valley regions to promote the trial and enhance accrual rates, through whichever means they use to carry out recruitment, including but not limited to social media, flyers etc. The CFAR CAB, comprised of people with HIV/AIDS or professionals in the treatment of substance use among those with HIV, has numerous linkages to community-based organizations that can be used to enhance participant recruitment should that be necessary. The Bradbury-Sullivan Center in Allentown, PA will also serve as a recruitment site, as well as visit site, to reduce the burden on subjects who live in that area. We will also advertise the study using poster, newspaper, and internet-based advertisements (this includes in-app advertising, Craigslist, and Twitter). Information about the study will be available on the CIRNA and iConnect websites. In addition, research staff will attend HIV/AIDS community events and community clinic intake hours to provide information about the study, distribute recruitment materials, and collect participant contact information via a secure, web-based data collection service. Additionally, we will place recruitment data requests with electronic research data warehouses such as Penn Data Store and Pennomics to obtain lists of pre-consented potential participants. ResearchMatch, a national health volunteer registry that was created by several academic institutions and supported by the U.S. National Institutes of Health as part of the Clinical Translational Science Award (CTSA) program, will also be utilized. ResearchMatch has a large population of volunteers who have consented to be contacted by researchers about health studies for which they may be eligible.

RAs and UPHS medical personnel will screen patients from UPENN and community-based HIV/AIDS clinics to identify potentially eligible and interested participants by phone or in person. Participants recruited through other methods will also be screened by phone or in person. Participants who are eligible and interested in the study will complete the Intake session tasks (Week 0) with research staff. The participant will review and sign an informed consent and HIPAA form, complete eligibility and baseline assessments, and be scheduled for a Week 1. The participant's eligibility will be confirmed by Drs. Leone and Ashare.

To ensure a high level of retention and adherence in this trial we will: 1) educate subjects about the benefits of protocol compliance; 2) schedule in-person sessions at convenient times (e.g., evenings); 3) use a TN adherence component in the counseling protocol (Gariti et al., 2009; Schnoll et al., 2008), and 4) as is standard practice in smoking cessation trials (Schnoll et al., 2010b; Niaura et al., 2005), provide modest financial compensation for session completion and transportation costs.

Referral Bonus Program

Participants who achieve their final booster session (Week 8) 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.

STUDY DESIGN

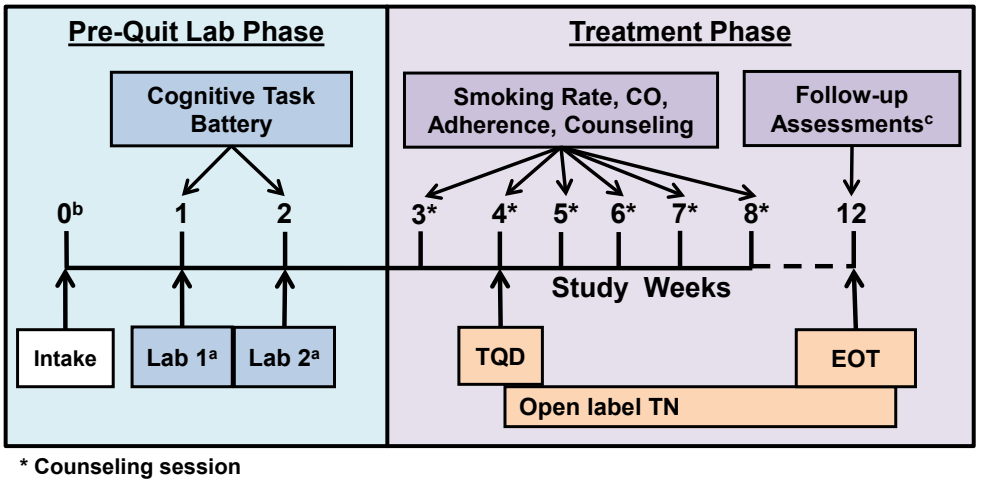
1. Phase

n/a.

2. Design

Main Study. This study will use a prospective observational matched-design to test whether HIV+ smokers (vs. HIV- smokers) are more likely to experience cognitive deficits during nicotine withdrawal and whether these deficits are predictive of smoking relapse. As shown in Figure 1, adult treatment-seeking smokers (N=300; 150 HIV+ and 150 HIV-) will complete this 12-week study, which is divided into two phases: a pre-quit laboratory phase (weeks 0-2) and a treatment phase (weeks 3-12). Subjects will complete two laboratory sessions during the pre-quit phase: once following 24 hours of mandatory smoking abstinence and once while smoking-as-usual (order counter-balanced; abstinence biochemically confirmed). A cognitive task battery assessing working memory, sustained attention, and response inhibition will be administered during each session. During the treatment phase, subjects will receive standard smoking cessation treatment, including six sessions of brief individual counseling (weeks 3-8) and eight weeks of open-label transdermal nicotine (TN) patch treatment (weeks 4-12) [34]. The primary outcomes will be: 1) cognitive performance (e.g., verbal and working memory) following 24-hours smoking abstinence (vs. smoking-as-usual) during the pre-quit phase, and 2) 7-day point-prevalence, biochemically confirmed abstinence rates at end-of-treatment (EOT) for the treatment phase. Since randomization is not possible in this study, we will rely on inclusion criteria and matching to reduce the potential for confounding. More specifically, participants will be

Figure 1. Study Time Points and Assessments



* Counseling session

[a] Session order (24-h abstinent vs. smoking as usual) randomized between-subjects

matched on age, race, education, and smoking rate.

Rhythm Monitoring Sub-Study. This sub-study will explore differences in arrhythmia burden between HIV+ and HIV- smokers and will also look at the relationship between arrhythmic burden and cognitive function. Fifty smokers (25 HIV+ and 25 HIV-) will be asked to wear a non-invasive rhythm monitoring device for two 2-week periods during the course of the study: for two weeks prior to smoking cessation treatment (weeks 2-4) and then two weeks near the end of treatment (weeks 8-10).

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 a randomization table with a high proportion of numbers that correspond to "chips" with little ($1) monetary value. Participants draw by choosing numbers between 1-500 upon completion of an objectively verified target behavior (e.g., attending an Intake visit), and bonuses are often provided for continued performance. A similar strategy has been successful in augmenting visit compliance in several treatment studies. All text reminders will be delivered using the Way 2 Health (W2H) software platform. Upon completion of all requirements for a given visit, participants will receive 5 lottery "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 contains 500 "chips" (numbers that correspond to monetary values within a table): 250 have a value of $0, 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, for maximum possible earnings of $120; (4) SR + IP + CM (IC): In this group, subjects will receive the targeted text messages and receive CM. The design of our study allows us to examine each strategy independently as well as combined to evaluate the optimal approach.

3. Study Duration

Length of Subject's Participation in Study

Subjects will participate in study related activities for approximately 4 months from initial eligibility assessment in the clinic through follow-up. A subject's length of participation may be affected by center or subject scheduling conflicts. Additionally, subjects may be contacted after study participation to clarify self-report data collected during their active participation, or for the collection of additional data or samples, if necessary, for data analysis. The Recruitment & Retention Pilot Study will conclude when all participants have completed the study.

Projected date of completion of the proposed study

We expect to complete accrual in approximately 63 months, with visit completion by June 2022. We expect to obtain our numbers in this timeframe by enrolling approximately 6 subjects per month.

Duration - Rhythm Monitoring Sub-study

Duration of enrollment in the cardio monitoring sub-study will be equivalent to the duration of the parent study (approximately 4 months). However, participants will only be required to wear the monitoring device for four weeks total throughout the course of the study. Recruitment for the sub-study ended in March 2020.

DRUGS OR DEVICES

Transdermal Nicotine

Subjects will receive TN in accordance with FDA guidelines based on self-reported number of cigarettes per day. The patch will be Nicoderm CQ as used in our previous clinical trials (Lerman et al., 2004; Schnoll et al., 2010). Patches will be dispensed several times throughout study participation and subjects will be instructed to begin using the patches the morning of the TQD (Figure 1). Because wearing nicotine patches at night may cause sleep disturbance (i.e., vivid dreams) (Jorenby et al., 1995; Richmond et al., 1994; Staner et al., 2006)), subjects will be instructed that they may remove the patch before going to sleep.

All patches will be purchased from a University of Pennsylvania approved vendor (GlaxoSmithKline). Upon receipt, an inventory will be performed, and a drug receipt log will be completed and signed by the person accepting the shipment. Study staff will count and verify that the shipment contains all the items noted in the shipment inventory. To ensure patch inventory is kept up to date, an on-going inventory will also be performed as patches are distributed. Patches will be stored in a double locked location (i.e., in a locked cabinet in a locked room) at room temperature.

Non-invasive Rhythm Monitoring (Sub-study only)

The device, developed by iRhythm Technologies Inc (San Francisco, CA), is a FDA-approved, compact (123 x 53 x 10.7 mm), lightweight (34 grams), and water-resistant, patch-based, lead wire-free, single-use ECG monitor that adheres to the left upper chest and provides 14 days of continuous beat-to-beat ECG data. The device has higher fidelity recordings and larger storage capabilities that can provide full disclosure ECG recordings beyond traditional 24-48 hour monitors (i.e., Holter). All rhythm monitoring devices will be purchased from iRhythm Technologies. At the end of the 2-week monitoring period, participants will return the device using a pre-labeled, prepaid mailer to the iRhythm Clinical Center (Lincolnshire, IL), which is an Independent Diagnostic Testing Facility where the data are analyzed. A digital signal-processing algorithm, which has been approved by the FDA for clinical use with oversight by Certified Cardiac Technicians, will characterize potential arrhythmias by detection of the heart rate, irregularity, and morphology.

SUICIDAL IDEATION AND BEHAVIOR

The C-SSRS will be administered in-person or remotely (phone call or videoconference) as part of the Intake tasks by a trained member of the staff. Individuals who endorse current (past month) suicidal ideation or two or more lifetime suicide attempts will be ineligible to participate. Any participant that reports a suicide attempt more than 2 years before enrollment will be evaluated by senior clinical staff (PM, Stephanie Josephson, LCSW, or Dr. Ashare) to assess final eligibility based on the complete psychological profile ascertained at the intake session. Because these assessments may cause an adverse emotional reaction, staff will be trained to deal with such reactions and to provide additional referrals if needed. If necessary, referrals to appropriate psychological services will be provided.

STUDY PROCEDURES

1. Procedures

Initial Eligibility Screening.

Recruited subjects will complete an initial eligibility assessment in the HIV/AIDS clinic or over the telephone. This assessment reduces the likelihood that participants attend an Intake Session only to learn that they are ineligible or to allow us to ascertain physician's clearance should the participants have a medical condition that requires approval (e.g., mild hypertension). If a potential participant cannot be reached by phone, staff may send a text for the purposes of scheduling an initial eligibility screening phone call. This will help to reach potential participants who express interest in the study but do not answer phone calls from unrecognized numbers or do not regularly listen to voicemail messages. Texts will be sent from a central study account and not from the personal cellphones of any research staff. Participants 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. Those participants who remain initially eligible will move forward with eligibility-determining tasks as part of the Intake session, which will be completed remotely and in-person. The Intake

session must occur within 60 days of the initial eligibility screening or the participant will have to be re-screened. Subjects will be contacted via phone call, text message, e-mail and/or postal mail to remind them about their scheduled intake visit date and time.

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

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

Remote Study Participation.
All study sessions can be conducted remotely with the exception of some Intake tasks, Lab 1 and Lab 2. We believe this will enable us to continue collection of data in a rigorous way while maintaining the safety of subjects. In the event that a participant is unable to attend an in-person visit, either due to personal reasons or office closure, procedures will be modified to allow for remote collection of data. The procedure for visit reminders will remain the same. Participants will be contacted via call or text to remind them of the time of their session, as well as to remind them that the session will be conducted by phone. Staff will call participants to complete all measures that can be completed by phone. If collected on-site using session paperwork, these data will be stored in the participants' charts and locked in secure filing cabinets, as is standard procedure. In the event that research staff are off-site, paperwork will be completed via RedCap. If RedCap is unavailable, they will utilize Pulse Secure to enable a secure, remote connection to their desktops and the secure server. Data collected remotely will be stored on our secure server, and later transcribed to paper measures and stored in participant charts or entered into RedCap. Items that are typically dispensed to participants at certain visits may be mailed to the participant, including a ClinCard for payment purposes, counseling binders and nicotine patches. If it is anticipated that a participant will have to begin the treatment phase of the study remotely (i.e. begin counseling and receive patches), the study physician will be consulted to ensure it is safe to proceed.

