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

Version 9, 07/16/18

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PROTOCOL TITLE

1. Full Title

Repurposing melatonin receptor agonists as adjunct treatments for smoking cessation. (NCT02560324)

2. Brief Title

Effect of ramelteon on smoking abstinence

STUDY SPONSORSHIP

1. Funding Sponsor

National Institute on Drug Abuse (R21 DA040902)

2. Primary Sponsor

Caryn Lerman, Ph.D., Director, CIRNA

PROTOCOL ABSTRACT

There is a need for novel approaches to optimize smoking cessation treatment to help more smokers quit. Sleep disturbance during nicotine withdrawal may be an important treatment target since existing treatments do not mitigate withdrawal-related sleep disturbance and difficulty sleeping predicts smoking relapse. We hypothesize that the FDA-approved melatonin receptor agonist, ramelteon, combined with transdermal nicotine replacement therapy (TN), will promote abstinence by attenuating withdrawal-related sleep disturbance. Using a well-validated medication screening paradigm, we propose a within-subject, placebo-controlled crossover design with one within-subjects factor of medication (ramelteon vs. placebo). Treatment-seeking smokers (n=50) will complete this 6-week study (two 2-week phases separated by a 2-week washout). Each phase includes 1 week of *ad libitum* smoking (baseline) and 1 week of medication (8mg ramelteon or placebo) plus TN while trying to abstain (quit assessment). Small monetary incentives will be provided for biochemically-confirmed abstinence. Subjects will keep daily sleep diaries and wear an armband while sleeping which provides objective indices of sleep (SensewearPro®). The primary outcome will be the number of biochemically-confirmed days abstinent (out of five). Intermediate outcomes include sleep onset latency (self-report) and sleep efficiency (SensewearPro® armband). 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 evaluate ramelteon as a potential smoking cessation aid in treatment-seeking smokers.

2. Primary Outcome Variable(s)

The primary outcome is the total number of days abstinent (biochemically verified) during a 5-day quit attempt.

3. Secondary Outcome Variable(s)

a. Sleep disturbance measures (sleep onset latency and sleep efficiency) with ramelteon treatment vs. placebo.
b. Predicting the ability to remain abstinent during the 5-day quit assessment week based on reduction in withdrawal-related sleep disturbance.

BACKGROUND

There is a Critical Need for Novel Smoking Cessation Treatments. Despite the fact that cigarette smoking continues to be the greatest preventable cause of morbidity and mortality, there are currently only three FDA-approved medications for nicotine dependence: nicotine replacement therapy (NRT; transdermal nicotine (TN), nasal spray, gum, lozenge), bupropion, and varenicline. Although TN doubles the odds of smoking cessation compared to placebo, the majority relapse within the first week [1, 2]. Importantly, we demonstrated that each additional day of abstinence during the first week nearly doubles the odds of success at end-of-treatment [3]. There is a clear need to identify novel approaches to optimize treatment to help more smokers maintain abstinence during this critical period. The development of a clinically valid model for early human screening of medications to treat nicotine dependence [4-6], coupled with an emphasis on "repurposing" existing medications, provides a practical approach to achieve this aim [7, 8]. These models can also be used to assess novel smoking cessation treatment targets, such as sleep disturbance.

Sleep Disturbance is a Treatment Target. Converging lines of evidence suggest that remediating sleep disturbance may be a novel therapeutic target as an adjunct treatment for nicotine dependence. First, nicotine withdrawal is associated with sleep disturbance, such as difficulty falling asleep and increased number of awakenings [9-11]. Second, existing nicotine dependence treatments do not mitigate sleep problems during a quit attempt; in fact, we and others have shown that TN [12-15] and varenicline [16] may exacerbate the problem. Third, sleep disturbance predicts smoking relapse in clinical trials and laboratory models of relapse [17-19]. Our preliminary data demonstrate that smokers who report longer sleep onset latency and wake more often are abstinent for fewer days using a model of short-term abstinence.

Medications to Improve Sleep as a Smoking Cessation Treatment. Pharmacotherapies that improve sleep may be efficacious adjunct smoking cessation treatments. However, FDA-approved medications for insomnia including benzodiazepines (e.g., zolpidem/Ambien®) and hypnotics (e.g., eszopiclone/Lunesta®, zaleplon/Sonata®) may produce next-day residual effects, such as memory impairment, difficulty concentrating, or mood symptoms [20], that may promote smoking relapse [21, 22]. The FDA-approved melatonin receptor agonist, ramelteon (Rozerem®; RAM) does not produce next-day residual effects, has a low abuse potential, is not classified as a controlled substance, and is safe to use with TN [23]. Critically, RAM is indicated for improving sleep onset latency (SOL), which is commonly reported among smokers [9, 24] and associated with abstinence in a model of short-term abstinence. We hypothesize that RAM, combined with TN, will promote smoking cessation by reducing withdrawal-related sleep disturbance.

Using a well-validated medication screening paradigm [4-6], we propose a within-subject, placebo-controlled crossover design with one within-subjects factor of short-term medication (ramelteon vs. placebo). Treatment-seeking smokers (n=50) will complete this 6-week study, which consists of two 2-week phases separated by a 2-week washout. Each phase includes 1 week of *ad libitum* smoking (baseline) and 1 week of medication (8mg ramelteon or placebo) plus TN while trying to abstain (quit assessment). For the duration of the study, subjects will be asked to keep sleep diaries and to wear an armband while sleeping, which provides objective indices of sleep duration and quality (SensewearPro®). Subjects will receive standard TN following completion of the study. The primary outcome will be the total number of days abstinent (out of 5), a measure that is highly predictive of longer-term quit success [3]. Intermediate outcomes include sleep onset latency (self-report) and sleep efficiency (SensewearPro®).

