Application for Review of Human Research: IRB Protocol Summary
Biomedical Research **Version 15: 8/17/2020**
IRB# 824504

Names of Investigators:

Name	Department (all at UPenn)
Robert Schnoll, Ph.D., Principal Investigator 3535 Market Street, Suite 4100, Philadelphia, PA 19104 215-746-7143 schnoll@pennmedicine.upenn.edu	Psychiatry
Rebecca Ashare, Ph.D., Co-I	Psychiatry
David Metzger, Ph.D., Co-I	Psychiatry
Frank Leone, MD, Study Physician	Medicine

PROTOCOL TITLE

1. Full Title
Effects of metformin on mood and cognition during nicotine withdrawal

2. Brief Title
Effects of metformin during nicotine withdrawal

STUDY SPONSORSHIP
1. Funding Sponsor
PA Department of Health

2. Primary Sponsor
University of Pennsylvania

ClinicalTrials.gov IDENTIFIER
NCT03593538

PROTOCOL ABSTRACT

There is a need for novel approaches to optimize smoking cessation treatment to help more smokers quit. Mood disturbance and cognitive deficits during nicotine withdrawal may be important treatment targets given their association with smoking relapse. In addition, factors such as HIV-1 infection may exacerbate abstinence effects on mood and cognitive deficits thus increasing the probability of smoking relapse among HIV-infected smokers (HIV+), compared to HIV-uninfected smokers (HIV-). We hypothesize that the FDA-approved medication, metformin, will attenuate withdrawal-related mood disturbance and cognitive deficits and we will explore whether HIV status moderates these effects. Using a well-validated abstinence challenge paradigm, we propose a placebo-controlled double-blind parallel arm study with one between-subjects factor of medication (low dose: 500 mg, high dose: 1500 mg, and placebo). Non-treatment seeking smokers (HIV-: n=54; and HIV+: n=30) will complete this 23-day study. After completing a baseline visit, subjects will complete 4 additional sessions (days 7, 14, 21, 23) to assess side effects, smoking rate, mood, craving, and withdrawal. Cognitive function will also be assessed on days 21 and 23. Subjects will be instructed to refrain from smoking for 24 hours prior to the laboratory session on day 23. The primary outcomes are mood and cognitive function during smoking abstinence (vs. smoking as usual). Secondary outcomes include smoking behavior (e.g., cigarettes per day, carbon monoxide) during the 3-week run-up period. These data will lay the foundation for a larger Phase IIb clinical trial.

OBJECTIVES

1. Overall Objectives

The objective of this proof-of-concept pilot study is to establish feasibility and generate measures of effect size to support future research to evaluate metformin as a potential smoking cessation aid and whether HIV status moderates these effects.

2. Primary Outcome Variable(s)

The primary outcomes are mood and cognitive function following 24h of smoking abstinence.

3. Secondary Outcome Variable(s)

Smoking behavior (e.g., cigarettes per day, carbon monoxide) during the 3-week run-up period.

BACKGROUND

Tobacco smoking is the leading cause of preventable death worldwide and presents a major public health burden [1, 2]. In the United States alone, tobacco smoking accounts for over 400,000 deaths per year, yet 17% of adults continue to smoke [3, 4]. Although the ability of smokers to quit has been aided by new medications and counseling, over 50% of smokers relapse in formal treatment programs within the first week following a quit attempt [5-7] and only 5-10% achieve long-term abstinence [8, 9]. In order to identify novel treatments for smoking cessation, a better understanding of the mechanisms by which relapse occurs is necessary. Two plausible behaviors to target are negative affect and cognitive function. Indeed, in the general population nicotine withdrawal produces increases in negative affect [10-12] and disruption of cognitive function [13-16], often within the first 24 h of abstinence [17, 18]. Importantly, withdrawal-related negative affect [19, 20] and cognitive impairment [21, 22] predict relapse.

Recent epidemiological evidence suggests that HIV+ smokers lose more life-years due to tobacco use than to HIV infection [23]. 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 [24, 25]. Smoking among HIV-infected individuals can exacerbate HIV-related symptoms, worsen overall quality of life [26-29], and increase the likelihood of death [30]. Between 39%-69% of HIV-infected individuals exhibit deficits in multiple cognitive domains including memory, attention, processing speed, verbal fluency, and executive function, known as HIV-associated neurocognitive disorders (HANDs) [31, 32]. These mild cognitive deficits are associated with functional disabilities including unemployment, difficulty driving, and poor adherence to HAART [33-35]. Moreover, rates of psychiatric comorbidity, such as depression, are twice as high among HIV-infected individuals, compared to uninfected individuals [36, 37]. Critically, smoking can accelerate the incidence and progression of HANDs [38, 39] and HIV+ smokers are more likely to report elevated symptoms of depression compared to nonsmokers [40, 41]. Cessation treatments for HIV+ individuals may need to target withdrawal symptoms associated with psychiatric comorbidity and cognitive impairment [42].

Mitigating these features of nicotine withdrawal will require the identification of *new targets* for the development of novel medications or repurposing of existing drugs to treat nicotine dependence. *We made the exciting discovery in mice that chronic nicotine exposure causes robust phosphorylation of AMPK (AMP-activated protein kinase), which is reversed upon nicotine withdrawal*. We found that by increasing pAMPK using the FDA approved drug metformin, we could reduce anxiety-like behavior and cognitive deficits following nicotine withdrawal in mice. This new target is particularly exciting, as it suggests that metformin, the widely used diabetes medication, could be repurposed to provide a novel treatment for nicotine addiction by attenuating negative affect and cognitive deficits during a quit attempt. Indeed, evidence suggests that metformin (vs. placebo) improves cognitive performance and reduces symptoms of depression among depressed patients with type-2 diabetes [43]. Among older adults with diabetes, metformin may attenuate cognitive decline [44]. Moreover, AMPK is a key metabolic regulator that senses the energy status of the cell and regulates fuel availability [45, 46] and recent evidence suggests that smoking cessation is associated with increased risk for metabolic syndrome [47]. A recent study reported increased diabetes and impaired fasting glucose three years following a quit attempt [48] and insulin resistance caused by smoking persists for two years following cessation [49]. Therefore, therapy that addresses not only the symptoms associated with nicotine withdrawal but also another leading cause of preventable disease, i.e. type 2 diabetes [50], would be of great benefit.

We hypothesize that because HIV-infected individuals are more likely to experience mood disturbance [36, 37] and cognitive dysfunction [38, 39], MET (vs. placebo) will attenuate increases in mood disturbance and cognitive dysfunction (verbal and working memory, executive function, and response inhibition) following 24 hours of smoking abstinence among HIV-infected smokers. We will also test whether MET (vs. placebo) reduces smoking behavior (e.g., cigarettes per day, carbon monoxide) during the 3-week drug run-up. Lastly, we will explore whether there is an added benefit to increasing the dose to 1500 mg (vs. 500 mg) without corresponding adverse effects. The proposed study is uniquely positioned to identify a potential new smoking cessation treatment for a population of smokers with high smoking relapse rates.