Intake Session (Week 0): Consent, Eligibility Determination, Baseline Measures.
Subjects who pass the pre-screening will be asked to complete tasks to determine their eligibility for the study. Tasks 1-6 listed below may be completed remotely by phone or by videoconference using BlueJeans (HIPAA-compliant), to reduce the length of in-person tasks. If remote, measures will be administered using RedCap surveys. The tasks may take up to 3-3.5-hours if completed entirely in-person. Subjects will be asked to:

1. Complete the consenting process remotely (per procedure outlined in the Consent Process section) or in-person. Staff will review the consent form and answer all questions. Staff will then administer a comprehension questionnaire and review incorrect answers as needed. If completed remotely, subjects who are unable to provide an electronic signature may be mailed a physical version of the consent that must be mailed back to us prior to continuing with the Intake tasks.
2. Complete mental status examinations (Mini International Neuropsychiatric Interview, and CSSRS and MADRS, YMRS, Bipolar Disorder Additional Screener, if necessary) with a trained research staff member.
3. Complete the Shipley Institute of Living Scale.
4. Complete a medical history and concomitant medication review and baseline measures to assess 1) background variables that may serve as covariates and will allow for the assessment of the study's external validity (e.g., smoking history, demographics), 2) mediators (e.g., affect, craving), and 3) baseline smoking behavior. HIV uninfected participants will also complete a brief High Exposure Risk questionnaire.

5. Complete a COVID-19 experience survey.
6. **Cardio monitoring sub-study only:** Complete additional cardiac medical history screening and health-behavior related measures.
7. Provide urine specimens for drug and (if applicable) pregnancy tests. Participants who test positive for study prohibited drugs (see Exclusion Criteria above and Measures below) may be ineligible. Approximately 8mL of the urine sample provided will be stored for analysis of nicotine metabolites. If the sample collection/storage is unsuccessful, this may be attempted again at a later time point.
8. Complete a carbon monoxide (CO) breath assessment to control for prior tobacco exposure. The handheld device uses a disposable mouthpiece, reports CO in parts per million (ppm), and takes about 3 minutes.
9. Complete a blood pressure assessment.
10. **HIV-negative only:** Complete an on-site HIV test with a nurse trained to administer HIV testing and to do required reporting and counseling should a participant test positive for HIV.
11. Provide one 10ml blood sample (2 teaspoons) to assess nicotine metabolite ratio (cotinine and 3-hydroxycotinine).
12. Provide one 8ml blood sample (2 teaspoons) for examining biomarkers of neuroinflammation.

HIV-positive participants will be asked to provide lab work to confirm recent viral load of less than or equal to 1000 copies/mL and CD4+ counts of greater than or equal to 200 cells/mm^3 within 12 months prior to enrollment. If a participant is unable to provide lab work, their clinic may be contacted to obtain the necessary documentation.

If eligible at this point, subjects will schedule their first laboratory session (Week 1).

Laboratory Session 1 (Week 1). This visit should occur within eight weeks of Intake. Allowances may be made for staff or subject scheduling conflicts. This in-person visit is expected to last 1-1.5 hours. During this visit, participants will:

1. Provide urine specimens for drug and (if applicable) pregnancy tests (See Exclusion Criteria above and Measures below).
2. Provide a CO sample.
    a. During the smoking session: To standardize smoking across participants, they will smoke a cigarette about 30-40 minutes prior to beginning the cognitive task battery, as in our past studies (Ashare and Hawk, 2012; Ashare et al., 2014; Ashare et al., 2013a; Tsaur et al., 2015)
    b. During the abstinent session: Participants must have CO readings less than 10ppm or less than 50% CO reading taken at Intake in order to be eligible for the study.
3. Complete questionnaires (see Table 1. Study Measures). Measures may be completed remotely via RedCap to reduce the length of in-person tasks.
4. MADRS, YMRS, Bipolar Disorder Additional Screener, if necessary. Screening measures may be completed remotely via RedCap to reduce the length of in-person tasks.
5. Complete a 1-hour battery of computer tasks which may include tasks assessing working memory (n-back), executive function (Stroop task), response inhibition (stop-signal task), and delay discounting.

Laboratory Session 2 (Week 2). Participants will complete the same activities they completed at Laboratory Session 1 in the alternate smoking condition. The following activities may also take place:

1. **Cardio monitoring sub-study only:** participants may have the non-invasive rhythm monitoring device applied by trained research staff. Participants will be instructed to wear the device for two weeks after which time they will return the device using the study provided pre-paid envelope.
2. Participants will be provided with an iCO monitor (carbon monoxide reader) and will be instructed on how to use it. They will be asked to use this device to measure and report their carbon monoxide levels for the counseling and follow-up sessions.
    a. The device connects to a smartphone or tablet and uses an app that they would download to display readings. If they are unable to use this device and report abstinence following the Pre-Quit session, they

may be asked to come to our center to complete the carbon monoxide assessment. We will use the recommended biochemically verified 7-day point prevalence abstinence variable which is defined as: (a) no self-reported smoking (not even a puff of a cigarette) for at least the 7 days prior to the assessment, and (b) biochemical verification of abstinence via breath CO (Hughes et al., 2003).

b. This device is intended for single use as it cannot be sanitized. We will ask that participants not share the device with friends or family to reduce the risk of contamination.

3. Participants may receive a binder containing all information necessary for their counseling sessions. If preferred, this paperwork may also be mailed or emailed to the participant.

Behavioral Counseling (Week 3-Week 8).

All subjects will receive manual-based counseling from a counselor trained and supervised by the PM or Dr. Ashare. The counseling protocol is based on PHS guidelines for smoking cessation treatment (Fiore et al., 2008), used in our studies with smokers with HIV (IRB Protocol #815435), cancer patients (Schnoll et al., 2010a), and the general population of smokers (Schnoll et al., 2010b; R01 DA025078). Counseling is included given its efficacy at helping smokers quit (Fiore et al., 2008) and to increase study retention. The counseling sessions are designed to enhance awareness of the harmful effects of smoking, assist the person in developing skills to quit and avoid relapse, and instruct the smoker on TN use. Counseling is provided to all participants until Week 8. Counseling will be provided by phone or videoconference primarily, and counselors are not blind to participant group status. Sessions can be arranged at convenient times for the participants, including evenings.

Pre-Quit Session (Week 3): The counseling program begins at Week 3 with a 1-hour "pre-quit" counseling session to prepare for the target quit day. This session focuses on reviewing the participant's history and experience with quitting as well as beliefs about smoking, quitting and perceived barriers to cessation. A quitting plan is initiated and involves identifying smoking triggers and strategies to increase the chance for success, including relying on social support to quit smoking and altering behaviors associated with smoking. TN will be mailed to the participant or dispensed prior to this session and the counselor will discuss the role of TN in withdrawal symptom management and provide directions on how to use TN.

Target Quit Day Session (Week 4): Participants will receive a 30-minute "quit-day" session to review the initial quit attempt, identify potential reasons for relapse, and review a plan for avoiding tempting situations. Adherence to nicotine patch use recommendations will be emphasized.

Relapse Prevention Sessions (Weeks 5-8): Participants will then receive 4 additional 20-minute booster sessions at Weeks 5 through 8 which focus on either reinforcing success and reviewing the quit plan or reestablishing a quit date and restarting the cessation process. The counseling sessions are designed to enhance awareness of the harmful effects of smoking, assist the person in developing skills to quit and avoid relapse, and instruct the smoker on varenicline use.

Cardio monitoring sub-study only: At Week 8 participants may have the non-invasive rhythm monitoring device applied by trained research staff. If necessary, they may be mailed the device and a staff member will contact them to walk through the application remotely. The application will be identical to the one at Lab session 2. Participants will be instructed to wear the device for two weeks after which time they will return the device using the study provided pre-paid envelope.

All counseling sessions may be audio-taped and a random 15% of sessions will be assessed for protocol adherence.

Transdermal Nicotine (Weeks 4-12).

All participants will receive transdermal nicotine (TN) to aid in quitting smoking. TN is available over the counter and is very well tolerated. Participants will use "the patch" in a tapering fashion as recommended by the manufacturer. Participants who smoke 10 or more cigarettes per day will adhere to the following dosing guidelines: 21 mg for 4 weeks; 14 mg for 2 weeks and 7 mg for 2 weeks. Participants who smoke between 5 and 9 cigarettes per day will follow a modified

dosing regimen: 14 mg for 6 weeks and 7 mg for 2 weeks. Participants who smoke between 1 and 4 cigarettes per day will also follow a modified dosing regimen: 7 mg for the full 8-week schedule. The 8-week regimen will commence the morning of the 2nd counseling session (**week 4; TQD**). Participants will be instructed not to smoke beginning that morning and apply a patch. Directions and rationale for use will be discussed during the pre-quit counseling session (**week 3**). Use is reviewed at every post-TQD session and TN will be distributed weekly. If a participant does not have enough patches to continue with their treatment schedule (e.g., used two patches in one day should one fall off), additional supplies of nicotine patches may be mailed or picked up by the participant, if appropriate.

End of Treatment Follow-up Visit (Week 12).

This visit may be used for biochemical verification of self-reported abstinence at EOT (**week 12; Figure 1**), the primary outcome measure for Aim 2. All participants will be asked to complete measures of smoking rate, CO (using iCO monitors if provided) and self-report questionnaires (see Measures).

End of Recruitment and Retention Pilot Debriefing Call.

After the participant has completed their final visit (due to completion, 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.

Bradbury-Sullivan Center Visits

HIV-positive participants recruited at the Bradbury-Sullivan Center who are unable to travel to our center in West Philadelphia without added burden, will have their in-person visits carried out at Bradbury-Sullivan to facilitate their participation in the study. The in-person portion of the Intake and Lab 1 visits will be combined to reduce the number of in-person visits. The Lab 2 visit will be carried out the following week. The Bradbury-Sullivan Center has guaranteed space to carry out proper sample collection and disposal for urine drug screens, as well as other visit tasks listed above, while maintaining a safe distance from subjects. Blood draws and storage of samples will not be carried out for visits conducted at Bradbury-Sullivan. The items that staff will carry to the center in a locked bag are listed below:

1. Encrypted laptop
2. Urine drug/pregnancy screens
3. Blood pressure monitor
4. Carbon monoxide monitoring device
5. Subject chart

Post-Study Follow-up

If necessary, subjects may be contacted after study participation to clarify self-report data collected during their active study participation, or for the collection of additional data or samples. Although procedures are in place to ensure data accuracy during active participation, there are instances when it may be necessary to conduct a post-study follow-up to collect samples which would further support analysis and/or data accuracy when analyzing study outcomes. If study staff are unable to contact a subject for follow-up, no further action will be taken.

COVID-19 Quitting Experience Survey

Enrolled participants who completed their study participation (EOT visit) as of 3/30/2020 may be contacted to complete a survey, intended to capture their experience quitting smoking during the COVID-19 pandemic. These participants will be asked to provide verbal consent for this data collection when contacted, as well as for any future contact needed to clarify any information collected during the survey. For participants enrolled after June 8, 2020, this survey will be administered as part of the Intake tasks.

Regardless of time point, participants will be asked to provide verbal consent for the recording of the survey before administration. If a participant does not consent to completing the survey or being recorded, the survey will not be administered. The survey will be recorded using staff recorders (typically used for recording counseling sessions). All

recordings will be stored on our secure server, and only staff will have access to those files. Recordings will be deleted once all data analysis is complete, approximately one year following the start of collection. Recordings will be used to ensure participant responses were captured exactly when the data is reviewed. Staff will complete the survey via RedCap (i.e. reading off questions and recording answers), and no other personal information will be collected.