CHARACTERISTICS OF THE STUDY POPULATION

1. Target Population

Fifty adult, treatment-seeking smokers, 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.

2. Accrual

In order to have 50 smokers complete all sessions, we will enroll (consent) 150 participants. We anticipate approximately 50% (n=75) of those who consent will meet final eligibility criteria. Of the 75 who are eligible, we

conservatively estimate 25% attrition to have 50 smokers complete the study. 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 receive ramelteon and placebo in counterbalanced order. Participants will be told that this study includes two practice quit attempts with an FDA-approved medication that is being tested as a possible new treatment for smoking cessation.

3. Key Inclusion Criteria

Smokers ages 18-65, who have smoked at least 10 cigarettes per day for the past 6 months, will be eligible to participate. They must be able to provide informed consent, and express interest in quitting smoking in the next 2 to 4 months. Using a scale from 0 to 100, they must rate their confidence that they will make a quit attempt in the next 2 months a 50 or higher. Following the current study, participants will be referred to a free smoking cessation program. Those who wish to quit sooner can be referred directly to another program.

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.
3. Provide a carbon monoxide (CO) breath sample reading less than 10 parts per million (ppm) at Intake.

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. Self-reports substance use disorders (abuse or dependence involving alcohol, opiates, cocaine or other stimulants, or benzodiazepines; not nicotine) in the last 6 months.
3. Self-reports daily use of marijuana. Individuals who report occasional use must agree to refrain from use for the duration of the study.
4. Providing a breath alcohol concentration (BrAC) reading of greater than or equal to 0.01 during any session.
5. A positive urine drug screen for cocaine, amphetamines, methamphetamines, benzodiazepines, PCP, methadone, barbiturates, marijuana, ecstasy (MDMA), oxycodone, tricyclic antidepressants, and opiates (low level cut-off 300 ng/mL) during any session.

Psychiatric Exclusion (as determined by self-report on phone screen, through MINI, and/or the Columbia Suicide Severity Rating Scale (C-SSRS) during Intake):

1. Current psychiatric disorders (depression, bipolar, schizophrenia, hypomanic/manic episode) as determined by self-report and/or MINI psychological interview.
2. Past history of psychiatric disorders (including suicide attempt) other than depression as determined by self-report and/or MINI psychological interview.
3. Suicide risk score on MINI greater than 1.
4. Current (past month) suicidal ideation or lifetime suicidal behavior on the C-SSRS.

Medical:

1. Females who are currently pregnant, planning a pregnancy during the study, or currently breastfeeding/lactating. All female subjects shall undergo a urine pregnancy test at the Intake and must agree in writing to use an approved method of contraception. Following enrollment, pregnancy tests will be conducted at the end of each baseline week.
2. For those with a history of jaundice/liver disease: liver function tests more than 20% outside of the normal range and/or 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 be determined on a case-by-case basis.
3. Heart/Cardiovascular disease (e.g., angina, coronary heart disease, stroke, etc.) in the past 6 months.
4. Endocrine or metabolic disorders (e.g., Type-I diabetes).

5. Blood disorders (e.g., anemia or hemophilia).
6. Uncontrolled hypertension (BP systolic greater than 159 and/or diastolic greater than 99)*.
7. Clinically significant dyssomnia (except insomnia; e.g. sleep apnea syndrome, narcolepsy) [25, 26].

* 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 instructed to sit comfortably for 10 minutes and then have a third blood pressure reading. If, after the third reading the SBP greater than 159 mmHg and the DBP greater than 99 mmHg, the individual will be ineligible to participate.

Medication:

1. Current use or recent discontinuation (within the past month) of any of the following medications:
    a. Anti-anxiety or panic disorder medications (e.g., clonazepam, alprazolam).
    b. Anti-psychotic medications (e.g., thorazine, Seroquel).
    c. Mood-stabilizers (e.g., Lithium, Lamictal/lamotrigine, valproic acid, Neurontin/gabapentin, Topamax/topiramate, Tegretol/carbamazepine).
    d. Prescription stimulants (e.g., Provigil, Ritalin, Adderall).
    e. Medications contraindicated with ramelteon (e.g., fluvoxamine, donepezil, doxepin, buprenorphine or other medications metabolized by certain cytochrome P450 enzymes)
    f. Hormonal birth control that contains ethinyl estradiol
    g. Other medications containing ethinyl estradiol
2. Current use or recent discontinuation (within the past 2 weeks) of any of the following medications (subjects must agree to refrain from using any other sleep aids while enrolled in the study):
    a. Sleep medications (e.g., zolpidem/Ambien, eszopiclone/Lunesta) [25, 26]
    b. Over-the-counter sleep aids (e.g., melatonin, diphenhydramine/Benadryl)
3. Daily use of opiate-containing medications for chronic pain (Duragesic/fentanyl patches, Percocet, Oxycontin). Smokers who report taking opiate-containing medications on an “as-needed” basis will be instructed to refrain from use until their study participation is over and informed that they will be tested to ensure they have complied with this requirement.
4. Known allergy to study medication (e.g., angioedema).