CHARACTERISTICS OF THE STUDY POPULATION

1. Target Population

Adult, non-treatment seeking smokers (HIV-: n=54; and HIV+: n=30), between the ages of 18-65, reporting consumption of at least 10 cigarettes per day for at least the past 6 months will be the target population for the study. HIV-infected smokers 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, either via blood test (see recruitment strategy below) or self-report.

2. Accrual

One hundred and sixty HIV- and ninety HIV+ subjects will be enrolled in order to have 54 HIV- and 30 HIV+ smokers complete all sessions, accounting conservatively for 30% attrition. Participants will first be screened over the phone and then complete an in-person Intake to ensure final eligibility. Enrolled participants will be randomized to one of the three groups: low dose (500 mg), high dose (1500 mg), or placebo.

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 for the past 6 months.
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 6 months prior to enrollment.
    b) HIV-uninfected smokers: no diagnosis of HIV, either via blood test or self-report.
3. Must not currently be interested in quitting smoking.
4. 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.
5. 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
6. Able to communicate fluently in English.
7. 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 self-report and/or present with the following criteria will not be eligible to participate in the study.

Smoking Behavior:

1. Current enrollment in a smoking cessation program, or use of other smoking cessation medications in the last month or plans to do either in the next 2 months.
2. Daily use of chewing tobacco, snuff and/or snus, or electronic cigarettes.

Alcohol/Drugs:

1. Self-report current alcohol consumption that exceeds 25 standard drinks/week over the past 6 months. Subjects will be told to limit or avoid the use of alcohol while in the study to avoid any adverse reactions to the study medication.
2. 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.
3. A positive urine drug screen for cocaine, amphetamines, methamphetamines, PCP, barbiturates and ecstasy (MDMA) at Intake, or any testing session (see Measures and Table 1 for details). Participants believed to have a false-positive result may continue in the study, with investigator approval.

Medical:

1. Females who self-report current pregnancy, planning a pregnancy during the study, or currently breastfeeding/lactating. All female subjects of child-bearing potential shall undergo a urine pregnancy test at the Intake, Baseline, PQ-Testing and 24-H Testing sessions.
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. Suicide risk as indicated by at least one of the following on the MINI/CSSRS (the PI &/or PM (LCSW) 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 or episodes of suicidal behavior
    c. Any suicide attempt or suicidal behavior within 2 years of enrollment
5. Self-reported kidney and/or liver disease or transplant untreated/unstable or within the past 6 months.
6. Heart/Cardiovascular disease (e.g., angina, coronary heart disease, stroke, etc.) in the past 6 months.
7. Type-1 or type-2 diabetes.
8. Uncontrolled hypertension (BP systolic greater than 159 and/or diastolic greater than 99)*.
9. Liver function tests more than 20% outside of the normal range; Gamma-glutamyl Transpepsidase (GGT) values more than 20% outside of the normal range. If Albumin/Globulin ratios are 20% outside of normal range the abnormal value will be evaluated for clinical significance by the Study Physician and eligibility will determined on a case-by-case basis.
10. Renal disease or renal dysfunction (e.g., serum creatinine levels ≥1.5 mg/dL [males], ≥1.4 mg/dL [females]).
11. A blood glucose level less than 70 mg/dl at any visit.

* Participants presenting with SBP greater than 159 mmHg and/or DBP greater than 99 mmHg at the Intake visit will be instructed to sit quietly for 10 minutes. Then the participant will have a second blood pressure reading taken after a 10-minute period. If, after the second reading the SBP greater than 159 mmHg and the DBP greater than 99 mmHg, the individual will be ineligible to participate, unless determined otherwise by the Study PI/Co-I or Study Physician, upon review.

Medication:

1. Current use or recent discontinuation (within the past 14 days) of any of the following medications:
    a. Anti-anxiety or panic disorder medications (e.g., clonazepam, alprazolam).
    b. Anti-psychotic medications as assessed on a case-by-case basis
    c. Glucophage/metformin
    d. Glyburide
    e. Furosemide or digoxin
    f. Nifedipine

g. Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin)

2. Participants who report taking prescription opiate-containing medications (Duragesic/fentanyl patches, Percocet, Oxycontin) will require physician approval prior to confirming final eligibility.
3. Current use of any smoking cessation medications (e.g., Chantix/varenicline, Zyban/bupropion, nicotine replacement therapy/gum/patch).
4. For safety reasons, HIV-infected smokers taking dolutegravir (Tivicay) or drugs that contain dolutegravir (e.g., Triumeq) should not take more than 1000 mg of metformin per day. Therefore, individuals taking dolutegravir will be force randomized to either the placebo condition or the low dose condition.

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

General Exclusion:

1. Current, anticipated, or pending enrollment in another research program over the next 2-3 months that could potentially affect subject safety and/or the study data/design as determined by the Principal Investigator and/or Study Physician.
2. Not planning to live in the area for the next two months.
3. Color blindness.
4. Any impairment (physical and/or neurological) including visual or other impairment preventing cognitive task performance.
5. Known allergy to study medication.
6. Planned radiologic studies involving the use of intravascular iodinated contrast materials (e.g., intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials) during the course of study participation.
7. Inability to provide informed consent or complete any of the study tasks as determined by the Principal Investigator.
8. Not able to effectively communicate in English (reading, writing, speaking).
9. Missing 3 or more doses during the medication period determined by self-report.

5. Vulnerable Populations

No children under the age of 18, pregnant women, fetuses, neonates, or prisoners are included in this research study.

6. Populations vulnerable to undue influence or coercion

Educationally or economically disadvantaged persons or cognitively impaired persons will be not be targeted for recruitment; however, they may be included in the current study. Because recruitment efforts for this study will be targeted to the greater Philadelphia area, University of Pennsylvania employees and students, and UPHS faculty and staff may be exposed to these advertisements and choose to respond. These individuals are eligible to participate if they meet all inclusion criteria. Status of participation in the current study will be independent of the participant's work or school activities.

7. Subject Recruitment

Participants will be recruited from several sources. Participants who have previously completed studies at our center and have agreed to be re-contacted for future studies will be contacted and invited to participate in this study. Additional recruitment via advertising (i.e., Craigslist, flyers, newspaper or TV ads) will be used to invite smokers from the general population.

Participants will be recruited from the Infectious Disease practices at the Hospital of the UPENN, Presbyterian Hospital, and Pennsylvania Hospital. The PMHARC 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 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 PMHARC Clinical Assessment Core (CAC) will use their connections with community-based HIV/AIDS organizations in the Delaware Valley region to promote the trial and enhance accrual rates. The PMHARC CAC, 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. 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, PennOmics, and PennSeek 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 (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 visit. 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); and 3) provide modest financial compensation for session completion and transportation costs.

Referral Bonus Program

Participants who achieve their final study visit (Day 23) 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).