The survey will include 24 questions recommended by the NIH for research pertaining to COVID-19, 11 questions related to smoking behavior and the pandemic formulated by staff, and the PHQ-2 and GAD-2 measures for depression and anxiety symptoms (4 questions total). If a participant scores a 3 or higher on either the PHQ-2 or GAD-2 measure, they will be offered resources for coping strategies.

Side Effect Monitoring.

The research team has a licensed, clinical social worker and physician to review initial eligibility and to monitor and address side effects during the trial. To reduce risk for adverse events, we will carefully assess eligibility to ensure that individuals with pre-existing conditions that can increase adverse event risk are excluded.

We will also frequently assess participant treatment reactions with established symptom checklists. These assessments are conducted before and during the 8-week treatment phase by a research staff member. Blood pressure assessments will be completed at the Intake and Lab sessions to establish safety for the treatment phase.
We will use an established coding and reporting system for side effects also used in our previous TN trials (Schnoll et al., 2015; Schnoll et al., 2010). In this system, personnel are trained to administer side effects measures. If a side effect report or a score on an established scale indicates a safety concern, Drs. Ashare and Leone will be notified per the Safety Monitoring and Reporting Protocol and will assume responsibility for the determination of a course of action (e.g., continue to monitor, stop TN). Participants are given contact information so that, if an adverse event occurs, they can contact study staff 24-hours a day. These side effects are also coded and managed by Drs. Ashare and Leone. Serious adverse events are reported to the IRB, NIDA, and FDA in accordance with DSMP reporting procedures and participants may be referred to a PENN out-patient department or to the ER.

Screening/Covariate Measures.

Demographics and Smoking History. Standard questionnaires will be administered remotely or in-person at the Intake visit to collect the following data: demographics (age, gender, marital status, education), age at smoking initiation, cigarette brand, length of prior abstinence periods and current smoking rate. 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 (Heatherton et al., 1991). The FTND scale has satisfactory internal consistency (Cronbach's alpha=. 64) and high test-retest reliability (r=. 88) (Pomerleau et al., 1994).

Urine Drug Screen. The urine drug screen will be administered at Intake, Lab session 1 and Lab session 2. The urine drug screen requires about 30ml of urine and indicates whether the subject has recently taken any of the following: cocaine, PCP, amphetamines, methamphetamines, tricyclic antidepressants, ecstasy, opiates, methadone, benzodiazepines, THC, and barbiturates. Participants with a positive urine drug screen for cocaine, methamphetamines, PCP, barbiturates, ecstasy (MDMA) may be deemed ineligible. The rationale for excluding these participants is because one of the primary outcomes in this study is cognitive function. Thus, excluding individuals who screen positive for substances that may interfere with their ability to perform the cognitive tasks (e.g., barbiturates may slow reaction times) reduces this potential source of variability. In an effort to remain CLIA-compliant, results from urine drug screening will not be shared with participants. Participants will be informed that the testing is for research purposes only and that they will be informed of their eligibility status, but not of the specific testing results.

Urine Pregnancy Test. At the Intake, Lab 1 and Lab 2 sessions, participants will be supplied with a simple, CLIA-waived urine pregnancy screen and informed that pregnant women are not advised to participate in this research study.

Participants will then be instructed to administer the pregnancy test independently and will inform study staff if they would like to continue participation after they have administered the pregnancy screen. Participants will be informed that there is no penalty for discontinuing participation at this point in the visit and that they will still receive travel reimbursement for the visit.

Blood Pressure

At the Intake, participants presenting with elevated blood pressure (i.e., systolic blood pressure greater than 159 and/or diastolic blood pressure greater than 99) will have a second blood pressure reading taken after a ten-minute period in which the participants will be instructed to sit comfortably. If, after the second reading, systolic blood pressure remains greater than 159 and/or diastolic remains greater than 99, the participant will be ineligible for the study. Participants may be invited back for another Intake at least 2 weeks after starting a physician approved blood pressure regimen.

Blood pressure will also be measured at the Lab 1 and Lab 2 sessions. If participants present with elevated blood pressure (above 159 mmHg systolic and/or 99 mmHg diastolic) at any of these visits, the participant will not receive TN at the Pre-Quit visit without approval from the SP or their physician's written approval.

Shipley Institute of Living Scale. All participants will complete the Shipley Institute of Living Scale (SILS) at the Intake visit, remotely via phone/videoconferencing or in-person. The SILS is a self-administered test designed to assess general intellectual functioning in adults and adolescents and to aid in identifying cognitive impairments (Zachary, 2000). 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. The SILS is considered a highly reliable assessment tool; with a good total score internal consistency (Cronbach's alpha= .92).

Medical History

A medical history will be conducted remotely or in-person as part of the Intake Session to review for any contraindications listed previously. The medical history review will be completed by a research staff member. For the HIV-infected group, duration since HIV/AIDS diagnosis, mode of transmission, and viral load and CD4+ counts will also be assessed. Current medication usage will be tracked at each time-point.

HAART Adherence

For the HIV+ group only: HAART adherence will be assessed with a self-report measure and confirmed with a TLFB report at each session following Intake.

Nicotine Metabolic Rate (3-HC/cotinine ratio/TNE).

One baseline blood sample will be collected at Intake and analyzed for nicotine metabolites to determine rate of nicotine metabolism. Nicotine is metabolized to cotinine and then to 3-HC by the P450 (CYP) 2A6 enzyme (Nakajima et al., 1996). The 3-HC/cotinine ratio is a stable measure of the rate of nicotine metabolism, which influences response to nicotine dependence treatments (Lerman et al., 2006; Patterson, Schnoll et al., 2008). Evidence also suggests that HIV-infected smokers metabolize nicotine faster than HIV-uninfected smokers (Earla et al., 2014). Therefore, the NMR will be evaluated as a potential moderator of abstinence-induced cognitive deficits and as a covariate in relapse analyses. Urinary concentrations of NIC and its nine metabolites will be analyzed using liquid chromatography tandem mass spectrometry, as described previously (T. Taghavi et al., submitted manuscript). Urine samples will be diluted and prepared using solid-phase extraction adapted from a previously established method (Miller et al., 2010). The limit of quantification was 1 ng/ml for all compounds. The primary outcome is Total nicotine equivalents (TNE), in nanomole per milligram creatinine, will be calculated as the molar sum of NIC and all nine metabolites (COT, 3HC, NIC-GLUC, COT-GLUC, 3HC-GLUC, NNO, CNO, NNIC, and NCOT) and will be corrected using scaled creatinine data. Urinary creatinine concentrations will be determined using a colorimetric assay according to protocol provided in the Creatinine Assay Kit (MAK080) purchased from Sigma-Aldrich (St. Louis, MO) with a SynergyMX Analyzer (BioTek, Winooski, VT). The

biosamples of individuals who complete the Pre-Quit visit will be sent to the laboratory of Dr. Rachel Tyndale at the University of Toronto for analysis. These analyses will be exploratory.

Neuroinflammation.
The 8.5 mL blood sample collected at Intake will be used to explore the association of biomarkers of neuroinflammation (e.g., C-Reactive Protein; Brain-Derived Neurotrophic Factor; Interleukin-6) with smoking status and cognition. Whole blood will be collected in one SST tube and centrifuged at 3100 RPM for 10 minutes for serum extraction. If separation is not complete, the sample will be centrifuged at the same RPM for an additional 5 minutes. Four 0.5mL serum aliquots will be stored in 2 mL Eppendorf tubes and stored at -80°C until analysis. The serum samples will be assayed by the Laboratory Biomarkers, Quantitative Pharmacology, Neuroimaging, and Neurobehavioral Characterization Core at the Penn Mental Health AIDS Research Center.

HIV Lab Assessment and HIV testing
For the HIV- group only: a rapid test for HIV infection to confirm HIV status will be conducted on-site by an experienced staff member using a drop of blood obtained through a finger stick. The results of the rapid test take approximately 20 minutes. If the rapid test appears to be reactive, a follow-up confirmatory test will be conducted using blood obtained through regular blood drawing procedure. The results of this follow-up test will take 5-7 days.

Viral Load Assessment
A viral load assessment, conducted as part of routine clinical care at Intake and again any time between Week 8 and Week 12, will be ascertained through medical record review and recorded (HIV+ group only).

Psychological and Subjective Measures.

Psychiatric History
Current major depression, lifetime prevalence of psychosis, bipolar disorder, schizophrenia, hypomanic/manic episodes, and substance abuse will be determined via self-report during the phone screen and via semi-structured interview using the Mini International Neuropsychiatric Interview (MINI). The MINI is a 10-15 minute structured interview developed by the World Health Organization to assess major DSM-IV Axis 1 psychiatric diagnoses. This instrument permits both current (past 30 days) and lifetime assessments of psychiatric illness, and recent data support its reliability and validity (Sheehan et al., 1998). The MINI will be administered by a trained research staff member at the Intake visit, remotely via phone/videoconferencing or in-person. There will be 100% review of paper MINIs by the project manager, Stephanie Josephson, LCSW, with relevant training, to maintain quality control. In the event the PM is unable to review MINIs this will be completed by the Principal Investigator, Rebecca Ashare, Ph.D.

Suicidal Behavior and Ideation (C-SSRS).
All participants will complete the C-SSRS (Screening Version) with a trained staff member at the Intake Visit, remotely via phone/videoconferencing or in-person. The C-SSRS is a structured interview that assesses the suicidal behavior and suicidal ideation in subjects (Posner et al., 2009; Posner et al., 2011). Occurrence of lifetime suicidal behavior is defined as having answered “yes” to at least 1 of the 4 suicidal behavior sub-categories (actual attempt, interrupted attempt, aborted attempt, and preparatory acts or behavior). Current suicidal ideation is defined as having answered “yes” to at least 1 of the suicidal ideation sub-categories (wish to be dead, non-specific active suicidal thoughts, active suicidal ideation with any methods without intent to act, active suicidal ideation with some intent to act [without specific plan], and active suicidal ideation with specific plan and intent) over the past month.

HIV High Exposure Risk Questionnaire
HIV negative participants will complete a brief HIV High Exposure Risk Questionnaire that assesses for recent new exposure to the virus. This information will be important toward understanding risk factors relevant to our HIV uninfected population. If a participant is deemed by the questionnaire to be recently at high risk of recent exposure, trained staff may recommend the participant seek additional testing.

Depression and Anxiety

The Hospital Depression and Anxiety Scale (HADS) (Zigmond and Snaith, 1983), a 14-item self-report measure, will assess depression and anxiety symptoms. This scale correlates with clinical ratings of depression and anxiety (Zigmond and Snaith, 1983) and is used with HIV-infected individuals (Savard et al., 1998). Because depressive symptoms are associated with deficits in cognitive function (Gotlib and Joormann, 2010) and lower HAART adherence (Wagner et al., 2011), the HADS will be evaluated as a potential moderator of abstinence effects on cognitive function and relapse. The HADS will be administered at each visit following the Intake, remotely or in-person.

Bipolar Disorder Symptoms

If a diagnosis of bipolar disorder is self-reported or revealed via the MINI at intake, the Montgomery-Asberg Depression Rating Scale (MADRS), Young Mania Rating Scale (YMRS), and a Bipolar Disorder Additional Screener will be completed at all study sessions to evaluate and monitor the presence and severity of bipolar disorder symptoms. An abbreviated version of the MINI may also be used to assess and monitor symptoms. These assessments will be completed remotely, or in-person.

Functional Impairment.

The Patient's Assessment of Own Functioning Inventory (PAOFI) will be used to assess cognitive difficulties in everyday life. The PAOFI assesses areas such as mental acuity, employment, social functioning, shopping, cooking, housekeeping, laundry, driving, use of public transportation, maintaining schedules, medication management, financial management, understanding media events, and child care (Chelune et al., 1986). The degree of functional impairment is used to distinguish between categories of HANDs (Antinori et al., 2007). This measure will be used to evaluate whether those with baseline functional impairment, or functional impairment during nicotine withdrawal, have more difficulty maintaining abstinence. This measure will be administered remotely or in-person.