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. Currently working night shift or rotating shift or other habitual alteration of the sleep/wake cycle [26].
4. Allergy to latex or adhesive tape.
5. Inability to provide informed consent or complete any of the study tasks as determined by the Principal Investigator.
6. Not able to effectively communicate in English (reading, writing, speaking).
7. Missing 2 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 two 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 TV, newspaper, radio, poster, and internet-based advertising (e.g., in-app ads, Craigslist, and iConnect) will be used to invite smokers from the general population.

STUDY DESIGN

1. Phase

Phase: II Randomized, double-blind, placebo-controlled trial

Figure 1. Overview of Study Design

PHASE	INTAKE	STUDY PERIOD 1								WASHOUT	STUDY PERIOD 2								
WEEK #	0	Baseline 1			Quit Week 2					3-4	Baseline 5			Quit Week 6					
STUDY VISITS	X	M	W	F	M TQD	T	W	TH	F	NONE	M	W	F	M TQD	T	W	TH	F	
MEDICATION	NONE				*RAM plus TN or PLA plus TN					NONE WASHOUT				*RAM plus TN or PLA plus TN					
ACTIVITY	Medical History Psych Screen	Monitoring Visits Sleep Monitoring			Observation Assessments Sleep Monitoring					NONE	Monitoring Visits Sleep Monitoring			Observation Assessments Sleep Monitoring					
SMOKING STATE	Smoking Ad Libitum				Monitored Abstinence					Smoking Ad Libitum				Monitored Abstinence					

** Treatment (RAM vs PLA) order randomized and counterbalanced across subjects; All subjects receive transdermal nicotine (TN). TQD=Target Quit Date*

2. Design

We propose to conduct a randomized, placebo-controlled, cross-over design with one within-subjects factor of medication (RAM vs. PLA; order counterbalanced). Each phase includes: 1 week of *ad libitum* smoking (baseline) and 1 week of medication (8mg RAM or PLA) plus TN while trying to abstain (quit assessment) (Figure 1).

3. Study Duration

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

Enrollment will start in October 2015 (after IRB approval is received). We estimate that we will need to telephone screen 1500 smokers to enroll (consent) 150 smokers into the study (accounting for 10% eligibility). Using a conservative estimate of attrition (50%), we expect to have 50 participants complete all sessions and study requirements. 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 7 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 phase 1 and the duration of the washout period. Thus, the maximum duration a participant can be in the study is 12 weeks.

Projected date of completion of the proposed study

We estimate that 50 people will have completed the study by March 2018, and that analyses and reporting will be complete by August 2018.

DRUGS OR DEVICES

Ramelteon

The study will be performed using 8mg of ramelteon, which is currently marketed for the treatment of sleep problems.

The proposed study follows the typical dosing regimen for RAM (8mg once a day), which is documented to be safe and well-tolerated [27-29]. Ramelteon will be purchased and packaged into blister packs by the Investigational Drug Service at the University of Pennsylvania. In accordance with FDA recommendations, subjects will be instructed to take study medication within 30 min prior to going to bed and avoid taking study medication with or immediately after a high fat meal.

An IND exemption has been approved for this study for ramelteon and TN 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

Ramelteon will be purchased and supplied via the University of Pennsylvania Investigational Drug Service (IDS number pending). 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. Ramelteon 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).

Kits will be ordered as needed by the research staff and stored in a locked cabinet at our center. Once the Study Physician (Dr. Leone) signs the prescription and a subject is assigned a treatment order (ramelteon first or placebo first), medication kits will be ordered and picked up from IDS by a member of the research staff. Once a new subject is enrolled and eligible, the research staff will assign the subject the next available PRN. Blister packs will then be labeled with the subject's study ID number. Each medication kit will consist of 6 days of 8mg ramelteon and 6 days of placebo (one for each quit assessment day plus an extra). The PRN and study ID number must match for each blister pack a subject receives. Medication will be stored at CIRNA as per manufacturer's guidelines.

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.

Transdermal Nicotine

Subjects will receive the 21 mg dose during each quit-assessment week. The patch will be Nicoderm CQ as used in our previous clinical trials [30, 31]. Subjects will be given the patches at the last visit during each Baseline week (weeks 1 and 5) and instructed to begin using the patches the morning of the TQD during each study period (Figure 1). Because wearing nicotine patches at night may cause sleep disturbance (i.e., vivid dreams) [32-34]), subjects will be instructed to remove the patch before going to sleep. Following completion of the study, we will offer all subjects open-label cessation treatment with TN to attract participation by smokers with strong motivation to quit.

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

patches are distributed. Patches will be stored in a double locked location (i.e., in a locked cabinet in a locked room) at room temperature.

SUICIDAL IDEATION AND BEHAVIOR

The C-SSRS will be administered at 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.