STUDY DESIGN

1. Phase

N/A

2. Design

We propose to conduct a randomized, placebo-controlled, parallel arm study with one between-subjects factor of medication (low dose, high dose, placebo). Once eligibility is confirmed after Intake, subjects will attend a clinic visit (day 0) to establish baseline smoking rate, mood, and cognition. Subjects will then be randomized to one of three groups (low dose: 500 mg, high dose: 1500 mg, or placebo) and will complete 4 additional sessions (days 7, 14, 21, 23) to assess side effects, smoking rate, mood, craving, and withdrawal (Figure 1). Cognitive function will also be assessed on days 21 and 23. Subjects will be instructed to refrain from smoking for 24 hours prior to the laboratory session on day 23 (Figure 1). Following FDA guidelines, the dosing regimen for metformin extended release (XR) will be 500 mg q.d for the low dose. For the high dose, the dosing regimen will be: 500 mg q.d (days 1-7); 1000 mg q.d (days 8-14); 1500 mg q.d (days 15-23).

Figure 1. Study Design

Group 1: PLA*																							
Group 2: LOW*			Run-up 1[a]							Run-up 2[a]							Run-up 2[a]						24h Abst/Lapse[a]
Group 3: HIGH*			Run-up 1[a]							Run-up 2[b]							Run-up 2[c]						24h Abst/Lapse[c]
Day	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Tasks		d e f							d e							d e							d e f		d e f g
	I	B	Week 1							Week 2							Week 3							Week 4	

Begin study drug

Start 24h Abstinence

Programmed Lapse

* Between-subjects parallel arm design; medication randomly assigned

[a] 500 mg q.d. dose metformin

[b] 500 mg b.i.d. dose metformin (1000 mg total)

[c] 500 mg t.i.d. dose metformin (1500 mg total)

B Baseline assessment

I Intake visit

[d] Study Visit: Side effects, TLFB, CO

[e] Subjective measures (mood, craving, withdrawal)

[f] Cognitive testing

[g] Assessment of smoking reward

3. Study Duration

Estimated length of time to enroll all subjects and complete the study

Enrollment will start in March 2016. We estimate that we will need to telephone screen 660 smokers to enroll 160 HIV- smokers into the study. We expect a drop-out rate of 30% based on prior experience and expect to have 54 HIV- smokers complete the study. In addition, we will telephone screen 400 HIV+ smokers to enroll 90 and have 30 HIV+ smokers complete the study. We estimate enrolling 4-5 smokers per month.

Length of a subject's participation time in study

We estimate it will take a minimum of 4 weeks for a participant to complete the entire study. However, this time period may be longer to accommodate participant schedules or scheduling difficulties between the Intake and baseline visit. Thus, the maximum duration a participant can be in the study is 10 weeks. Additionally, subjects may be contacted after study participation to clarify self-report data collected during their active participation, if necessary for data analysis.

Projected date of completion of the proposed study

We estimate that 54 HIV- and 30 HIV+ smokers will have completed the study by January 2021, and that analyses and reporting will be complete by April 2021.

DRUGS OR DEVICES

Metformin

The study will be performed using metformin, which is currently marketed for the treatment of type 2 diabetes mellitus.

The proposed study follows the typical dosing regimen for metformin for both the low and high dose groups. The dosing regimen for metformin extended release (XR) will be 500 mg q.d for the low dose. For the high dose, the dosing regimen will be: 500 mg q.d (days 1-7); 1000 mg q.d (days 8-14); 1500 mg q.d (days 15-23). This dosing regimen is documented to be safe and well-tolerated in prior clinical studies with no gender or age effects on its pharmacokinetics [51, 52]. Participants will be instructed to take the study medication once daily with their evening meal. Metformin will be purchased and packaged into blister packs by the Investigational Drug Service at the University of Pennsylvania.

An IND exemption has been granted for this study as the results will not be reported to the FDA to support a new drug indication.

Supply, Preparation, Storage, Packaging and Dispensing of Study Medication

Metformin will be purchased and supplied via the University of Pennsylvania Investigational Drug Service (P1377). Matched placebo will be made in-house using sucrose filler in gel capsules. The IDS will store the medication as per the manufacturer guidelines. Specifically, medication will be stored at room temperature (20 – 25 degrees centigrade) and in airtight containers. Metformin and the matching placebo will be packaged in blister packs. IDS will oversee the labeling of all study medication, and will assign each kit, which contains medication for one subject, a unique Pharmacy Randomization Number (PRN).

Once the Study Physician (Dr. Leone) or Nurse Practitioner signs the prescription, medication kits will be ordered and picked up from IDS by a member of the research staff. These kits will be stored in a locked cabinet at our center. Medication will be stored at CIRNA as per manufacturer's guidelines. If needed, staff may request that IDS ship the study medication directly to a subject. IDS will oversee the randomization of subjects to a medication group based on sex, and will label each kit with the subject's study ID number and PRN. The PRN and study ID number must match for each blister pack a subject receives. Each medication kit will consist of 23 days of metformin or placebo (see above for dosing guidelines). To maintain double-blind procedures, all groups will take the same number of pills each day. For example, when the high dose group reaches the 1500 mg dose they will take 3 active pills containing 500 mg each of metformin, the low dose group will take 1 active pill containing 500 mg metformin and 2 placebo pills each day, and the placebo group will take 3 placebo pills.

Regular study drug reconciliation will be performed to document drug assigned, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form and signed by the research staff member who completed the reconciliation.

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated by the research staff. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

SUICIDAL IDEATION

The C-SSRS will be administered remotely (via phone or videoconferencing) as part of the Intake visit by a trained member of the staff. Individuals who endorse current (past month) suicidal ideation or lifetime suicidal behavior will be ineligible to participate. 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. In addition, the CES-D will be administered at follow-up visits to monitor changes in depressive symptoms throughout the trial.

STUDY PROCEDURES

1. Procedures

This is a randomized, double-blind placebo-controlled, parallel arm pilot study of the effects of a low vs. high dose of metformin on abstinence-induced negative mood and cognitive deficits. Participants will complete Intake tasks to determine final eligibility before being enrolled into the study. Study visits will be completed either in-person at our center, or remotely (via phone or videoconferencing). Once eligibility is confirmed, subjects will attend a clinic visit (day 0) to establish baseline smoking rate, mood, and cognition. Subjects will then be randomized to one of three groups (low dose: 500 mg, high dose: 1500 mg, or placebo) and will complete 4 additional sessions (days 7, 14, 21, 23) to assess side effects, smoking rate, mood, craving, and withdrawal (Figure 1). Cognitive function will also be assessed on days 21 and 23. Subjects will be instructed to refrain from smoking for 24 hours prior to the laboratory session on day 23.

2. Study Visits

- Telephone 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 elegibility-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.

- Visit Reminders. Subjects will be contacted via phone call, text message, e-mail and/or postal mail to remind them about their scheduled sessions. Subjects will be asked to indicate their preference after screening.

- Remote Study Participation. If needed, study sessions may be carried out remotely, including some Intake tasks. This enables us to continue collection of data in a rigorous way while maintaining the safety of subjects. Additionally, if 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 shipped to the participant, including study medication and a ClinCard, for payment purposes.

- Intake (Day -1). Participants who pass the pre-screening will be asked to complete tasks to determine their eligibility for the study. Tasks 1-5 listed below may be completed remotely by phone or 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 2.5-hours if completed entirely in-person. Subjects will be asked to:

    1. Complete the consenting process remotely (per procedure outlined in the Informed Consent 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 signed and returned to us prior to continuing with the Intake tasks.
    2. Complete mental status exams (MINI and C-SSRS and MADRS, YMRS, Bipolar Disorder Additional Screener, if necessary) with trained research staff member.