Positive and Negative Affect.

The Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988), a 20-item Likert-format self-report measure, will be used to assess Positive Affect (PA; 10 items, e.g., enthusiastic, strong) and Negative Affect (NA; 10 items, e.g., distressed, upset), two dominant and generally orthogonal dimensions of affect. PA and NA (PANAS) will be assessed at all study visits (except Intake; remotely or in-person). PA and NA will be assessed using a 24-h time reference for all visits following the Intake.

Withdrawal Symptoms.

The Minnesota Nicotine Withdrawal Scale - Revised version (MNWS-R) (Hughes, 2007d) captures the current state of nicotine withdrawal (Hughes, 2007a; Hughes and Hatsukami, 1986). The scale assesses eight DSM-IV items of nicotine withdrawal including: dysphoria or depressed mood, insomnia, irritability/frustration/anger, anxiety, decreased heart rate, difficulty concentrating, restlessness, and increased appetite/weight gain. 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. This will be administered at all study visits (except Intake; remotely or in-person). Withdrawal will be assessed using a 24-h time reference for all visits following the Intake.

Craving.

The 10-item brief QSU questionnaire on smoking urges (Cox et al., 2001) will be used to assess craving for cigarettes during the medication run-up period. The QSU-B contains 2 subscales (anticipation of reward, relief from negative affect). Craving has also been related to long-term cessation outcome in many, but not all, clinical studies (Killen and Fortmann, 1997). This will be administered at all study visits (except Intake; remotely or in-person). Similar to withdrawal symptoms, craving will be assessed using a 24-h time reference at all visits following the Intake.

Sleep Quality.

The Pittsburgh Sleep Quality Index (PSQI) is a 9-item measure that assesses the quality and patterns of sleep over the past month. It measures seven areas: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep

disturbances, use of sleep medication, and daytime dysfunction. Scoring is based on a 0 to 3 scale, whereby 3 reflects the negative extreme. A sum of 5 or greater indicates a poor sleeper (Buysse et al., 1989). The PSQI has good internal consistency (Cronbach's alpha=0.83), validity, and reliability, and is sensitive to treatment (Backhaus et al., 2002; King et al., 1997). The outcome is the global PSQI score.

Social Support.
Social support during a smoking cessation attempt will be assessed with the abbreviated Partner Interaction Questionnaire (PIQ; Cohen and Lichtenstein, 1990). This 20-item version of the PIQ asks participants to rate the degree to which they expect certain behaviors from their spouse/partner, friend, or relative. It assesses for both positive (e.g., helps you think of substitutes for smoking) and negative behaviors (expressed doubt about your ability to quit/stay quit).

Alternative Reinforcers.
A 45-item version of the Pleasant Events Schedule (PES) (MacPhillamy and Lewinsohn, 1982) will be used to measure traditionally rewarding activities that occur in a person's natural environment (Audrain-McGovern et al., 2011). The cross-product score of frequency (0=none to 2=often) and level of enjoyableness (0=none to 2=very) for each item provides a measure of activity reward. Participants are also asked whether they associate the activity with smoking or the urge to smoke. If the activity is associated with smoking, it is considered a complementary reinforcer. If the activity is not associated with smoking, it is considered a substitute reinforcer. The cross products of substitute reinforcers are summed to provide a score for substitute alternative reinforcers and those for complementary reinforcers are summed to provide a score for complementary alternative reinforcers. Scores have been associated with depression (Audrain-McGovern et al., 2011), discriminate between ex-smokers and current smokers, and predict smoking abstinence in cessation treatment (Audrain-McGovern et al., 2009; Goelz et al., 2014).

Risks and Benefits of Quitting.
The 40-item PRBQ (McKee et al., 2005) uses a 7-point Likert Scale (1=no chance, 7=certain to happen) to assess the likelihood of six potential risks and six potential benefits of quitting occurring if the participant were to stop smoking. The risk subscales were: 1) Weight Gain (I will gain weight.); 2) Negative Affect (I will be more irritable.); 3) Difficulty Concentrating (I will be less able to concentrate.); 4) Social Ostracism (I will feel uncomfortable around smokers.); 5) Loss of Enjoyment (I will miss the taste of cigarettes.); 6) Craving (I will desire a cigarette.). The benefits subscales were: 1) Health; 2) Well-being; 3) Self-esteem; 4) Financial; 5) Physical Appeal; and 6) Social Approval.

Subjective Cognitive Complaints. The PROMIS (Patient-Reported Outcomes Measurement Information System) is a set of person-centered measures that evaluates and monitors physical, mental, and social health in adults and children. The PROMIS Short Form v2.0 Cognitive Function Abilities Subset 8a will be used to assess subjective cognitive complaints. Each of the 8 items are scores from 1 (Not at all) to 5 (Very much). This measure has been validated in medical outpatient samples (Saffer et al., 2015) and among those living with HIV (Solorio et al., 2016).

Treatment Measures.

Concomitant Medication Review.
Subjects will be asked about their use of medications (over the counter and prescription) and substances that may alter subjects' response to the study medication. The Study Physician/Health Care Provider will advise as to whether other medications being taken are contraindicated and prescribe appropriate action from there (i.e., discontinuation of the study medication). The concomitant medication review will be completed at every study visit following the Intake.

TN Adherence.
We will assess self-reported use of patches and may collect unused patches (if applicable) when participants report to our center for study tasks. Any patch adherence that was not collected during the treatment period will be collected at the follow-up assessment at Week 12.

Side Effects.
A checklist of side effects based on the product insert will be administered to participants at all study visits after the Intake. Checklists will be reviewed by staff following completion to confirm participant description of any experienced side effect matches the severity chosen, based on the severity classifications outlined on the form. The frequency and severity of common side effects of TN (Schnoll et al., 2015; Schnoll et al., 2010) will be rated on a 0 (none) to 3 (severe) scale. An open-ended side effects question will also be included. Furthermore, participants will receive written instructions to call the Health Care Provider/Study Physician should they experience any severe side effects or adverse events between study visits. There are no known HAART/TN interactions.

Neurocognitive Outcomes
Neuropsychological tests will be administered in a quiet laboratory testing room on a Dell® desktop computer running the most recent and compatible version of Windows® at the CIRNA. Unless otherwise noted, all tasks will be administered via E-Prime 2.0 (Psychology Software Tools, Inc.). The computerized battery is administered in a random order using clickable icons. Total administration time is about 30 minutes. The outcomes and associated tasks are:

Executive Function. Two tasks will be used to assess executive function: a working memory N-Back task and the Stroop test. In the traditional N-back task, sequences of letters or numbers are displayed, and subjects respond with a button press to a single target using the following rules. During the 1-back condition, subjects respond if the image is identical to the one preceding it. In the 2-back condition, they respond if the stimulus is identical to the one two trials before. In the 3-back condition they respond if the image is identical to the one three trials before. The version of the N-back used in this study utilizes fractal images in place of letters or numbers. The active baseline condition (0-back) is a simple target detection task. The primary outcomes will be total correct and correct reaction time (task duration: about 18 minutes).

The Stroop test will be used to assess executive function. In the Stroop test (Stroop, 1935), participants view a series of words on a computer monitor and using the keyboard, are asked to press the key associated with the color of the word rather than the word itself. Congruent trials are trials in which the word and color match (e.g., the word “green” appears in the color green). Incongruent trials are trials in which, the words are printed in colors that do not match the colors of the words (e.g., the word "red" might appear in green). The primary outcome is the interference score, which is the reaction time to incongruent trials minus the reaction time to congruent trials and measures the ability to suppress a habitual response in favor of an unusual one, accounting for overall speed of naming. Task duration is 5 min.

Verbal Learning and Memory. The Hopkins Verbal Learning Test – Revised (HVLT-R) assesses verbal learning and memory (immediate recall, delayed recall, delayed recognition) (Brandt, 1991). The task has been validated in individuals 16 to 92 years old and within brain-disordered populations (e.g., Alzheimer’s disease, amnestic disorders) as a measure of verbal learning and memory (Benedict et al., 1998). There are six alternate forms, each consisting of a list of 12 nouns (targets) with four words drawn from each of three semantic categories. The semantic categories differ across the six forms, but the forms are very similar in their psychometric properties. The HVLT-R has high test-retest reliability, and its construct, concurrent, and discriminant validity have been well-established (Shapiro et al., 1999). Raw scores are derived for Total Recall, Delayed Recall, Retention (% retained), and a Recognition Discrimination Index. Verbal memory has been shown to be a cognitive domain negatively affected by HIV infection (Antinori et al., 2007; Robertson and Yosief, 2014; Woods et al., 2004). There are two primary outcomes: Total Recall and Delayed Recall. Task duration is 5-10 min with a 25-min delay.

Response Inhibition. The Stop Signal Task (SST) is a measure of response inhibition used in previous work with smokers and shown to be sensitive to abstinence (Ashare and Hawk, 2012; Tsaur et al., 2015). In this task, participants are instructed to respond to left and right-facing arrows on the computer screen. Following practice trials, participants complete three 64-trial task blocks with stop signals (an 800-Hz, 100-ms, 70-dB tone) presented on 25% of trials. The initial stop delay in each block is 250ms and adjusts ±50ms depending on whether the participant successfully inhibits (Logan et al., 1997). Trials consist of a 500-ms warning stimulus, a 1,000-ms go signal (left- and right-facing arrows), and 1,000-ms blank screen inter-trial interval. The primary outcome is stop signal reaction time (SSRT), calculated as the mean RT on go-trials (MRT) minus mean stop delay (MSD). Task duration is 10 min.

Delay Discounting Task. In this paradigm, participants choose between a smaller reward available immediately (e.g., $500 today) and a larger reward available after a longer delay (e.g., $1000 in a month). In this task, people differ in their degree of *delay discounting*, the extent to which they forgo larger monetary magnitudes in the future in order to obtain immediate rewards. As in previous work, the delayed reward will be fixed (e.g., $1000) and the magnitude of the immediate reward adjusts based on the subject's responses (Du et al., 2002). Subjects will make 42 choices (6 trials for each of 7 delays: 1 day, 1 week, 1 month, 3 months, 1 year, 5 years, and 25 years). The primary behavioral outcome will be the subject's *discount rate.* Discount rates will be estimated by fitting a logistic regression that assumes a person's decisions are a stochastic function of the difference in subjective value between the two options (Wileyto et al., 2004). Keeping with standard behavioral findings (Kable and Glimcher, 2007, 2010; Kirby and Santiesteban, 2003; Mazur, 1987), we will assume that subjective value (*SV*) is a hyperbolic function of the reward amount (*A*) and delay (*D*): $SV = A/(1+kD)$, where *k* is the participant's discount rate. Larger values of *k* indicate a greater degree of discounting future rewards. Participants will be told that the questions are hypothetical and that they should make their choices according to what they would choose if they were going to receive that amount. Task duration: approximately 5 minutes.

Outcomes Variables.

Abstinence (primary).

Smoking status will be assessed using the reliable and valid timeline follow-back method (Brown et al., 1998) and by using CO breath samples to biochemically verify the self-report as in prior work (Lerman et al., 2004; Lerman et al., 2015; Schnoll et al., 2015; Schnoll et al., 2010). Participants will be considered to be abstinent if they self-report abstinence (not even a puff of a cigarette) for ≥7 days prior to each assessment beginning 1-week post-TQD (week 4) and provide or report a CO measurement of less than 5 ppm (Cropsey et al., 2014; Perkins et al., 2013). As per convention, participants are assumed to be smoking if they self-report smoking, cannot be reached to provide data at the time-point, fail to provide a breath sample at the time-point, or provide a breath sample at the time-point ≥ 5 ppm (Cropsey et al., 2014; Perkins et al., 2013). The primary outcome will be 7-day point-prevalence abstinence at EOT.

Other Smoking Measures (secondary).