STUDY PROCEDURES

1. Procedures

This is a randomized placebo-controlled study of the effects of ramelteon, compared to placebo, on ability to quit smoking. Participants will complete an Intake at the Center for Interdisciplinary Research on Nicotine Addiction (CIRNA) before being enrolled into the study. All study visits will be completed at the CIRNA. Participants will complete two 2-week phases separated by a two-week washout period. Each phase will involve one week of *ad libitum* smoking (Baseline) and one week of medication (RAM vs. PLA) as well as TN treatment while trying to abstain (Quit Assessment). Each Baseline week, subjects will attend a brief visit on Monday, Wednesday, and Friday to assess smoking rate, blood pressure, CO and BrAC samples, side effects, withdrawal, craving, and affect. Subjects' sleep diaries will be collected and the SensewearPro® data will be downloaded to confirm compliance. During the quit assessment weeks, subjects will take the assigned study medication on each weekday and urine samples will be collected to confirm compliance. They will be asked to try their best to abstain from smoking will receive $10/day for each day that self-reported abstinence is biochemically-confirmed (CO<5ppm). They will complete 20-min visits on each weekday to verify abstinence and complete measures.

2. Study Visits

- Telephone Screening. Individuals interested in participating will be screened by an experienced research technician to determine initial study eligibility. If the subject meets preliminary phone eligibility and is interested in participating, he/she will be invited to attend a 2.5-hour Intake visit. Subjects will be contacted via phone call, text message, e-mail, and/or postal mail to remind them about their scheduled intake visit date and time. Method of preference will be collected over the phone.

- Intake (Week 0). In this 2.5-hour visit, participants will have their eligibility confirmed (using the previously detailed inclusion/exclusion criteria listed above). A schedule of activities for the day include:

    1. Arrive at the CIRNA and hear detailed description of the study and have any questions answered by a staff member from the CIRNA
    2. Complete combined study consent/HIPAA form
    3. Provide urine specimens for drug and (if applicable) pregnancy tests. Participants who test positive for either the urine drug screen and/or pregnancy test will be ineligible.
    4. Provide CO breath sample. Participants must have CO readings greater than or equal to 10ppm in order to be eligible for the study
    5. Provide BrAC measurements. Participants must have readings less than 0.01 in order to be eligible for the study
    6. Provide a blood pressure reading (See Blood Pressure Procedures under Screening/Covariate Measures)
    7. Complete routine medical history (self-report) with a member of the research staff
    8. Complete a psychological interview (MINI) and the C-SSRS with a trained research staff member (Description under Screening/Covariate Measures)
    9. Complete brief physical examination (led by a medical professional)
    10. Have height and weight measured (led by study staff)
    11. For individuals who report a history of jaundice/liver disease: provide an 8.5ml blood sample drawn for the assessment of liver function (LFTs and GGT enzyme levels). They will receive final confirmation of eligibility via phone call based on the liver function tests.

If a participant is ineligible due to any of the above criteria during the Intake, he/she will only be compensated $10 for travel. However, if a participant tests positive for study prohibited drugs, he/she will not receive any compensation.

Otherwise, if a participant meets the above eligibility criteria at the Intake, he/she will be asked to complete the following:

12. Complete questionnaires (demographics, nicotine dependence, smoking rate, withdrawal, and smoking urges)
13. Receive instructions on how to record their daily sleep diaries and report their sleep and wake times
14. Be randomized to receive RAM or PLA during the first phase
15. Finalize their study schedule

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. Female participants will also be asked to use an approved method of contraception through the study.

- Final Eligibility Phone Call (only for individuals with a history of jaundice/liver disease). 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. Albumin/Globulin ratios 20% outside of normal range will be evaluated for clinical significance by the Study Physician and eligibility will be determined on a case-by-case basis.

  Ineligible subjects may be referred to other studies at our center. Eligible subjects will schedule all other study visits and be randomized to receive RAM or PLA during the first phase. During the first study visit, participants will receive instructions on how to use the SensewearPro® and record their daily sleep diaries.

- Baseline Weeks (Weeks 1 and 5). Participants will complete three observation visits during the Baseline weeks on Monday, Wednesday, and Friday. The visits on Monday and Wednesday will last approximately 20 minutes. The start of the first phase can be scheduled within 2 days of the Intake but no more than 30 days can elapse between Intake and start of the first phase. At the observation visits participants will:

  1. Arrive at CIRNA and provide a CO and BrAC sample (Participants must have BrAC readings less than 0.01 in order to be eligible for the study).
  2. Provide a blood pressure sample (See Blood Pressure Procedures under Screening/covariate measures).
  3. Complete questionnaires (smoking rate, concomitant medication review, sleep, withdrawal, smoking urges, mood, and side effects).
  4. Have sleep diaries collected and data stored on armband downloaded by research technician. Research staff will review adherence.

  At the first (Monday) visit of Baseline Week 1 and 5, the participant will receive his or her SensewearPro® armband. At Baseline Week 1, the participant will receive an instructional packet and a research staff member will review how to use the armband and charger correctly.

  The third (Friday) visit of each Baseline Week will last approximately 40 minutes. During this visit, subjects will:
  1. Provide urine specimens for drug and (if applicable) pregnancy tests (Friday visit only). Participants who test positive for either the urine drug screen and/or pregnancy test will be withdrawn from the study.

2. Meet with a smoking cessation counselor for a 20-min coaching session to prepare them for the practice quit attempt. The counselor will review coping strategies for managing triggers and withdrawal symptoms.
3. Participants will receive their study medication and nicotine patches. Study staff will review instructions for taking the study medication and applying the nicotine patches.

These sessions can be scheduled for any time of day. Ideally, the subsequent sessions would be at the same time of day, but can be scheduled up to 3 hours earlier or later. However, the sessions may go beyond 3 hours as determined by PI discretion.