3. Complete routine medical history (self-report), including concomitant medication review with a member of the research staff.
4. Complete the Shipley Institute of Living Scale
5. Complete baseline measures
6. Provide urine specimens for drug and (if applicable) pregnancy tests. Participants who test positive for either the urine drug screen and/or pregnancy test may be ineligible. Participants believed to have a false-positive result may continue in the study, with investigator approval.
7. Provide a CO breath sample.
8. Complete physiological measures such as blood pressure, height and weight.
9. Complete brief physical examination (led by a medical professional). If the provider is off-site this will be conducted via telehealth.
10. Provide an 8.5ml blood sample drawn for the assessment of liver function (LFTs and GGT enzyme levels) and creatinine levels. They will receive final confirmation of eligibility via phone call based on the blood test results.

If a participant meets the above eligibility criteria at the Intake, they will finalize their study schedule with staff.

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

- Final Eligibility Phone Call. When liver function tests have been reviewed and authorized by the Study Physician, a study staff member will call the subjects to inform them of their final eligibility.

  Final Eligibility is defined as: Liver function test results and GGT liver enzyme levels that are no more than 20% outside the normal, clinical range and serum creatinine levels less than 1.5 mg/dL [males], less than 1.4 mg/dL [females]). Albumin/Globulin ratios 20% outside of normal range will be evaluated for clinical significance by the Study Physician and eligibility will determined on a case-by-case basis.

  Eligible subjects will confirm the study schedule and be randomized to a medication group. Ineligible subjects may be referred to other studies at our center.

- Baseline Session (Day 0). Participants will complete a 1.5-hour Baseline session before starting study medication. The Baseline session must be scheduled at least 2 days after Intake, but no more than 30 days can elapse between Intake and Baseline. At the Baseline session participants will:
  1. Provide a CO sample.
  2. Provide urine specimens for drug and (if applicable) pregnancy tests. Participants who test positive for the urine drug screen may be withdrawn from the study. Participants believed to have a false-positive result may continue in the study, with investigator approval.
  3. Complete a blood pressure measurement (See Blood Pressure Procedures under Screening/covariate measures).
  4. Have their blood glucose measured via a handheld glucose monitoring test (see Measures: Screening/Covariates). Subjects who have a low blood glucose level (i.e., less than 70 mg/dl) will be provided a beverage containing at least 15 g carbohydrates (e.g., 4 oz of fruit juice).
  5. Provide two 10 ml and 2 8.5 ml blood samples (less than 3 tablespoons) for examining biomarkers of neuroinflammation (HIV+ subjects only).
  6. Complete questionnaires (smoking rate, concomitant medication review, withdrawal, smoking urges, mood, subjective effects, and side effects). *
  7. MADRS, YMRS, Bipolar Disorder Additional Screener, if necessary*
  8. Complete cognitive tasks which may include tasks assessing working memory (n-back), verbal learning memory (HVLT-R), cognitive flexibility (color shape task), response inhibition (stop-signal task), and delay discounting.

9. Be given instructions for study medication. Medication may be mailed to the participant or provided at the session.

* Some tasks may be completed remotely to reduce the length of in-person visits.

This session can be scheduled any time of day. However, the timing of this session will influence when the Day 21 and Day 23 testing appointments are scheduled. Ideally, the subsequent testing sessions would be at the same time of day but can be scheduled up to 3 hours earlier or later than the Baseline session. However, the sessions may go beyond 3 hours as determined by PI/Co-I discretion.

- Remote Check-In(Days 7 and 14). These sessions will be completed remotely via phone or videoconference and will last about 20 minutes. Participants will be asked to:

  1. Report their smoking rate (timeline followback; TLFB)
  2. Report their medication adherence
  3. Report side effects and complete a concomitant medication review
  4. Complete measures for mood, smoking urges, withdrawal symptoms, and subjective effects
  5. Complete the MADRS, YMRS, Bipolar Disorder Additional Screener, if necessary
  6. Review instructions for medication

  This visit can be scheduled any time during the day and can be moved by plus or minus 1 day to accommodate for participant's schedule.

- Pre-Quit Testing Day (Day 21). Participants will be asked to bring their study medication to this visit. During this 2-hour visit, participants will complete the same activities they completed at the Baseline Session except that they will complete additional measures of pill count.

- Mandatory 24-H Abstinence Period. On Day 22, participants will receive a telephone call to remind them to begin their practice quit attempt approximately 24 hours before their scheduled 24-H testing session on Day 23. Participants will also be reminded that in order to remain eligible for the study, they must remain abstinent during this 24-hour period.

- 24-H Testing Day (Day 23). The 24-H Testing Day occurs after approximately 24 hours of abstinence from nicotine. The Testing Day Visit takes about 2 hours to complete and is split into two parts. The procedures participants will complete within each part of the Testing Day Visit are as follows:
  - 24-H Testing Day Part 1

    On Day 23 Part 1, participants will provide:
    1. A CO sample to verify abstinence. Mandatory abstinence will be biochemically confirmed by a CO reading of less than or equal to 8 ppm. If the CO reading is not less than 9 ppm, but there is a 50% reduction from the CO collected at the Baseline Visit, this will be considered sufficient and the participant may continue as scheduled. If neither condition is met, but participant reports abstinence, investigator approval will be needed for participant to continue with the session. If a participant smokes (self-reported or biochemically confirmed) during the mandatory abstinence period, they may be withdrawn from the study.
    2. A urine sample for a urine drug screen and (if applicable) pregnancy test. If urine drug screen is positive, participants may be withdrawn from the study. Participants believed to have a false-positive result may continue in the study, with investigator approval.
    3. Blood pressure (See Blood Pressure Procedures under Screening/covariate measures)
    4. Have their blood glucose measured via a handheld glucose monitoring test (see Measures: Screening/Covariates). Subjects who have a low blood glucose level (i.e., less than 70 mg/dl) will be provided a beverage containing at least 15 g carbohydrates (e.g., 4 oz of fruit juice).
    5. Report their medication adherence/review pill count*
    6. Report side effects and concomitant medication review*
    7. Complete questionnaires (mood, smoking urges, attention, and withdrawal symptoms) *

8. MADRS, YMRS, Bipolar Disorder Additional Screener, if necessary*
9. Complete a cognitive task battery (described below)

- 24-H Testing Day Part 2 (Programmed Lapse)
    1. Participants will be instructed to smoke one of their own cigarettes in the CIRNA Smoking Laboratory.
    2. Following the programmed lapse, participants will complete the assessments of the subjective and rewarding effects of the 'programmed lapse' cigarette (Table 1).

* Some tasks may be completed remotely to reduce the length of in-person visits.

2.1 Post-Study Follow-up

If necessary, subjects may be contacted after study participation to clarify self-report data collected during their active study participation. 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 maintain data accuracy when analyzing study outcomes. If study staff are unable to contact a subject for follow-up, no further action will be taken.