The total number of days abstinent during the first 7 days following the TQD, confirmed with CO, will be a secondary outcome measure. We have shown that this measure is highly predictive of long-term abstinence (Ashare et al., 2013b). Other secondary smoking outcomes include: prolonged abstinence to EOT (week 12) where relapse is 7 consecutive days of self-reported smoking, after a 2-week grace period; continuous abstinence at EOT (no smoking between the TQD and the follow-up; time to 7-day relapse (no grace period); and lapse (smoking episodes not lasting 7 days) and recovery (return to 24-hour abstinence) events (see (Schnoll et al., 2010)).

> *Cessation/Smoking Rate:* Daily smoking (presence and rate) will be assessed at each visit after the Intake Session with the well validated timeline follow-back method (TLFB). These data can be used to assess the timing and rates of lapses (smoking episodes not lasting 7 days), recovery events (return to abstinence), and relapse events, as well as to monitor changes in smoking rates (i.e., # cigarettes/day). These data will also be used to compute and assess secondary measures of smoking cessation (e.g., continuous and prolonged abstinence).
>
> *Carbon Monoxide (CO) Test:* Carbon monoxide will be measured by staff at Intake and the Lab sessions. Following Lab session 2, subjects will be asked to self-report their CO levels using an iCO device (carbon monoxide reader) that will be provided to them at Lab session 2. The iCO smokerlyzer (CoVita, Santa Barbara, CA) is a personal breath smokerlyzer monitor for use with a smartphone or tablet. It works in conjunction with the Smokerlyzer app on iOS and android phones or tablets. The iCO device provides biofeedback from a simple breath test, and it also allows users to track their progress. The app also provides an exhalation guide to coach users on the proper technique to ensure accurate results. The device can be connected to the users' phone through the headphone jack or via Bluetooth. Participants with iOS devices who require adapters will be provided with them by staff. Participants who do not have a smartphone or tablet, or are unable to use the device, will be asked to report to our center for a carbon monoxide assessment if they report abstinence. Since the iCO device cannot be sanitized and does not come with changeable mouthpieces, participants will be advised to limit use of the device to only themselves.

Rhythm Monitoring Sub-Study Measures.

Cardiac Supplemental Medical History.
A supplemental medical history will be conducted remotely or in-person as part of the Intake tasks, to review for sub-study eligibility. The supplemental medical history will be completed by a research staff member and any indications will be reviewed by the study PI/study physician to determine eligibility for the cardio monitoring sub-study.

Risk Assessment Battery (RAB).
This is a self-report questionnaire designed to assess high-risk behaviors associated with HIV transmission. The measure yields two scores: Drug Risk Behavior (e.g. sharing needles, IV drug use) and Sex Risk Behavior (e.g., exchanging sex for drugs, unprotected sexual activity).

The BASIS-24.
The BASIS-24 is a 24 item self-report inventory designed to measure mental health status from the patient's point of view. The items cover 6 domains including: depression/functioning, interpersonal relationships, psychotic symptoms, alcohol/drug use, and emotional lability.

The SF-12.
This measure is used to assess health-related psychosocial functioning. This well-validated, self-report tool measures 8 health-related dimensions: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, general mental health, social functioning, energy/fatigue, and general health perceptions.

Quick Inventory of Depressive Symptomatology- Self Report (QIDS).
The QIDS is a 16-item self-report measure designed to assess the severity of depressive symptoms using the criterion symptoms designated by the DSM-IV.

Atrial Fibrillation (AF) Burden.
AF burden based on non-invasive rhythm monitoring device data collected during two different study period (weeks 0-2 and weeks 8-10). Determination of AF will be confirmed by technicians with no knowledge of the present study, and only episodes of definite AF lasting > 30 seconds will be included (Solomon et al., 2016). These findings will be reviewed by Dr. Deo, who will be blinded to other clinical characteristics. We will calculate the cumulative burden of AF as the percentage of analyzable wear time spent in AF. Total analyzable wear time will be calculated from the point of activation to the point of last recorded analyzable signal. This method will provide us an opportunity to compare uniformly across participants who may have different amount of device wear time.

Recruitment & Retention Pilot Outcomes

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.

Impressions of Research.

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

Table 1. Study Time Points and Measures

Study Week		0	1	2	3	4	5	6	7	8	12	
Session	Phone Screen	Intake	L1	L2	PQ	TQD	C1	C2	C3	C4	EOT	Post-Study
TREATMENT												
TN						X	X	X	X	X	X	
Counseling[d]					X	X	X	X	X	X		
SCREENING/COVARIATES												
Demographics/Smoking Hx/FTND[d]		X										
Urine Drug Screen		X	X	X								
Urine Pregnancy Screen		X	X	X								
Blood Pressure		X	X	X								
Shipley IQ[d]		X										
Medical History[d]		X										
Concomitant Medication Review[d]		X	X	X	X	X	X	X	X	X	X	
Adherence to Anti-retrovirals*[d]			X	X	X	X	X	X	X	X	X	
Nicotine Metabolite Ratio (urine and plasma)		X										
Neuroinflammation		X										
Viral Load Assessment*		X								X[a]		
HIV Lab Assessment/HIV Blood Test[+]		X										
Debriefing Phone Call												X
PSYCHOLOGICAL AND SUBJECTIVE MEASURES												
Psychiatric Hx (MINI)[d]		X										
Suicidality (C-SSRS)[d]		X										
Bipolar Disorder Symptoms (MADRS, YMRS, additional screener)[b d]		x	x	x	x	x	x	x	x	x	x	
HIV High Exposure Risk Questionnaire[+ d]		X										
Depression/Anxiety (HADS) [d]			X	X	X	X	X	X	X	X	X	
Functional Impairment (PAOFI) [d]			X	X	X	X	X	X	X	X	X	
Affect (PANAS) [d]			X	X	X	X	X	X	X	X	X	
Nicotine Withdrawal (MNWS-R) [d]			X	X	X	X	X	X	X	X	X	
Smoking Urges (QSU-B) [d]			X	X	X	X	X	X	X	X	X	
Sleep Quality (PSQI) [d]			X	X		X					X	
Social Support (PIQ) [d]		X									X	
Alternative Reinforcers (PES) [d]		X									X	
Perceived Risks and Benefits of Quitting (PRBQ) [d]		X										
Subjective Cognitive Complaints [d]			X	X	X	X	X				X	
Impact of COVID-19 on Smoking Survey [d]		X										X[f]
TREATMENT MEASURES												
TN Adherence [d]						X	X	X	X	X	X	
TN Side Effects (SEC) [d]					X	X	X	X	X	X	X	
NEUROCOGNITIVE OUTCOMES												
Executive Function (N-back, Stroop)			X	X								
Verbal Learning & Memory (HVLT)			X	X								
Response Inhibition (Stop task)			X	X								
Delay Discounting Task			X	X								
SMOKING OUTCOMES												
Carbon Monoxide (CO)[e]		X	X	X	X	X	X	X	X	X	X	
Smoking Rate (TLFB) [d]			X	X	X	X	X	X	X	X	X	
RHYTHM MONITORING SUB-STUDY ONLY												
Cardiac Supplemental Medical History [d]		X										
Risk Assessment Battery [d]		X										
BASIS-24 [d]		X										
SF-12 [d]		X										
Quick Inventory of Depression Symptomatology [d]		X										

Rhythm Monitoring Device Application[c]				X						X		
RECRTUITMENT PILOT OUTCOMES												
% Eligible at Intake		X										
Attitudes Toward Research	X					X						X
Compared Riskiness Scale [d]	X	X										
Perceived Coercion Scale [d]		X										
Previous Experience with Research Studies	X											
Prior Persuasion Questions [d]		X										
Personal Financial Well-Being	X											

Note. L1 and L2 = laboratory session 1 and 2, respectively; PQ = Pre-Quit visit; TQD = Target Quit Date; EOT = End-of-Treatment; MINI = Mini International Neuropsychiatric Interview; C-SSRS = Columbia Suicide Severity Rating Scale; HVLT = Hopkins Verbal Learning Test

* HIV-infected group only

+ HIV negative group only

[a] A viral load assessment, conducted as part of routine clinical care any time between Week 4 and Week 12, will be ascertained through medical record review or contact with health clinic and recorded.

[b]Only administered if a diagnosis of bipolar disorder is self-reported or revealed via MINI at intake

[c]Rhythm monitoring devices are worn for two weeks. The second device may be mailed to participants for self-application if an in-person visit is not necessary.

[d]Measures will primarily be completed remotely via phone or videoconference to limit the length of in-person visits (if applicable)

[e]Weeks 3-12, participants will self-report using the iCO device. If unable to use the device, and abstinence is reported, participants may be asked to come to our center for CO verification.

[f]Only administered to participants who were enrolled and active on 3/16/2020 and completed their EOT (Week 12) on or after 3/30/2020.

2. Statistical Analysis

Power Analysis and Sample Size.

Our study is a longitudinal between-subject design that seeks to test the following hypotheses: 1) that HIV+ smokers experience larger abstinence-induced cognitive deficits than HIV- smokers (Aim 1); 2) have lower quit-rates than HIV- smokers following standard treatment (Aim 2); and 3) that the association between HIV status and relapse is mediated by abstinence-induced cognitive deficits (Aim 3). We have designed our study to achieve 80% power, testing at a global α=0.05 for each of the hypothesis families (Figure 1). Our sample size of 300 was determined primarily by Aim 2. Based on prior work, we expect a ~15% difference in abstinence rates between HIV+ and HIV- smokers (Ferketich et al., 2013; Humfleet et al., 2013; Matthews et al., 2013; Silagy et al., 2004). With 150 HIV+ vs. 150 HIV- smokers, we have 80% power to detect a difference of ~15 percentage points in point-prevalence abstinence (60% vs. 45%, 50% vs. 35%, 40% vs. 25%), using a z-test on log-odds with a type 1 error of 5%. For Aim 1, we will test the HIV status by abstinence condition (24-h abstinence vs. smoking-as-usual) interaction for 5 cognitive measures using a linear regression with one between- and one within-subjects factor. We will correct for 5 tests using α=0.01. We have 80% power to detect medium effect sizes (Cohen's d=0.4). For Aim 3, we will test whether abstinence-induced cognitive deficits predict quit rates and, using SEM, test whether cognitive deficits mediate the effect of HIV status on quitting. The primary aim will be to test the overall fraction of the effect mediated, which will be tested at α=0.05, which gives 80% power to detect small to medium effects (d=0.32). For our exploratory aim, the component individual deficits will be treated as secondary and tested individually as part of an exploratory analysis, also with a 5% type 1 error. To characterize cognitive deficits in HIV+ smokers, 150 subjects will give us an estimate for each measure with a 95% CI that is 0.32 standard deviations wide (Upper – Lower limits). We will estimate the within-subject correlation for these as repeated measures, with a 95% CI that is 0.32 wide (Upper – Lower) if r=0, 0.24 if r=0.5, and 0.14 if r=0.75. Power was calculated using PASS software, NCSS, Kaysville, UT.

Recruitment & Retention Pilot:

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.

Sensitivity Analysis

Given the substantial changes required to study procedures due to the COVID-19 pandemic, we will conduct a sensitivity analysis to evaluate the impact of the transition to remote visits on study results. We will utilize a 'clustering' approach

and assess the impact of clustering by analyzing outcomes with and without taking clustering into account: comparing the analysis that ignores clustering (i.e. assumes that the data are independent) to a method that will account for clustering (Thabane et al., 2013). To account for clustering, we will include a variable to compare subjects who completed the trial pre-COVID (all in-person) to those who completed the trial post-COVID (mostly remote visits with some in-person tasks).

Data Analysis.

Dr. Wileyto will conduct analyses using Stata, SAS, or R-Language software. Preliminary analyses will determine whether data meet distributional assumptions, and use appropriate transformations where they do not. We will also determine whether subject characteristics (e.g., gender, nicotine dependence, depression, NMR) are associated with HIV status or outcomes using either cross-tabulation (chi-square), *t*-tests, or correlations. Variables showing potential to predict outcome (p=0.2) will be tested for entry as controlling variables. In the event of items missing at random on survey measures, missing items will be imputed prior to calculating final scores using conditional means, estimated with an iterated version of Buck's method (Gleason and Staelin, 1975). Dropout and missed sessions present a more serious issue. The best way to deal with this more serious missing data is to avoid the problem in the first place by keeping subjects connected to the trial and motivated to complete measures. Our clinical trials have a record of >80% compliance and retention rates, thanks to our monitoring of participants and use of incentives to offset costs for travel. Primary analyses will include all subjects who went through the laboratory phase and began NRT treatment; we will assume those who provide incomplete smoking data are smoking. This assumption is the convention in smoking cessation research, but can attenuate the differences between study groups. We will, in addition, conduct analyses with other missing data assumptions, including a completers only analysis, to examine the sensitivity of the primary findings to our assumptions.