- Quit Assessment Weeks (Weeks 2 and 6). Participants will attend a 20 minute study visit every weekday of their quit assessment week. They will be asked to bring their study medication to this visit to verify medication adherence/pill counts. During this session, which will last approximately 20 minutes, participants will complete measures of:
    1. Blood pressure (See Blood Pressure Procedures under Screening/covariate measures)
    2. CO breath sample
        a. To increase abstinence motivation, participants will receive $10/day (in cash) for each day for self-reported abstinence that is biochemically-confirmed. On Monday, a CO reading of less than 10ppm or less than 50% of CO breath sample taken during the Baseline week will be sufficient as biochemically-confirmed abstinence. At all other visits, a CO reading less than 5 ppm will be considered as biochemically-confirmed abstinence.
    3. BrAC sample
    4. Smoking rate (timeline followback; TLFB)
    5. Medication adherence (pill count)
    6. Side effects and concomitant medication review
        a. If moderate to severe adverse events are reported, the PI/Study Physician will be consulted and a decision will be made as to whether to proceed with the study.
    7. Mood, smoking urges, withdrawal symptoms, sleep measures

    At the last visit of the first Quit Assessment Week (Week 2), the SensewearPro® armband and charger will be collected from the participant, as he or she will not be using the SensewearPro® armband during the washout period. If the participant continues the study, the participant will receive the SensewearPro® armband at their first visit of the second Baseline Week (Week 5).

    These sessions can be scheduled for any time of day. Ideally, the subsequent sessions would be at the same time of day, but can be scheduled up to 3 hours earlier or later. However, the sessions may go beyond 3 hours as determined by PI discretion.

    At the final visit of the study, participants will be offered information (i.e. flyer, brochure, etc.) about a smoking cessation research program at the CIRNA. If no cessation studies are available or the participant does not wish to participate, they will be provided a list of referrals to other cessation programs in the greater Philadelphia area (e.g., the Comprehensive Smoking Treatment Program at UPenn Presbyterian). The participant's decision whether or not to receive this information will be documented. Participants will return the SensewearPro armband and will be given a summary report of their physical activity and sleep patterns.

- Washout Weeks (Weeks 3 and 4): During these two weeks, participants will not have any study visits or take any study medication. They will be instructed to smoke *ad libitum*. Subjects who abstain during week 2 will be required to resume smoking during week 3 to remain in the study. Subjects will be told that they may withdraw from the study if they choose not to resume smoking. We expect few subjects to discontinue the study for this reason [4, 35, 36].

3. Description of Measures and Variables

3.1 Screening/Covariate Measures

Demographics and Smoking History. Standard questionnaires will be self-administered at the Intake visit to collect the following data: demographics (age, gender, marital status, education), age at smoking initiation, cigarette brand, length of prior abstinence periods and current smoking rate. The Fagerstrom Test for Nicotine Dependence (FTND) will also be administered. The FTND is a 6-item, self-report measure of nicotine dependence derived from the Fagerstrom Tolerance Questionnaire [37]. The FTND scale has satisfactory internal consistency (Cronbach's alpha=. 64) and high test-retest reliability (r=. 88) [38].

Medical History. A medical history (self-report) and a physical examination will be conducted at the Intake visit to review for any contraindications listed previously. The medical history (including height and weight) will be completed by a research staff member.

Psychiatric History. Current major depression, lifetime prevalence of psychosis, bipolar disorder, schizophrenia, hypomanic/manic episodes, and substance abuse will be determined via self-report during the phone screen and via semi-structured interview using the Mini International Neuropsychiatric Interview (MINI). The MINI is a 10-15 minute structured interview developed by the World Health Organization to assess major DSM-IV Axis 1 psychiatric diagnoses. This instrument permits both current (past 30 days) and lifetime assessments of psychiatric illness, and recent data support its reliability and validity [39]. The MINI will be administered by a trained research staff member at the Intake visit. There will be 100% review of paper MINIs by Dr. Hole, a clinical psychologist with relevant training, to maintain quality control.

Suicidal Behavior and Ideation (C-SSRS). All participants will complete the C-SSRS (Screening Version) with a trained staff member at the Intake Visit. The C-SSRS is a structured interview that assesses the suicidal behavior and suicidal ideation in subjects [40, 41]. 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.

Urine Drug Screen. The urine drug screen will be administered at Intake and the last visit of each baseline week (Friday of weeks 1 and 5). The urine drug screen requires about 30ml of urine and indicates whether the subject has recently taken any exclusionary drugs (marijuana, cocaine, PCP, amphetamines, methamphetamines, tricyclic antidepressants, ecstasy, opiates, methadone, benzodiazepines, and barbiturates). Participants with a positive urine drug screen for any substance listed above will be deemed ineligible. In an effort to remain CLIA-compliant, results from urine drug screening will not be shared with participants. Participants will be informed that the testing is for research purposes only and that they will be informed of their eligibility status, but not of the specific testing results.

Urine Pregnancy Test. At the Intake and the last visit of each baseline week (Friday of weeks 1 and 5), 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.

Breath Alcohol Concentration. The breath alcohol concentration (BrAC) assessment will be administered at the Intake visit and all subsequent study visits. The breath alcohol monitor assesses expired breath for alcohol content. A reading greater than or equal to 0.01 at any session indicates alcohol consumption within the last 14 hours and will result in the participant being withdrawn from the study.

Table 1. Measures and Time Points.