3. Description of Measures and Variables

3.1 Screening/Covariate Measures

Demographics and Smoking History. Standard questionnaires will be administered remotely or in-person at Intake 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 [53]. The FTND scale has satisfactory internal consistency (Cronbach's alpha=. 64) and high test-retest reliability (r=. 88) [54].

Medical History. A medical history (self-report) and a physical examination will be conducted remotely or in-person at Intake to review for any contraindications listed previously. If the NP/provider is off-site, staff will coordinate a telehealth visit for the participant while they are at the center, via phone, FaceTime or BlueJeans (both HIPAA-compliant). The medical history (including height and weight) 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 be assessed. Current medication usage will be tracked at each time-point.

Psychiatric/Substance Use 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 [55]. The MINI will be administered by a trained research staff member remotely or in-person as part of the Intake session. There will be 100% review of paper MINIs by the PM, a licensed clinical social worker, with relevant training, to maintain quality control. Dr. Ashare, a clinical psychologist, will serve as back-up when needed.

Suicidal Behavior and Ideation (C-SSRS). All participants will complete the C-SSRS (Screening Version) with a trained staff member remotely or in-person. The C-SSRS is a structured interview that assesses the suicidal behavior and suicidal ideation in subjects [56, 57]. 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.

Carbon Monoxide. Carbon monoxide (CO) measures will be made using a Vitalograph Breath CO Analyzer (McNeil International, Inc., Lenexa, KS). The manufacturer will have calibrated this device within the past year. A new, disposable cardboard mouthpiece will be provided for each participant. The device has a digital screen which reports CO levels in parts per million (ppm). Participants will be asked to provide a CO breath sample by taking a large breath, holding their breath for two seconds, releasing the breath, then taking another deep breath and holding their breath for 10 seconds, as per the recommendations of the American Thoracic Society. Then, when instructed to do so, participants will exhale as forcefully and as long as they are comfortably capable. The largest value displayed is recorded during all CO breath samples. CO breath samples will be collected at each in-person study 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, unless determined otherwise by the Study PI/Co-I or Study Physician, upon review.

Blood pressure will be measured at all subsequent in-person visits. If participants present with elevated blood pressure (i.e., systolic blood pressure greater than 159 and/or diastolic blood pressure greater than 99) at any subsequent visit, the staff will follow the same steps listed above. If, after the second reading, systolic blood pressure remains greater than 159 and/or diastolic remains greater than 99, the Study Physician or Study PI will be consulted to discuss whether the participant should continue taking the study medication. Research staff will follow up with the participant accordingly.

Shipley Institute of Living Scale. All participants will complete the Shipley Institute of Living Scale (SILS) remotely or in-person as part of the Intake session. The SILS is a self-administered test designed to assess general intellectual functioning in adults and adolescents and to aid in identifying cognitive impairments [58]. 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 and is considered a highly reliable assessment tool; with a good total score internal consistency (Cronbach's alpha= .92).

Urine Drug Screen. The urine drug screen will be administered at Intake and each testing session (baseline, day 21, and day 23). The urine drug screen requires about 30ml of urine and indicates whether the subject has recently taken any exclusionary drugs (cocaine, PCP, amphetamines, methamphetamines, ecstasy and barbiturates). Participants with a positive urine drug screen for any substance listed above other than THC, opiates, or methadone will 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., benzodiazepines 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. In addition, the current protocol does not utilize PennChart and therefore, results of the screening will not be added to participants' electronic medical records.

Urine Pregnancy Test. At the Intake and each testing session (Baseline, day 21, and day 23), 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.

Depression and Anxiety. The Hospital Depression and Anxiety Scale (HADS) [59], a 14-item self-report measure, will assess depression and anxiety symptoms. This scale correlates with clinical ratings of depression and anxiety [59] and is used with HIV-infected individuals [60]. Because depressive symptoms are associated with deficits in cognitive function [61] and lower HAART adherence [62], 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.

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, remotely or in-person, at all study sessions to evaluate and monitor the presence and severity of bipolar disorder symptoms.

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 [63]. The degree of functional impairment is used to distinguish between categories of HANDs [64]. This measure will be used to evaluate whether those with baseline functional impairment, or functional impairment during nicotine withdrawal, have more difficulty maintaining abstinence.

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.

Liver Function, Gamma-glutamyl Transpepsidase, and Creatinine tests. One 8.5ml blood sample will be drawn at the Intake visit. Blood will be collected and placed in a serum-separator tube (SST) and mixed thoroughly. Samples will be centrifuged at 3100 rpm for 10 minutes. If separation is not complete, the sample will be centrifuged at the same RPM for an additional 5 minutes. The following chemistry will be assessed:

1. Total protein.
2. Albumin.
3. Globulin.
4. Albumin/Globulin ratio.
5. Bilirubin (total, conjugated and unconjugated)
6. Aspartate amino transferase (AST).
7. Alanine amino transferase (ALT).
8. Alkaline phosphatase (AP).
9. Gamma glutamyl transferase (Gamma-GT)
10. Creatinine.

Neuroinflammation. Blood samples will be collected at Baseline and Pre-Quit Testing visits to explore the association of biomarkers of neuroinflammation using a 6 cytokine assay (e.g., C-Reactive Protein; Interleukin-6) with smoking status and cognition (HIV+ group only). Whole blood will be collected in two EDTA tubes and two SST tubes at each visit and delivered to the Laboratory Biomarkers, Quantitative Pharmacology, Neuroimaging, and Neurobehavioral Characterization Core at the Penn Mental Health AIDS Research Center for storage and analysis.

Blood Glucose. Because metformin may lower blood glucose, glucose levels will be measured at each in-person study visit. As recommended by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), blood glucose levels in non-diabetic individuals less than 70 mg/dl may indicate hypoglycemia. The Abbott Precision Xtra Blood Glucose & Ketone Monitoring System will be used to measure blood glucose (https://freestyleserver.com/Payloads/IFU/2017july/ART24315-002_rev-A_WEB.pdf). This device is indicated for home

and professional use. As recommended by the manufacturer, the device will be cleaned and disinfected after each use. A trained member of the research staff will obtain a drop of blood (approximately 0.3 microliter) via a finger prick using a lancing device. The device provides a blood glucose reading within 60 seconds. Individuals who have a blood glucose level less than 70 mg/dl will be provided a beverage containing 15 g of carbohydrate (e.g., fruit juice or soft drink) and asked to wait in the laboratory. After 15 minutes, blood glucose will be rechecked to ensure it is greater than 70 mg/dl before allowing the participant to leave. Participants who present with blood glucose less than 70 mg/dl may be withdrawn from the study.

3.2 Treatment Variables

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.

Side Effects. A checklist of side effects based on the product insert will be administered 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 metformin 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.

Pill Count/Adherence. Medication adherence will be assessed by pill count at each study visit [65].

3.3 Primary Outcomes

Mood: Positive and Negative Affect. The Positive and Negative Affect Schedule (PANAS) [66], 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 the Intake). PA and NA will be assessed using a "past week" time reference for all visits except the 24-h testing visit on Day 23, which will use a 24-h time reference.