Aim 1. We will analyze neurocognitive data with multiple linear regression using a GLM framework. The outcomes will be cognitive deficits measured as a change in response values (see **Section D.4.d.** for description) due to abstinence challenge (24-h abstinence vs. smoking-as-usual). The hypothesized interaction effect of HIV+ status by abstinence condition will be tested by including dichotomous predictors, and examining the corresponding z-score. Although the groups will be matched on key variables, we may also include a small number of covariates (e.g., nicotine dependence, Shipley IQ) that show potential to control for error, admitted to the model at p=0.1. In conjunction with Aim 1, we will be estimating cognitive measures for the HIV+ group, within-subject correlations, and deficits that arise from abstinence challenge. We will summarize point estimates and provide 95% confidence intervals.

Aim 2. We will analyze point-prevalence quit rates using logistic regression. The hypothesized effect of HIV status (HIV+ vs. HIV-) will be tested by including a dichotomous term using the z-score. A small number of other potential controlling variables will be tested for inclusion (p=0.1). Outcomes of the logistic regression analyses will be characterized by odds ratios (e.g., odds of quitting smoking) and 95% confidence intervals. Point-prevalence quit rates at EOT are the primary outcome. Secondarily, we will conduct logistic regression analyses for other assessments of quit rates, including prolonged and continuous abstinence.

Aim 3. Assuming that we find a significant effect of HIV+ status on abstinence at EOT, we will use a correlational and regression-based path model approach for examining mediation of HIV status effects (MacKinnon et al., 2007). Candidate mediators include five cognitive performance task measures (Neurocognitive Outcomes and Table 1), and will be represented as pre-post differences, continuously distributed and treated as normal. The effects of HIV status on candidate mediators, and of mediators on outcome will be assessed using a generalized path model (Stata GSEM), with the model reporting standardized coefficients. The path model partitions the effect of group on outcome into direct (and unexplained) effects versus mediated effects. We will then test the overall mediation hypothesis using the proportion of group effect explained [87, 88, 90] and the strength of each mediating pathway as follows. We will estimate the model for HIV status predicting abstinence without mediators, to estimate the direct effect of status in the unadjusted model ($\hat{\beta}^{\dagger}$). We will then test whether HIV status predicts the candidate mediators, and in turn, test whether mediators predict abstinence in an adjusted group effect model, and estimate the effect of HIV status in the mediator adjusted model ($\hat{\beta}^{*}$). Finally, we will calculate the proportion of HIV status effect explained, which is calculated as $1-\left(\hat{\beta}^{*}/\hat{\beta}^{\dagger}\right)$; the standard error for this quantity is calculated using the delta method, and the mediation hypothesis will be tested using a z-test. The

primary analysis tested at α=0.05 will be global mediation – when all candidate mediators are included in the model, a significant proportion of the HIV status effect will be explained. We will also conduct a secondary analysis using products of the coefficients along each mediating path using a delta-method based z-test.

Exploratory Aim. Using the path model described above we will quantify the proportion of variance explained by each cognitive domain (e.g., executive function, verbal memory, and response inhibition) in the relationship between HIV status and abstinence rates. Since this test is exploratory, we do not have specific hypotheses about which domain will account for more variance and these analyses will be used for hypothesis generating for future work.

Power Analysis, Sample Size and Data Analysis Rhythm Monitoring Sub-Study.

Sample Size.

Our study is a longitudinal between-subject design that seeks to test the following hypotheses: 1) that HIV+ smokers have higher AF burden than HIV- smokers (Aim 1); 2) AF burden will be associated with worse cognitive function (Aim 2) and more depressive symptoms (Aim 3); and 3) that the association between AF burden and cognition and depression will be strong among HIV-infected smokers. Our sample size of 50 participants was determined primarily by Aim 1. Because we are interested in AF burden (a continuous measure) rather than a diagnosis of AF, we have 80% power to detect a medium to large effect size (d=0.7), using a t-test with a type 1 error of 5%. For Aims 2 and 3, we have 80% power to detect a correlation of r=0.4 between AF burden and cognition and depressive symptoms, with α=0.01 to correct for multiple outcomes. The current pilot data will be used to derive effect size estimates to support a larger clinical study.

Data Analysis.

Descriptive statistics (mean, median, standard deviation, skewness, frequency, etc) will be provided for each outcome measure from the rhythm monitoring device and for the sample characteristics (age, sex). Log-transformation will be considered for continuous outcomes with skewed distributions. Multiple comparisons will be corrected and 5% type I error will be maintained to guard against the problem of false positives due to multiple testing.

Aim 1 will use linear regression with AF burden as the primary outcome and HIV status as a between-subjects factor. Cross-sectional associations between arrhythmia burden and cognitive function (Aim 2) and depression indices (Aim 3) at baseline will be assessed using multivariable linear regression with HIV status as a between-subjects factor. All models will include relevant covariates (e.g., smoking rate, age, sex). For our exploratory aim, longitudinal associations between arrhythmia burden and cognitive and psychiatric measures will be assessed using multivariable linear regression relating a) arrhythmia at baseline and b) changes in arrhythmia burden to changes in cognitive function/psychiatric measures. We will test the HIV status by time interaction and include a dichotomous variable for smoking status at end-of-treatment (abstinent vs. relapsed).

3. Confidentiality

All subject information will be kept in a secure filing cabinet that is accessible only to authorized study personnel. All databases containing subject information will be password protected, and again, accessible only to authorized study personnel. Each subject will have a unique study ID number for all data collected. In all data sets we will use ID numbers, only. A separate data set linking names with ID numbers will be accessible only by the senior project staff. All communications about subjects will use the ID number only and never include names or other personal information. All data will be stored until all analyses are completed. No data will be shared with any unauthorized party (i.e., aside from study personnel and regulatory officials). Any publication of data will not identify subjects by name or with an identifier that could be used to reveal identity.

Data collected in MS Access and REDCap databases will be stored on a secure server administered by the Penn Medicine Academic Computing Services (PMACS) organization 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 will also be employed so a user has access only to the functions necessary to complete applicable operations 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. Daily backups are performed to protect data against accidental destruction or corruption.

Remote study sessions will be conducted via phone or via BlueJeans, which is a HIPAA-compliant platform with security features including a room lock to ensure that communications within the platform remain private.
Data will be accessible the study Principal Investigator, Co-Investigators, the Study Physician, other study staff and the UPenn IRB and Office of Human Research.

iRhythm Technologies Inc. will retrieve and process the stored ECG data from the rhythm monitoring device. These data will be transmitted to study investigators at the University of Pennsylvania for analysis. The participant study identification number will be the only identifier utilized. Participants will receive immediate notification of any serious arrhythmias discovered by the study staff and will be encouraged to follow up with their PCP.
How will confidentiality of data be maintained? Check all that apply.
☒ 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.
☒ Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information.
☒ Whenever feasible, identifiers will be removed from study-related information.
☐ A Certificate of Confidentiality will be obtained, because the research could place the subject at risk of criminal or civil liability or cause damage to the subject's financial standing, employability, or liability.
☐ A waiver of documentation of consent is being requested, because the only link between the subject and the study would be the consent document and the primary risk is a breach of confidentiality. (This is not an option for FDA-regulated research.)
☐ Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys.
☒ Audio and/or video recordings will be transcribed and then destroyed to eliminate audible identification of subjects.
☐ Other (specify):

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

4. Subject Privacy/Protected Health Information
The following personal health information will be collected as part of this study:

- Name, address, telephone number, email address
- Date of birth
- Social Security Number (W-9 form)
- Some personal information that may be considered sensitive, such as medical history, psychological history, alcohol use history, etc.
- Results from physical examinations, tests or procedures, including urine drug screening
- Information on smoking, cognition, or HIV-related biomarkers from the urine and blood samples provided at the Intake Session
- Medical Record Number
- Results from HIV testing for individuals who must have their HIV status confirmed on-site
- Results from cardio rhythm monitoring (if applicable)

Every possible precaution, as described above, will be taken to ensure that the privacy of subjects' personal health information will be maintained. Potential participants will be contacted over the phone after responding to recruitment advertisements. Participants will undergo an initial phone screening where preliminary eligibility for the research study will be determined. Only if a participant is initially eligible, will they complete Intake tasks, remotely or in-person, to confirm eligibility. All in-person screenings and participant sessions will be conducted in private rooms with a trained member of the research staff. All data collected over the phone or in-person will be collected by research staff who have completed the CITI Protection of Human Subjects Research Training as well as HIPAA Compliance Training. Information will never be recorded with identifiers other than study ID. Results will not be communicated to other personnel or to the subjects. Data will be accessible to the Study Investigators, Study Physician, study staff, UPenn IRB, Office of Clinical Research, authorized UPenn staff (e.g. accounting and billing matters, provide treatment, etc.).

Future Use of Data and/or Biospecimens.

Participants will be given the option to let us store their biospecimens (blood and urine) and information for use in future research. This storage may be for an indefinite amount of time. The information and samples provided may be shared with other research institutions, e.g. The Abramson Cancer Center at Penn, or researchers working with the NIH who want to learn more about nicotine addiction and/or better ways to help people quit smoking. Whole genome sequencing will not be conducted on samples. We will protect participant confidentiality by first labeling their information and samples with an identification number only (not their name). We will restrict access to the databases that hold their personal information. Their samples will be stored in a locked, private bank, which only authorized personnel will have access to. Permission to store their information and samples for use in future research is optional and they will indicate their choice at the end of the consent form. Participants may withdraw their permission at any time by contacting study staff and letting us know they no longer want their information and samples to be stored for use in future research. Participant samples may be used to create products, including some that may be sold and/or make money for others. If this happens, there are no plans to tell the participant, or to pay them, or to give any compensation to them or their family. Additionally, we will not follow up with participants about the specific research that will be done, and individual research results obtained as part of future research will not be shared with them.

5. Tissue Specimens

Blood.

Two samples (one 10 mL and one 8 mL) of blood will be drawn at the Intake visit to evaluate the nicotine metabolite ratio and neuroinflammatory markers. All specimens are to be collected solely for research purposes. For participants who must have their HIV status confirmed on-site, a finger-prick rapid blood test will be completed at Intake visit. Participants who attend visits at the Bradbury-Sullivan Center will not undergo a blood draw, and will only be HIV-positive, therefore no rapid test will be conducted.

Urine.

A urine sample will be required at the Intake Session, Lab Session 1, and Lab Session 2 for drug screenings. Subjects who test positive for study prohibited drugs will be deemed ineligible. All female participants of child-bearing potential will complete urine pregnancy tests. Approximately 8mL of the urine collected for drug screen will be stored to evaluate nicotine metabolites, unless the visit is conducted at the Bradbury-Sullivan Center, where storage will not be possible. This will be for research purposes only.

6. Genetic Testing

N/A

RISK/BENEFIT ASSESSMENT

1. Potential Study Risks

A detailed description of the study will be given to all subjects, which will include the risks of participation, assurance of full confidentiality, and the knowledge that their freedom to refuse participation or withdraw from the project will not

affect the availability of treatment at the University of Pennsylvania. Informed consent procedures will comply with current standards of the IRB at the University of Pennsylvania. Subjects can choose, as an alternative, to not enroll in this study. Adverse reactions will be assessed and reported as required by Federal law and the regulations of PENN.

Blood Draw. Blood draws may result in bruising and/or slight bleeding at the needle site. This is rare and happens infrequently. Occasionally, blood drawing results in a feeling of faintness. This too is rare. A trained professional will draw blood, so the chances of these discomforts are minimal. Procedures are in place to ensure that PHI is not linked with the results of this research.