Activity (Week #)	Intake	Baseline (1 & 5)			Quit Assessment (2 & 6)				
Day	**0**	**Mon**	**Wed**	**Fri**	**Mon**	**Tue**	**Wed**	**Thu**	**Fri**
TREATMENT									
Ramelteon (RAM) or Placebo					X[a]	X[a]	X[a]	X[a]	X[a]
Transdermal Nicotine (TN)					X	X	X	X	X
SCREENING/COVARIATES									
Demographics	X								
Smoking History/FTND	X								
Medical/ ETOH History (self-report)	X								
Psychiatric History (Self-report and MINI)	X								
Suicidal Behavior/ Ideation (C-SSRS)	X								
Urine drug/pregnancy screen	X			X					
Breath alcohol	X	X	X	X	X	X	X	X	X
Blood pressure	X	X	X	X	X	X	X	X	X
Blood draw (liver function tests)[b]	X								
Brief counseling				X					
TREATMENT VARIABLES									
Concomitant Medication Review	X	X	X	X	X	X	X	X	X
RAM Adherence (pill count)					X	X	X	X	X
TN Adherence					X	X	X	X	X
Side Effects (TN and RAM)		X	X	X	X	X	X	X	X
INTERMEDIATE OUTCOMES									
Sleep Diary		X	X	X	X	X	X	X	X
Pittsburgh Sleep Quality Index (PSQI)		X	X	X	X	X	X	X	X
Sleep efficiency (SensewearPro)		X	X	X	X	X	X	X	X
Depression Symptoms (CESD)	X			X					X
Withdrawal, Craving, Affect		X	X	X	X	X	X	X	X
SMOKING OUTCOMES									
Cessation/Smoking Rate (TLFB)	X	X	X	X	X	X	X	X	X
Carbon Monoxide (CO) Test	X	X	X	X	X	X	X	X	X

Note. No visits or assessments during washout (weeks 3-4). FTND=Fagerstrom Test for Nicotine Dependence; CESD= Center for Epidemiological Studies on Depression; TLFB=Timeline Followback
a study medication taken the previous night; b only for those with a history of jaundice/liver disease

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 the SBP is greater than 159 mmHg and/or the DBP is greater than 99 mmHg, the individual will be instructed to sit comfortably for 10 minutes and then have a third blood pressure reading. If, after the third reading the SBP is greater than 159 mmHg and/or the DBP is greater than 99 mmHg, the individual will be ineligible to participate.

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 mmHg and/or diastolic blood pressure greater than 99 mmHg) at any subsequent visit, the staff will follow the same steps listed above. If, after a third reading, systolic blood pressure remains greater than 159 mmHg and/or diastolic remains greater than 99 mmHg, the subject will be told to not take the next dose of study medication. If a participant presents with a SBP between 151-159 mmHg and/or DBP between 91-99 mmHg at the Intake or any visit during a Baseline week, the research staff will inform the participant that they have mild, Stage I, hypertension and advise they consult with a physician. The participant will remain eligible for the study and receive nicotine patches as scheduled. The research staff will notify the Study Physician/Health Care Provider who will review the blood pressure reading and determine whether it is safe for the subject to continue. Research staff will follow up with the participant accordingly.

Liver Function Tests and Gamma-glutamyl Transpepsidase. Only individuals with a history of jaundice/liver disease will provide a blood sample for liver function tests. One 8.5ml blood sample will be drawn at the Intake visit to conduct liver function tests. Blood will be collected and placed in a serum-separator tube (SST) and mixed thoroughly. Samples will be centrifuged at 3000 rpm for 15 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).

Brief counseling. These 20-minute sessions will occur during the final visit of each Baseline week (Friday). This counseling session will be similar to previous studies in our center (IRB#815789). Specifically, a trained smoking cessation counselor will review reasons for smoking and common withdrawal symptoms. Counselors will work with participants to develop plans to manage triggers, avoid cigarettes, and gather social support. Participants will also be taught a breathing relaxation technique for handling stressful situations.

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.

Pill Count/Adherence. Medication adherence will be assessed by pill count at each study visit or telephone session [42]. We will assess patch use by participants' self-report and collect unused patches at the end of the week.

Side Effects. A checklist of side effects based on the product insert will be administered to participants at all study visits after the Intake. The frequency and severity of common side effects of RAM [43] and TN [30, 44] 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.

3.3 Intermediate Outcomes

Subjective Sleep Measures: As in Dr. Dinges' prior work, subjects will complete sleep diaries daily within 1h of getting out of bed and prior to going to sleep and will provide time-stamped phone records for time to bed and time awake [45-48]. These well-validated sleep diaries assess subjective SOL, total sleep time, number of awakenings and perceived quality of sleep. The diaries will be used to verify the sleep parameters derived from the SensewearPro® armbands [49, 50].

The Pittsburgh Sleep Quality Index (PSQI) is a 9-item measure that assesses the quality and patterns of sleep over the past month. It measures seven areas: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. Scoring is based on a 0 to 3 scale, whereby 3 reflects the negative extreme. A sum of "5" or greater indicates a "poor" sleeper [51]. The PSQI has good internal consistency (α=0.83), validity, and reliability, and is sensitive to treatment [52, 53]. The outcome is the global PSQI score and will be evaluated as a moderator of RAM's effects on abstinence.