Neurocognitive Measures. Neuropsychological tests will be administered in a quiet laboratory testing room on a Dell® desktop computer running on 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 ~ 45 min. The tasks are:

- *N-back Working Memory Task*: 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. The version of the N-back used in this study utilizes fractal images in place of letters or numbers. 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 active baseline condition (0-back) is a simple target detection task. The primary outcomes will be total correct and correct reaction time (task duration: ~18 minutes).
- *Stop Signal Task (SST):* The SST is a measure of response inhibition, or the ability to inhibit a prepotent response, and has been used in previous work with smokers [13]. In this task, participants are instructed to press labeled keyboard keys as quickly and as accurately as possible to indicate the direction the arrow faced ("z" for left; "/" for right). Following a 32-trial practice, stop signals (an 800-Hz, 100-ms, 70-dB tone) are presented on 25% of trials for a 32-trial practice and three task blocks of 64 trials each. The initial stop delay in each block is 250 ms and adjusts by 50 ms increments depending on whether the participant is able to successfully inhibit a response [67]. The adjusting stop delay allows the determination of the delay at which inhibition occurs on approximately 50% of trials. All trials consist of a 500-ms warning stimulus followed by a 1,000-ms go signal (left- and right-facing arrows) and 1,000-ms blank screen intertrial interval. Mean RT for each block is calculated based on valid responses (i.e., RT greater than 200 ms),

and only blocks with 20–80% inhibition and at least 80% accuracy are included in analyses. Stop signal reaction time (SSRT) is the primary dependent variable and is calculated by subtracting the mean stop delay from the mean RT on go-trials (task duration: ~10 minutes).

- *Color Shape Task*: The Color Shape Task is a measure of flexibility. In each trial of this task (Miyake, Emerson, Padilla, & Ahn, 2004), a cue letter (C or S) appears above a colored rectangle with a shape in it (outline of a circle or triangle). Participants are instructed to indicate whether the color is red or green when the cue is C, and whether the shape was a circle or triangle when the cue is S. The colored rectangles are approximately 1.7" wide and 1.4" high, the circles were approximately 1.1" in diameter, and the triangles were 1.25" on each side. The color-shape figure appears in the center of the screen and the cue letters are centered 3/8" above its top edge.
- *HVLT Task:* 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.
- *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.

3.4 Secondary Outcomes

Smoking Rate (TLFB). We will assess the number of cigarettes smoked on each day throughout the study. A standard timeline follow-back (TLFB) method will be used [68], as we have done previously [69] to assess self-reported smoking rate.

Withdrawal Symptoms. The "Minnesota Nicotine Withdrawal Scale - Revised version"(MNWS_R) [70] captures the current state of nicotine withdrawal [71, 72]. 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 the Intake). Withdrawal will be assessed using a "past week" time reference for all visits except the 24-H testing visit on Day 23, which will use a 24-h time reference.

Craving. The 10-item brief QSU questionnaire on smoking urges [73] 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 [74]. This will be administered at all study visits (except the Intake). Similar to withdrawal symptoms, craving will be assessed using a "past week" time reference for all visits except the 24-H testing visit on Day 23, which will use a 24-h time reference.

Cigarette Ratings and Subjective Effects. The Cigarette Evaluation Scale (CES), developed to assess subjective effects of smoking [75], is an 11-item Likert-format measure. Questions include items for nausea and dizziness, craving relief, and

Table 1. Study Measures

State	Intake	Baseline	Remote Check-In [b]	Pre-Quit Testing	24-H Abstinent	Programmed Lapse
Study Visit Days	**-1**	**0**	**7, 14**	**21**	**23 Part 1**	**23 Part 2**
Screening Variables/Covariates						
Demographics	X					
Nicotine Dependence (FTND/Cigarette Brand)	X					
Smoking/ETOH History	X					
Medical History	X					
Height/Weight*	X	X		X		
Psychiatric/Substance Use Hx (MINI)	X					
Suicidal Ideation/Bx (C-SSRS)	X					
Bipolar Disorder Symptoms (MADRS, YMRS, additional screener)[a]	X	X	X	X	X	
Carbon Monoxide (CO)	X	X		X	X	X
Blood Pressure	X	X		X	X	
Shipley Institute of Living Scale	X					
Urine Drug Screen	X	X		X	X	
Pregnancy Screen	X	X		X	X	
Depression/Anxiety (HADS)	X	X	X	X	X	
Functional Impairment (PAOFI)	X					
Risk Assessment Battery (HIV+ group only)	X					
BASIS-24	X					
SF-12	X					
Quick Inventory of Depression Symptoms	X					
Liver and Renal Function test	X					
Neuroinflammation (HIV+ group only)		X		X		
Blood Glucose		X		X	X	
Treatment Variables						
Concomitant Medication Review		X	X	X	X	
Medication Side Effects		X	X	X	X	
Pill Count			X	X	X	
Primary Outcomes						
Mood (PANAS)		X	X	X	X (24h)	X (now)
Neurocognitive Test Battery		X		X	X	
Secondary Outcomes						
Cigarette Consumption (TLFB)		X	X	X	X	X
Withdrawal (MNWS-R)		X	X	X	X (24h)	X (now)
Craving (QSU-B)		X	X	X	X (24h)	X (now)
Subjective Effects, Cigarette Ratings (CES, SQ)		X	X	X		X

*Note: Height and weight will be collected at intake visit, weight only will be collected at each subsequent study visit except day 23
[a] Only administered if a diagnosis of bipolar disorder is self-reported or revealed via the MINI at intake
[b] These visits will be completed remotely via phone or videoconference

enjoyment of airway sensations. The Rose Sensory Questionnaire (SQ), a 9-item Likert-format measure, will be used to assess how much they liked the cigarette smoked and how high in nicotine the cigarettes appeared to be. The questionnaire also includes a diagram of the respiratory tract and asks participants to rate the strength of the cigarette puffs on their tongue, nose, back of mouth and throat, windpipe, and chest. The CES and SQ will be administered at each visit following the Intake.

2. Statistical Analysis

Sample size and analysis. For this analysis we will be estimating summary statistics by group, including means, standard deviations, within-subject correlations, and related confidence intervals. Our sample of 18 per group will yield 95% confidence intervals with limits that fall less than 1/2 SD from the mean. For correlation, the 95% CI length will be no larger than 0.94 if r=0, and substantially narrower for r not= 0. Because the goal of this study is to demonstrate feasibility and provide preliminary data, we will not conduct formal hypothesis testing. We will use these measures to estimate interaction effect sizes to plan future research.

3. Confidentiality

All participant information will be kept in a secure filing cabinet that is accessible only to authorized study personnel. All study databases containing participant information will be password protected, and accessible only to authorized study personnel. Any study communications made by e-mail will use ID numbers and not include names or other personal information. All data sets will use ID numbers only.

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.

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, CIRNA 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):* ____

All research personnel associated with this study have completed the CITI-Protection of Human Subjects Research Training as well as HIPAA Compliance Training. Trained staff will assess eligibility, introduce the study rationale, procedures, study risks, and collect combined informed consent/ HIPAA authorization form.