HIV Testing. Rapid HIV blood testing may result in mild pain from the finger stick and feelings of anxiety about HIV status results. Staff members administering HIV tests will be trained to provide counseling and recommendations for continued care to participants should they receive a positive result.

Assessments. Subjects may experience emotional distress during 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 assessments and will be trained to deal with such reactions and to provide additional referrals if needed. In addition, if assessments indicate psychiatric concerns, referrals to appropriate psychological services will be provided.

Transdermal Nicotine (TN) Replacement Therapy. All participants will receive transdermal nicotine (TN) patch therapy to aid in quitting smoking. This therapy is available over the counter and is very well tolerated. Nausea, vomiting, weakness, dizziness, and rapid heartbeat occur rarely and are most often caused by continuing to smoke while using the patch. In some cases, nicotine patch use may delay wound healing and may contribute to the risk of peptic ulcer formation. Some individuals who use the patch experience minor skin irritation, such as redness, rash, or minor swelling, and insomnia and dream abnormalities. Sleep problems are a primary mechanism of interest. Participants who experience insomnia and/or dream abnormalities may be instructed to remove the patch during the night while sleeping. Symptoms of an allergic reaction may include difficulty breathing or rash. All of these reactions cease once the patch is removed.

During the pre-quit counseling visit (week 3), the counselor will review the purpose of using the nicotine patch (e.g., to help manage withdrawal symptoms; not a substitute for behavioral quitting strategies), provide directions on how to use the patch (e.g., abstinence from smoking, patch location, time, activity, and potential skin reactions), and answer any questions.

Increased blood pressure and heart rate are possible side effects of TN patch therapy. Blood pressure will be closely monitored at the Intake and Lab sessions prior to the treatment phase. Expanding the upper limit of the blood pressure to less than 160/100 does not increase the risk to subjects enrolled in this trial. The risk of increased blood pressure is no greater than the risk from smoking and quitting smoking will lower an individual's risk. Irregular or rapid heartbeat and palpitations will also be screened for at each visit in the treatment phase.

Participants will complete a patch side effects checklist at each visit. Staff/the PI will review the checklists for serious and persistent side effects. These will be communicated immediately to the study physician. Participants will be instructed to promptly discontinue the patch and contact the SP/PI if they experience severe or persistent local skin reactions (e.g., severe redness, itching, or swelling) at the site of patch application or a generalized skin reaction (e.g., raised patches, hives, or generalized rash). Any serious adverse reactions or significant side effects of TN will be medically evaluated by the study physician. Patch use by such individuals will be monitored and adjusted as needed. Based on our previous experience with NRT studies (Lerman et al., 2004; Schnoll et al., 2010), we expect few serious adverse events. Nevertheless, the study physician will be available to assist with any adverse events and participant safety issues.

Depending on the nature of the side effects the study physician may reduce the dose of the patch or recommend that the participant discontinue the patch.

Reproductive Risks. Because transdermal nicotine safety for an unborn baby is unknown, participants will be told that they should not become pregnant while in this study. Women in the study should not nurse a baby. If the woman is of childbearing potential, she must use an adequate form of contraception or abstain from sexual intercourse for the duration of the study. If the woman is pregnant or breast feeding, she may not participate in this study, and if she becomes pregnant during the study, transdermal nicotine will be immediately discontinued and the subject will be permitted to continue with counseling and assessments only. Women will be asked to take a pregnancy test at the intake session, as well as laboratory sessions 1 and 2.

Withdrawal Syndrome. Many individuals who quit smoking exhibit a pattern of symptoms related to withdrawal from tobacco use. These symptoms include sadness and anxiety, irritability, anger, difficulty concentrating, appetite change and weight gain, insomnia, and decreased heart rate. Eliminating the risk for these would not be possible, although in most cases these events are short-lived and have low intensity, lasting for 1-2 weeks. The study personnel will be trained to recognize these symptoms and educate the participants about them (e.g., their duration, methods for reducing them).

Non-invasive Rhythm Monitoring Device Risks. Based on extensive clinical and research experience, there are very minimal risks of 14-day ECG monitoring using the rhythm monitoring device. Mild skin irritation from the device and feelings of anxiety engendered by the knowledge that their cardiac rhythm is being monitored are possible. Any arrhythmia that occurs during the wear period will be evaluated at the time the device is analyzed. As noted above, Dr. Deo will review all iRhythm reports including the rhythm tracings and, along with Dr. Ashare, will contact any participant with 1) wide QRS tachycardia > 120 beats per minute (bpm) and sustained for > 30 seconds, 2) complete heart block, 3) sinus pauses > 3 seconds, 4) bradycardia less than 40 bpm and sustained for > 30 seconds, 5) AF/atrial flutter with average heart rate less than 40 bpm or > 180 bpm and sustained for 60 seconds, 6) narrow QRS tachycardia > 180 bpm and sustained for 60 seconds. If clinically warranted, Dr. Deo will refer participants to the Penn Arrhythmia Center for more formalized clinical assessment.

Potential Loss of Confidentiality: Every attempt will be made by the investigators to maintain all information collected in this study strictly confidential. We will store subject information in a secure room with limited access. Only people working on this research project can access subject information. We will control access to the computer files that hold this information. This information will not be released to anyone. When the results of the study are published, no names or identifying information will be used.

2. Potential Study Benefits

All participants who enroll in this study will receive behavioral counseling to aid them in their effort to quit smoking. They may also benefit from the knowledge that they are contributing in an important way to potentially furthering scientific knowledge concerning ways to improve cessation treatment for smokers.

3. Alternatives to Participation

As an alternative to enrolling in this study, participants may choose to continue to smoke or to seek assistance with quitting smoking through other treatment programs located in their area, including contacting the national quit-line. At any point in this trial, subjects may decide not to continue in their participation.

4. Data and Safety Monitoring

Who will monitor this study? Check all that apply.

☒ Principal Investigator

☐ Sponsor or contract research organization

☐ NCI sponsored cooperative group
☐ Cancer Center (if mandated by CTSMRC)
☐ Medical monitor
☒ Safety monitoring committee
☐ Data and safety monitoring board

Data and Safety Monitoring will be conducted by the Principal Investigators and the Study Physician. They will review all possible Adverse Events (AEs) and Serious Adverse Events (SAEs). They will ensure that this information is captured in a comprehensive manner and reported according to Good Clinical Practice (GCP). The Principal Investigators, Study Physician, and the research staff will oversee and complete the monitoring process. Monitoring will be performed on an ongoing basis in accordance with the University of Pennsylvania Sponsor-Investigator Standard Operating Procedure PM 004.

The Principal Investigators are responsible for:

1. Obtaining IRB review and approval of a clinical investigation before the investigation is initiated and ensuring continuing review of the study by the IRB in accordance with 21 CFR Part 56;
2. Obtaining informed consent in accordance with 21 CFR Part 50; and
3. Assuring that all staff and subjects understand and accept the obligations incurred in undertaking this study in accordance with 21 CFR Parts 812, 813 and any other applicable regulations.

The research staff is responsible for collecting and recording all clinical data. This includes ensuring that all source documents exist for the data on the Case Report Forms (CRFs), ensuring all fields are completed appropriately, and all corrections are done according to GCPs. Any inconsistencies/deviations will be documented on the CRFs and such findings will be reviewed at the weekly study meetings.

The Project Manager will oversee staff training. Training will include a review of the study protocol, informed consent, telephone screen, CRFs and the procedures that are in place regarding session check-in, data collection, data entry and quality control. All applicable regulations will be reviewed and the roles/responsibilities of each staff member will be explained. All questions will be answered and the training will be documented in a training log, which will be initialed by those involved. The Project Manager will also confirm all appropriate documentation of informed consent and storage of consents in a separate consent binder, and will maintain the study regulatory binder.

The Project Manager, PI, and Study Physician will work together to confirm eligibility criteria. The PI/PM will review charts for each subject to confirm eligibility and will document this review by signing/initialing and dating the final eligibility checklist in each chart.

The data managers will be responsible for creating all CRFs and ensuring that all data will be entered and stored in a manner consistent with the design of the approved CRFs. They will also be responsible for developing the data entry/quality control producers for this study.

a. Enrollment will be complete when 300 subjects (150 HIV+ and 150 HIV-) complete all study requirements. On average, 6 subjects will be enrolled per month. During the course of the study, safety and data quality monitoring will be performed on an ongoing basis in accordance with the University of Pennsylvania Sponsor-Investigator Standard Operating Procedure PM 004 and any findings will be reviewed on a regular basis with the Investigators at the regular study meeting. The monitoring will include a regular assessment of the number and type of serious adverse events. The first monitoring day will occur no more than two weeks after the first subject is entered.

4.2 Adverse Event Reporting and Monitoring

Adverse Event (AE)

An Adverse Event (AE) is a subcategory of the broader category of "Unanticipated Problems Posing Risk to Subject or Others." An adverse event is defined as:

- Any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease occurring at any stage of the study
- 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
- May include an exacerbation of a pre-existing condition, intercurrent illness or injury, drug interaction, drug overdose, failure of expected action or significant worsening of the disease under study
- An event that may compromise the rights, safety, or welfare of research subjects

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

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

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They 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 adverse events must be reported is the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 7 days following the last administration of study treatment. A compilation of any Adverse Events will be provided in the annual and final progress reports to NIDA.

Preexisting Condition
A preexisting condition is one that is present at the start of the study. A preexisting condition will be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings
At screening, any clinically significant abnormality will be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event
All unresolved adverse events will be followed by the investigators until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, a research team member will 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 adverse event that results in hospitalization or prolonged hospitalization will be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

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 will ***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.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Other kinds of events can be labeled "serious adverse events" at the discretion of the investigator.

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided: The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Severity Grading Scale for Adverse Events

Many disease specific groups have developed toxicity grading scales. For example, most cancer clinical trials use the Common Terminology Criteria for Adverse Events (CTCAE) developed by the NCI. The CTCAE provides a descriptive terminology which is utilized for adverse event reporting. A grading (severity) scale is provided for each adverse event term (http://ctep.info.nih.gov). If no guidelines exist, then the following scale can be used:

• Mild: Noticeable to the subject, does not interfere with the subject's daily activities, usually does not require additional therapy, dose reduction, or discontinuation of the study.

• Moderate: Interferes with the subject's daily activities, possibly requires additional therapy, but does not require discontinuation of the study.

• Severe: Severely limits the subject's daily activities and may require discontinuation of the study. This would include all adverse events defined as "serious adverse events".

Attribution/Association with the Drug or Intervention:

An assessment of the relationship between the adverse event and the drug/intervention will be made for each occurrence by the Principal Investigator.

Adverse Event Attribution Categories:

• Unrelated - The AE is clearly NOT related to the intervention
• Possible - The AE may be related to the intervention
• Probably - The AE is likely related to the intervention
• Definitely - The AE is clearly related to the intervention

4.3 Recording of Adverse Events

At each contact with the subject after the Intake, the study research assistant will seek information on adverse events by specific questioning using a side effect checklist and, as appropriate, by examination. Side effects will be monitored through a two-pronged approach. First, participants will complete a side effects checklist (SEC) at each study visit after the Intake reporting with a frame of reference since their last study visit. The SEC will assess the frequency and severity of common side-effects associated with TN. These items will be rated by participants on a 0 (none) to 3 (severe) scale, and can be summed to provide an overall side effects index.

Second, trained staff will ask participants a non-structured, open-ended question (SEC Open-ended) at each study visit with a one-week frame of reference to assess if participants are experiencing any additional symptoms or medical concerns that may be related to their participation in the study.

Research staff are trained to inquire (time of onset, nature of issue reported, possible relation to transdermal nicotine treatment, review of previously reported side effects or concerns, etc.) about any notable side effects or medical concern reported by participants. Based on published reports using the 21, 14, and 7 mg doses of TN we expect few side effects and we expect these side effects to be mild and transient in nature. Any severe (or a pattern of moderate) side effects or notable medical concern will be treated as adverse events, and reported to the Study Physician to determine the severity of the AE, the relationship of the event to the study drug and decide the course of action for the study subject. This consult, including all relevant information, will be documented via email. The Study Physician is knowledgeable of side effects related to transdermal nicotine and is qualified to manage possible side effects. Mild side effects will not be reported as adverse events, but will be recorded and monitored by study staff.
All adverse events occurring during each study period will be recorded. 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. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

4.4 Reporting of Serious Adverse Events and Unanticipated Problems

The following information about adverse events will be reported:

- Study Identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment
- Welfare of subjects.