Sleep Efficiency (SensewearPro armbands): A multi-method approach is necessary to capture different components of insomnia symptoms [54], such as self-report, polysomnography (PSG) or actigraphy [50]. Compared to PSG, actigraphy provides concordance rates between 80% and 95% for wake/sleep detection, enables data collection for weeks to months, and is less expensive [50, 55, 56]). The SensewearPro® armbands (BodyMedia, Inc. Pittsburgh, PA) measure body movement, like actigraphy, and acquire additional physiological signals, including surface body temperature, galvanic skin response, and heat flux [57]. The armbands provide 89% concordance with PSG data and identify sleep and wakefulness with moderate to high sensitivity and specificity [57]. Subjects will wear the armband during each phase (weeks 1, 2, 5, and 6), and will be provided $4/day for each day they wear the armband and complete the sleep diary plus $50 if they provide at least 18 of 22 days of data (85%). Subjects will be instructed to remove the armband only for bathing purposes or water activity. The data will be downloaded to the Sensewear Professional software (v8.0; Bodymedia, Pittsburgh, PA) at each visit to confirm compliance using a threshold of 90% on body time. Following PSG standards, the first and last nights will not be analyzed to allow for adaptation [50, 55, 56]. The outcome is sleep efficiency. Participants will not be responsible for lost or otherwise compromised armbands.

Depression symptoms. The 20-item Center for Epidemiological Studies on Depression scale (CESD) will assess depressive symptoms [58, 59]. It has high internal consistency (α=0.85) and scores greater than16 correlate with clinical ratings of depression [60]. Participants will rate the intensity of their symptoms in the past week on the following scale: 0 = rarely, or none of the time (less than once a day), 1 = some, or a little of the time (1-2 days), 2 = occasionally, or a moderate amount of time (3-4 days), 3 = most, or all of the time (5-7 days) and a summary score will be calculated. The CESD will be administered at the Intake and on the last visit of each Baseline and Quit Assessment week.

Withdrawal Symptoms. The "Minnesota Nicotine Withdrawal Scale - Revised version"(MNWS_R) [61] captures the current state of nicotine withdrawal [62, 63]. 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 24-h time reference for all visits following the Intake.

Craving. The 10-item brief QSU questionnaire on smoking urges [64] 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 [65]. This will be administered at all study visits (except the Intake). Similar to withdrawal symptoms, craving will be assessed using a 24-h time reference at all visits following the Intake.

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 24-h time reference for all visits following the Intake.

3.4 Smoking 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 [67], as we have done previously [68] to assess self-reported smoking rate. During each quit week, abstinence will be assessed daily by self-report of no smoking at all over the prior 24 hours and an expired-air CO less than 5 ppm (except for the Monday visit when CO may be less than 10ppm or less than 50% Baseline CO). This stringent biochemical criterion for validating smoking cessation has been shown to be more sensitive to detect smoking and specific to verify abstinence than higher CO cut-offs [69].

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 then exhaling twice. Then, they will take another deep breath and hold 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 study visit. At the Intake, participants must have CO readings greater than or equal to 10ppm in order to be eligible for the study.

2. Statistical Analysis

Sample size.

Effect sizes for power analyses were derived from prior work on TN effects on days of abstinence (Aim 1) [6], studies demonstrating RAM's effects on sleep (Aim 2), and our preliminary data. All significance levels will be set at 0.05. Our primary hypothesis is that RAM will increase the number of days abstinent (out of 5), compared to placebo. In prior validation work, the average number of days abstinent for TN was 2.0±0.3 [6]. Fifty subjects provide 80% power to detect a difference of 0.55 days between RAM and PLA, using a SD of 1.36 and a within-subjects correlation of 0.78 [31].

For Aim 2, meta-analyses indicate that RAM is associated with reducing SOL by 4.3 min and increasing sleep efficiency by 4.42% [70]. Our preliminary data suggest that TN increases sleep disturbance by 58% (d=0.28) in abstinent smokers and that abstinence increases SOL by ~5 min and decreases sleep efficiency by ~5%. Fifty subjects provide 80% power to detect differences of 6 min in SOL and 5% in sleep efficiency between RAM and PLA, using a within-subject correlation between 0.4 and 0.8. Thus, Aims 1 and 2 are sufficiently powered.

Statistical Analysis.

For Aim 1 (H1), a within-subject ANOVA will test the primary hypothesis for effects of RAM (vs. PLA) on number of days abstinent during the quit week.

For Aim 2 (H2a), separate 2 drug (RAM vs. PLA) x 2 week (baseline vs. quit week) repeated measures ANOVAs will test the effects of RAM on SOL and sleep efficiency. Drug and week are within-subject factors and sleep measures will be averaged across days within each baseline and quit week. We are primarily interested in the drug x week interaction to test whether RAM (vs. placebo) attenuates sleep disturbance during the quit week, relative to baseline. Thus, each period has its own baseline control comparison. A supplemental analysis will include only days during the quit week when subjects are abstinent.

For Aim H2b, linear regression models will test whether sleep disturbance predicts number of days abstinent and

whether this relationship varies by treatment. Models will include covariates (e.g., baseline depression/anxiety, FTND, sex, and age). We will also examine correlations between sleep disturbance data and nicotine withdrawal and depression/anxiety symptoms in both groups.

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.