5. Privacy

The following protected health information will be collected as part of this study:

- Name
- Medical Record Number

- Street address, city, county, zip code
- Telephone numbers
- Email address
- Date of birth
- Medical and drug use history
- Social Security Number
- Results from all questionnaires, tests, or procedures
- Results from urine drug screening/pregnancy test
- Results from blood for liver/kidney function test and glucose monitoring
- Information on smoking, cognition, or HIV-related biomarkers from blood sample

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 to confirm eligibility. All data collected over the phone and during in-person visits 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. A separate list of names with ID numbers will be accessible only by authorized personnel. All records will be kept in locked filing cabinets to maintain confidentiality. Results will not be communicated to other personnel or to the subjects. All analyses will be conducted on de-identified data. 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.) and the Food and Drug Administration.

6. Tissue Specimens

Urine. A urine sample will be required at Intake and all testing sessions (Baseline, day 21 and day 23) for the drug and pregnancy screening. Participants who test positive for study prohibited drugs use may be deemed ineligible. Participants believed to have a false-positive result may continue in the study, with investigator approval. All female participants of child-bearing potential will complete urine pregnancy tests.

Blood. One 8.5 mL sample of blood will be drawn at the Intake visit to evaluate liver and renal function. At the Baseline and Pre-Quit Testing visits four samples (two 10 ml and two 8.5 ml) will be drawn to assess neuroinflammatory markers. A drop of blood (approximately 0.3 microliter) will also be collected at each visit following the Intake to assess blood glucose levels.

RISK/BENEFIT ASSESSMENT

1. Potential Study Risks

Potential Risks of the Medication: The following are the common side effects that have been reported with metformin XR treatment: diarrhea, nausea, and vomiting. Diarrhea led to discontinuation in 0.6% of patients. Side effects will be assessed at baseline and each subsequent visit (a total of 5 times throughout the study).

In addition to the side effects mentioned above, other rare side effects of metformin XR have been reported including: lactic acidosis, abdominal pain, constipation, distention abdomen, dyspepsia/heartburn, flatulence, dizziness, headache, upper respiratory infection, and taste disturbance.

All of these side effects shall be queried using a side effects checklist as described above.

Metformin has been shown to be safe and well-tolerated in non-diabetic individuals including normal glucose tolerant, obese African Americans [76]; obese children and adolescents [77]; individuals at risk for developing diabetes [78]; and women with polycystic ovary syndrome [79]. Nevertheless, because metformin has the potential to lower blood glucose levels, even in non-diabetic individuals, participants' blood glucose levels will be monitored at each study visit following the Intake (see Measures: Screening/Covariates for description).

For individuals currently taking anti-retroviral (HAART) medications: There are no known HAART/metformin drug interactions. Specifically, metformin is not metabolized and is excreted unchanged in the urine. The non-nucleoside reverse transcriptase inhibitors, protease inhibitors, raltegravir, and maraviroc are hepatically cleared and are therefore not contraindicated. Because dolutegravir (Tivicay) or drugs that contain dolutegravir (e.g., Triumeq) can double metformin levels, participants taking dolutegravir will be limited to no more than 1000 mg metformin per day. Therefore, individuals taking dolutegravir will be force randomized to either the placebo condition or the low dose condition.

Stringent exclusion criteria are in place to limit the chance of these side effects. Liver and kidney function will be assessed at Intake to ensure participant safety. Additionally, participants will be informed about these possible side effects and be made aware to watch for any of these symptoms and report them as soon as possible to the research staff. Participants will be instructed to take the study medication once daily with their evening meal. They will also be warned that they should limit their consumption of alcohol. All side effects will be closely monitored, and the study physician consulted should moderate or severe side effects be reported. In case any participant experiences severe side effects or an adverse event, they will be encouraged to contact the study physician (Dr. Leone) and study PI (Dr. Schnoll) immediately for appropriate intervention. The study physician's emergency contact numbers shall be on the medication blister pack, the study consent form, and a study brochure all participants will be provided with once they enroll into the study.

Pregnancy: There are no adequate and well-controlled studies in pregnant women with metformin. Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about two and six times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin. Thus, metformin should not be used during pregnancy. All female participants of child bearing potential will complete a pregnancy test at the Intake session.

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.

Inflammation Results: The blood samples collected to evaluate markers of inflammation will be stored in the PMHARC Core Lab biobank, which can be accessed only by authorized study personnel. Because this is experimental, and we do not yet understand the role of these markers in smoking behavior, participants will not receive the results or feedback from the inflammation assays.

Confidentiality and Loss of Privacy: Protection of privacy of subjects in research studies is of utmost importance, particularly when health history information is collected. Information will never be recorded with identifiers other than study ID. A separate list of names with ID numbers will be accessible only by the database manager. All records will be kept in locked filing cabinets to maintain confidentiality. Results will not be communicated to other personnel or to the subjects. All analyses will be conducted on de-identified data.

Withdrawal: Many individuals who smoke cigarettes exhibit a pattern of symptoms associated with withdrawal from cigarette use. These symptoms can include: sadness and anxiety, irritability, difficulty concentrating, anger, appetite change and weight gain, insomnia, and decreased heart rate. These events are generally of low risk. The study personnel will be trained to recognize these symptoms and educate the participants about them (e.g., their duration, methods for reducing them).

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. 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.

2. Potential Study Benefits

Participants who enroll in this study will benefit from the knowledge that they are contributing in an important way to potentially furthering scientific knowledge concerning ways to improve smoking cessation treatment.

3. Alternatives to Participation

At any point in the study participants may decide not to continue in their 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 the area, other quit-smoking studies at our Center, or contacting the national quit-line.

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

4.1 Data and Safety Monitoring Committee

Data and Safety Monitoring will be conducted by the 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 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 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 double-blind placebo-controlled study in accordance with 21 CFR Parts 312, 511, 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 (Dr. Schnoll)/Co-I and Study Physician will work together to confirm eligibility criteria. The Study Physician/Nurse Practitioner and PI (Dr. Schnoll)/Co-I will review charts for each subject and will document reviews by signing and dating the final eligibility checklist in each chart, and the medical history and physical form.

The research staff and Project Manager will ensure all medication is properly ordered and received from IDS, stored at the center, labeled, and distributed to subjects.

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.

Enrollment will be complete when 84 subjects complete all study requirements. On average, 3-4 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

- 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 an investigator.

Adverse Event Attribution Categories:
• Unrelated - The AE is clearly NOT related to the intervention

- Possibly - 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 metformin. 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. Participants will also complete 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. Trained staff will review participant responses and collect additional information as needed from the participant.

Research staff are trained to inquire (time of onset, nature of issue reported, possible relation to metformin treatment, review of previously reported side effects or concerns, etc.) about any notable side effects or medical concern reported by participants. Any severe (or a pattern of moderate) side effects or notable medical concern will be reported to the Project Manager, Study Physician, and PI/Co-I to determine a course of action (e.g. continue to monitor, reduce medication, stop medication). This consult, including all relevant information, will be documented via email. The Study Physician is knowledgeable of side effects related to metformin and is qualified to manage possible side effects.