4.5 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 adverse event (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 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 (An event is "related to the research procedures" if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research 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
Concerning deaths that occur during the course of a research study, the following describes the more rapid reporting requirement of the Penn IRB for specific situations:

- Report the event within 24 hours when the death is unforeseen (unexpected) and indicates participants or others are at increased risk of harm.
- Report the event within 72 hours, for all other deaths, regardless of whether the death is related to study participation.

For reportable deaths, the initial submission to the Penn IRB may be made by contacting the IRB Director or Associate Director. The AE/Unanticipated Problem Form is required as a follow up to the initial submission.

Reporting SAEs
• Penn Subjects (including subjects at networks, affiliates or investigator-initiated sites);
All on-site grade 3 or higher AEs or ADRs regardless of attribution or expectedness will be submitted to the IRB within 30 days. SAEs or SADRs for Penn subjects regardless of attribution or expectedness will be submitted to the IRB within 10 days. Reports will continue to be sent to the IRB for 90 days following the last date the subject received study treatment/therapy or was exposed to an investigational device. All unexpected deaths or deaths related to the study agent(s)/device(s) must be reported within 24 hours. All other deaths should be reported within 30 days.

Other Reportable events:

- For clinical drug trials, 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 cause the sponsor to modify the investigators brochure, 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 in the study.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- **Exception**: A one time, intentional action or process that departs from the IRB and CTSRMC approved study protocol, intended for one occurrence. If the action disrupts the study progress, such that the study design or outcome (endpoints) may be compromised, or the action compromises the safety and welfare of study subjects, advance documented IRB approval is required.
- For exceptions on Industry or Cooperative group sponsored protocols, written approval must be obtained from the Sponsor prior to submitting your exception request to the IRB.
- For in-house studies with a Medical Monitor or Safety Monitoring Committee (not DSMB), approval must be obtained from the Medical Monitor or Safety Monitoring Committee prior to submitting your exception request to the IRB.
- **Deviation:** A one time, unintentional action or process that departs from the IRB approved study protocol, involving one incident and identified retrospectively, after the event occurred. If the impact on the protocol disrupts the study design, may affect the outcome (endpoints) or compromises the safety and welfare of the subjects, the deviation must be reported to the IRB within 10 business days.

Data, Safety and Monitoring Report. The PI will provide a summary of the DSM report on an annual basis as part of the progress report. The DSM report will include the expected versus actual recruitment rates, treatment retention rates, any quality assurance or regulatory issues that occurred during the past year, summary of AEs and SAEs, and any actions or changes with respect to the protocol.

Evidence of Training in Human Subject Research. All research personnel associated with this study have completed the CITI-Protection of Human Subjects Research Training as well as HIPAA Compliance Training.

5. Management of Information for Multi-center Research where a Penn Investigator is the Lead Investigator of a multi-center study, or Penn is the lead site in a multi-site study.

This is a single-site study.

6. Risk/Benefit Assessment

There is minimal risk for serious adverse events. The treatments and procedures used in this study have been shown to be relatively safe. TN has also been studied in several clinical trials and shown to be safe and efficacious. Nevertheless, there are risks in participating in this trial, which are described above. However, the risks of participating in this trial are offset by the potential benefits for participants and society. 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 with HIV/AIDS. All smokers will receive behavioral counseling for smoking cessation and TN.

SUBJECT COMPENSATION

Subjects will be compensated for their time up to $380 (Table 2). This includes transportation expenses related to their participation in the study, with $10 for each in-person visit. In place of $10/session to cover travel expenses, subjects may elect to use a round-trip car ride service (i.e., Lyft) which will be arranged and paid for in full by the research study. If they choose to use the ride service, they will not receive $10 for travel reimbursement. For visits following the Lab sessions, subjects may only be reimbursed for travel if they come to our center for carbon monoxide verification after reporting abstinence. Travel will not be reimbursed for sessions completed entirely by phone.

The "task completion" compensation will depend on participant compliance (arriving on time for in-person sessions, demonstrating effort during cognitive testing etc.). If a participant does not follow study instructions, the task completion compensation may be withheld.

The Greenphire ClinCard will be the primary form of payment for this study. The ClinCard is a reloadable, pre-paid card for the purposes of compensation. Compensation will be loaded onto the ClinCard within 24 hours of completed visits. Staff may ask participants to provide a Social Security Number, or complete a W-9 for this purpose, after determining eligibility so that a ClinCard can be assigned. Clincards may be mailed to subjects following the eligibility determination for the study.

If a participant is ineligible at any point during the study (including after Intake tasks) due to any of the above-mentioned criteria, they will only be compensated $10 for travel, if that had been asked to come to the center and opted out of the ride service.

Participants enrolled in the cardio monitoring sub-study will receive a $40 bonus once cardio monitoring devices have been successfully returned. This will be done via a prepaid envelope provided after application. Participants who successfully 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.

Upon completion of all requirements for a given visit, participants randomized to CM will receive 5 lottery "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 study completion bonus will be 5 extra draws. Thus, at each visit, subjects will have the opportunity to make 5 draws, 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).

Week	Study Visit	Visit Compensation	Task Completion	Travel[5]	Bonus	Total	Lottery[6]
0	Intake	$20	--	$10		$30	5 draws
1	Lab 1	$40	$10	$10		$60	5 draws
2	Lab 2	$40	$10	$10		$60	5 draws
3	Pre-Quit Visit	$20	$10	–		$30	5 draws
4	Clinic Visit (TQD)	$20	$10	–		$30	5 draws
5	Clinic Visit	$20	$10	–		$30	5 draws
6	Clinic Visit	$20	$10	–		$30	5 draws
7	Clinic Visit	$20	$10	–		$30	5 draws
8	Clinic Visit	$20	$10	–		$30	5 draws
12	Follow-Up (EOT)	$40	$10	–		$50	Up to 10 draws
				Study Total:		$**380**	
N/A	Cardio Device Return				$80[1,2,3]	$80	

		Total w/ Cardio Device Return	**$460**	
N/A	Referral Bonus	$60[4]	$60	
		Total w/ Referrals	**$440**	

[1]Eligible participants who consent to cardio monitoring sub-study ONLY
[2]Devices are returned via mail using a pre-paid envelope that has been provided; compensation is loaded to ClinCard when devices have been received by iRhythm
[3]Table shows compensation for both successful cardio device returns
[4] Table shows compensation for three successful referrals
[5] Only paid if subject opts-out of the round-trip car ride service for in-person visits; will be paid if you are asked to come to our center to verify abstinence for clinic visits or follow-up.
[6] Participants may be given 5 "draws" for the chance to earn additional monetary incentives. As a bonus for completing the study, participants will get an additional 5 draws during their final visit.

Traveling via the Ride Service
Participants may elect to use "Roundtrip", which is a car ride service that partners with Lyft to coordinate roundtrip rides to study appointments. Participants will be asked for their preference when scheduling the Intake session via phone, and at each session preceding an in-person session once enrolled. Study staff will schedule each ride using participants' first name, last name, and phone number via Roundtrip's HIPAA compliant platform. Participants will receive a reminder call 24-48 hours prior to their visit to confirm their visit, interest in using the ride service, and preferred pickup/drop-off locations. If the study staff cannot reach participants by 5pm the day prior to their visit, their ride will be cancelled. Participants will still be permitted to attend the visit and will receive $10 to cover travel expenses. If participants need to cancel a previously confirmed ride, they must do so by contacting the study staff immediately, preferably by 5pm the day before their appointment. If participants fail to notify study staff within this timeframe, they may no longer be permitted to use the ride service at future study visits.

INFORMED CONSENT

1. Consent Process

A fully trained study staff member will obtain informed consent using the combined consent and HIPAA form approved by the PENN IRB. This process will take place before study data are collected and prior to any treatment. The consenting process may occur remotely or in person as part of the Intake session. If completed remotely, subjects will be contacted via Blue Jeans (HIPAA-compliant) for a videoconference or by phone. Reviewing the consent form will be completed using a RedCap survey. Staff will email or text the survey link to subjects. Whether in person or remote, staff will review the study description, and all study procedures, potential risks, and information about the study medication will be addressed. Subjects will be given the opportunity to read the consent form in full. Following this, subject questions will be answered, and staff will administer comprehension questions to ensure subject understanding. Any incorrect answers will be addressed by the staff member completing consent. If remote, subjects will indicate within the RedCap survey if they wish to participate and will then be prompted to enter their First and Last name and sign the form using their finger or mouse. Subjects who are unable to provide an electronic signature may be mailed a physical version of the consent that must be mailed back to us prior to continuing with the Intake tasks. If needed, staff may also ask subjects to sign a physical version of the form at their first in-person visit for record keeping. Subjects will be able to download their signed version of the form from RedCap, and staff will also download a version to be saved to the electronic regulatory binder on our secure server, or, printed and placed in our physical binder. If in-person, subjects will receive a physical copy of the combined consent and HIPAA form for their records. Subjects will also be given the PI and Study Physician's contact information should they wish to speak to either of them during the course of the study regarding their consent or the study procedures. The consent process will take place in English, there will be no waiting period, no coercion to participate, and all subjects will be considered competent to provide informed consent (i.e., they will be asked if they understand what they are consenting for).

In collaboration with IRB Protocol #820043, participants who consent to participate in the cardio rhythm monitoring sub-study will also be asked to complete the PMHARC Database and Specimen Repository consent form. This consent allows participants to grant permission for the storage of their data and/or samples, as well as allow future contact regarding new studies.

2. Waiver of Authorization

Verbal consent will be attained from participants via phone for contact that occurs after their study participation has ended. This contact will only be made to collect data that they have already consented to provide as part of the study, and no additional PHI will be collected. Participants will have the option to not answer additional questions related to their participation in the study. If we are unable to get into contact with a participant, the data will be marked as missing.

RESOURCES NECESSARY FOR HUMAN RESEARCH PROTECTION

Training and Quality Assurance

Given ongoing smoking cessation trials (R01 DA033681), systems for training and QA are established to ensure accurate eligibility screening and recruitment, accurate data collection, entry, and management, and optimal delivery of the study protocol. A new Manual of Operations (MOP) will be devised for this study, given unique procedures and measures. Dr. Metzger, who coordinates behavioral research within the PENN CFAR, will assist with staff training to ensure that unique issues related to the population are integrated into the MOP. Training sessions will occur over the first 3 months and annually. Monthly team meetings will review progress, assess adherence, and determine the need for protocol changes or additional training/QA. A study-specific Data and Safety Monitoring Committee will provide oversight. The MOP will ensure that the trial is conducted in a uniform manner over time and across staff. The MOP will describe roles and responsibilities for personnel and provide a detailed description of procedures for each point of contact with participants. For each visit/week, a checklist of events (e.g., measures, counseling) will be created that will be completed by study personnel. CRFs will be created for each measure at each week, and every participant will have a study binder, with sections for every visit/week. Every visit will be “milestoned” (e.g., attended, missed, scheduled) to ensure proper tracking of participants through the trial. A treatment manual for counseling is developed and will be provided to the counselors. The PM/Dr. Ashare will train the counselors using mock participants and didactic instruction. Lastly, a manual for data collection and entry is developed for the RAs and the PM/Dr. Ashare will train the RAs and provide supervision. Ms. Ware, who oversees this DMS, has already developed this DMS for use in other smoking cessation trials. All training will involve didactic instruction in the MOP and mock sessions for all assessments, counseling, and the DMS by the Project Manager and Dr. Ashare. QA focuses on protocol adherence and data validity. We conduct 100% QA checks on study data. This involves comparison of all hard copy CRFs to computer data. In addition, we may audio-tape all counseling sessions and assess protocol adherence by selecting a random 15% of sessions for review.

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