Based on published reports using the 500 and 1500 mg doses of metformin we expect few side effects and we expect these side effects to be mild and transient in nature. However, in the unlikely event of an adverse event (AE) the study physician/investigator will 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. The study physician/investigator will determine the relationship of toxicity of the study medication as not related, possibly related, probably related, or definitely related using standard criteria.

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 and the ACC CTSRMC

Notifying the Penn Institutional Review Board (IRB)

A reportable event is an adverse event or incident that has the potential to be classified by the IRB as an unanticipated

problem posing risks to participants or others. In general, an incident is determined to be a reportable event when it is both

1. unexpected in terms of nature or severity or frequency
2. probably or definitely related to participation in the research.

If an adverse event that meets these criteria, the IRB requires investigators to submit within 10 business days of discovery. However, if the event involved a death and indicates that participants or others are at risk of increased harm, investigators should report within 3 days. If the investigator does not have enough information to complete the Reportable Event form within this timeframe, a Reportable Event Form will be submitted and indicate that a follow up report will be provided once additional information has been obtained.

Reportable Events include:

(1) ADVERSE MEDICAL EVENTS WHICH ARE BOTH RELATED AND UNEXPECTED:

- An event is considered "related to the research procedures" if the cause of the event is deemed probably or definitely related to the investigational product or a procedure that was performed for the purposes of the research.
- A "suspected adverse reaction" could be considered a reportable event when there is reasonable possibility that the drug/investigational product caused the adverse event. For these reporting purposes, reasonable possibility means there is evidence to suggest a causal relationship between the drug/investigational product and the event
- If the Sponsor determination notes a causal relationship between the event and the investigational drug/product without required revisions to the consent form or other study documents and/or the report indicates that the event does not alter the risk profile of the investigational drug/product, the event should not be classified as reportable
- An event is "unexpected" if it is not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, the investigator's brochure/package insert, or, the current IRB –approved informed consent document. An event can also be considered unexpected if is not listed at the specificity or severity that has previously been observed and described in the protocol-related documents.
- "Unexpected" also refers to events that are mentioned in the investigator's brochure/package insert as occurring with a class of drugs or as anticipated, but, are not mentioned as to have been

(2) UNANTICIPATED ADVERSE MEDICAL DEVICE REACTION:

- Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

(3) NON-MEDICAL EVENTS - THE IRB ALSO REQUIRES PROMPT REPORTING OF THE FOLLOWING EVENTS:

- Withdrawal from marketing for safety concerns of a drug, device, or biologic used in a research protocol.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team
- Breach of confidentiality
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study
- Premature completion of a study for any reason

All adverse events that are not considered reportable events as defined above will be submitted to the IRB at the time of Continuing Review.

Notifying the Abramson Cancer Center Clinical Trials Scientific Review and Monitoring Committee (ACC CTSRMC)

All adverse events meeting the following reporting requirements will be entered into the Penn Clinical Trials Management System (PennCTMS) AE/SAE form.

On-Site subjects

1. All grade 3 or higher events regardless of attribution or expectedness within 10 business days of knowledge.
2. All unexpected deaths within two business day of knowledge.
3. All others deaths within 30 days of knowledge. Deaths of subjects greater than 90 days from the last study treatment/intervention are not reportable unless a longer time frame is specified in the protocol.

Exceptions:

1. Grade 3 or 4 events that are judged by a Study Investigator to be clearly unrelated to protocol therapy. The reason for determining that the event is unrelated must be clearly documented in the source document.
2. Grade 3 or 4 events that are probably or definitely related to progression of disease as judged by a Study Investigator. The fact that this event is related to disease progression must be clearly documented in the source document.
3. Grade 3 or 4 events that are probably or definitely related to an FDA approved agent. The fact that this event is related to the FDA approved agent must be clearly documented in the source document.

Protocol Exceptions

An exception is 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 and ACC approval is required.

Protocol Deviations

A deviation is a one time, unintentional action or process that departs from the IRB and CTSRMC 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 major deviation must be reported to the ACC and the IRB within 10 business days of discovery.

Minor deviations that do not meet the definition above will be explained in a memo to file or recorded on a deviation log and will contain documentation of an investigator's assessment of the impact of the deviation on safety and study outcomes. Minor deviations will be reported to the IRB and ACC at the time of Continuing Review.

Data, Safety and Monitoring Report. An investigator 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.

Not applicable

Risk/Benefit Assessment

The importance of this research outweighs the risks to subjects, which are minor. There is minimal risk for serious adverse events. The treatments and procedures used in this study have been shown to be relatively safe. Numerous clinical trials have demonstrated the safety and efficacy of metformin. Research staff will monitor subjects closely during their participation. Data from this project will serve as preliminary data to formally test metformin as an adjunct medication to smoking cessation treatment.

SUBJECT COMPENSATION

Participants will receive compensation for each session they complete and can receive up to $280 for completing all study requirements (including travel reimbursement). 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 and their total visit compensation will be up to $240. Travel will not be reimbursed for sessions designated as "in-person", if they have to be completed by phone.

Task completion compensation will depend on participants arriving on time for study visits and following study instructions. If they do not follow instructions, 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 subject is found ineligible at any session due to any of the above-mentioned criteria, they will only be compensated $10 for travel, unless they have elected to use the ride service for that session.

Subjects 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. Compensation distribution is shown in the table below:

Day	Study Visit	Visit Compensation	Task Completion	Travel[3]	Bonus	Total
-1	Intake	$20	-	$10		$30
0	Baseline	$30	$10	$10		$50
7	Remote Check-In	$10	$10			$20
14	Remote Check-In	$10	$10			$20
21	Pre-Quit Testing	$30	$10	$10		$50
23	24-Hr Testing	$40	$10	$10	$50[1]	$110
				Study Total:		**$280**
N/A	Referral Bonus				$60[2]	$60
				Total w/ Referrals:		**$340**

[1]Bonus awarded for completion of ALL study visits

[2]Table shows total compensation for three successful referrals

[3]Only paid if subject opts-out of the round-trip car ride service; will not be paid if a visit has to be completed by phone

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 within 24-48 hours prior to their study 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 study 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. Participants will be asked to provide a location within 15 miles of our center when booking the ride service.

INFORMED CONSENT

1. Consent Process

Informed consent will be obtained 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 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 and PowerPoint to visualize key points. Staff will email or text the survey link to subjects. The PowerPoint will either be sent to participants or shared using screen share via BlueJeans. 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, HIV+ participants asked to provide additional blood samples at Baseline and PQ-Testing sessions 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

1. Staff Training

Drs. Ashare and Schnoll will oversee the development of protocols for laboratory related tasks and training of staff in these protocols. Dr. Ashare will be responsible for the development of procedures pertaining to all other study visits and implementing and monitoring ongoing staff training procedures accordingly. An initial, intensive training period will be implemented followed by quarterly in-service trainings that will be coordinated by Dr. Ashare. 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.

2. Study Facilities

This project will be conducted at and through the PENN Center for Interdisciplinary Research on Nicotine Addiction (CIRNA), which has numerous similar protocols and well-developed procedures for staff training, data collection and storage, and study completion. The facilities available for this project include a large conference room, individual consulting rooms with computer/internet access, storage rooms, smoking lab, sample collection rooms, office space for study personnel, and data management facilities.

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