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
- Street address, city, county, zip code
- Telephone numbers
- Email address
- Date of birth
- Medical and drug use history
- Last 4 digits of Social Security Number
- Results from all questionnaires, tests, or procedures
- Data collected from SensewearPro armbands
- Urine for drug screening/pregnancy test
- Blood for liver function test (for those with history of jaundice/liver disease)

6. Tissue Specimens

Urine. A urine sample will be required at all sessions for the drug and pregnancy screening. Participants who test positive for study prohibited drugs use will be deemed ineligible, as will women who have a positive pregnancy test. All female participants of child-bearing potential will complete urine pregnancy tests.

Blood. (only for those with history of jaundice/liver disease) An 8.5ml sample of blood will be drawn at the Intake visit to evaluate liver function.

RISK/BENEFIT ASSESSMENT

1. Potential Study Risks

Potential Risks of the Medication: The following are the common side effects that have been reported with ramelteon treatment: drowsiness, tiredness, dizziness, and nausea. All of these side effects have been mild and

transient in nature. These symptoms have occurred in approximately 3% of subjects in clinical trials (Takeda Pharmaceutical, 2005). Side effects will be assessed at baseline of each period and each subsequent visit (a total of 16 times throughout the study). The incidence of side effects is lower with the 8mg dose (as compared to the 16mg dose); which is the dose that has been selected in the proposed project.

In addition to the side effects mentioned above, other rare side effects of ramelteon have been reported:

- Severe anaphylactic and anaphylactoid reactions such as angioedema (swelling of the tongue and larynx), difficulty swallowing, vomiting, and throat closing.
- Abnormal thoughts and behavioral changes such as hallucinations, suicidal thoughts, bizarre behavior, agitation and mania, amnesia, and anxiety
- Complex behaviors such as "sleep-driving" and other behaviors (e.g., preparing and eating food, making phone calls)
- Hormone effects including decreased testosterone and increased prolactin

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

Stringent exclusion criteria are in place to limit the chance of these side effects. 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. All subjects will be instructed to take the study medication 30 minutes before going to bed. They will also be warned they should not drive or operate machinery after taking ramelteon and 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. Ashare) 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.

Transdermal Nicotine (TN) Replacement Therapy: All participants will receive transdermal nicotine (TN) patch therapy to aid in quitting smoking. This therapy is available over the counter and is very well tolerated. Participants will use the 21 mg patch for 5 days during each quit assessment week. Nausea, vomiting, weakness, dizziness, and rapid heartbeat occur rarely and are most often caused by continuing to smoke while using the patch. In addition, there is a risk of peptic ulcer formation and delayed wound healing associated with nicotine replacement therapies. Some individuals who use the patch experience minor skin irritation, such as redness, rash, or minor swelling, and insomnia and dream abnormalities. Because sleep problems are a primary mechanism of interest, participants will be instructed to remove the patch during the night while sleeping to avoid dream abnormalities. All of these reactions cease once the patch is removed.

During the third visit of each baseline week (weeks 1 and 5), a member of the research staff will review the purpose of using the nicotine patch (e.g., to help manage withdrawal symptoms; not a substitute for behavioral quitting strategies), provide directions on how to use the patch (e.g., abstinence from smoking, patch location, time, activity, and potential skin reactions), and answer any questions.

Because increased blood pressure is a side effect of TN patch therapy, blood pressure will be closely monitored at each visit. Expanding the upper limit of the blood pressure to less than 160/100 does not increase the risk to subjects enrolled in this trial. The risk of increased blood pressure is no greater than the risk from smoking and quitting smoking will lower an individual's risk. If a participant presents with a SBP between 151-159 mmHg and/or DBP between 91-99 mmHg at the Intake or Pre-Quit visit, the research staff will inform the participant that they have mild, Stage I, hypertension and advise they consult with a physician. The participant will remain eligible for the study and receive nicotine patches as scheduled.

Participants will complete a patch side effects checklist at each visit (in addition to those listed above for ramelteon). The PI will review the checklists for serious and persistent side effects. These will be communicated immediately to the study physician, Dr. Leone. Participants will be instructed to promptly discontinue the patch and contact the PI if they experience severe or persistent local skin reactions (e.g., severe redness, itching, or swelling) at the site of patch application or a generalized skin reaction (e.g., raised patches, hives, or generalized rash). Any serious adverse reactions or significant side effects of TN will be medically evaluated by the study physician. Patch use by such individuals will be monitored and adjusted as needed. Based on our previous

experience with NRT studies [30, 31], we expect few serious adverse events. Nevertheless, the study physician, Dr. Leone, will be available to assist with any adverse events and participant safety issues. Depending on the nature of the side effects, Dr. Leone may reduce the dose of the patch or recommend that the participant discontinue the patch.

Pregnancy: In animal studies, ramelteon produced evidence of developmental toxicity, including teratogenic effects, in rats at doses much greater than the recommended human dose (RHD) of 8 mg/day. There are no adequate and well-controlled studies in pregnant women. Thus, ramelteon must not be used during pregnancy. All female participants of child bearing potential must have a negative pregnancy test at the Intake session and prior to receiving study medication (Baseline Visit 3 of each medication period).

Blood Draw: (only for individuals with a history of liver disease/jaundice) 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.

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). TN will also help reduce withdrawal symptoms.

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. All smokers will receive standard treatment with TN to aid them in their effort to quit smoking and will learn skills to stay quit as a result of participating.

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 Principal Investigators and the Study Physician. They will review all possible Adverse Events (AEs) and Serious Adverse Events (SAEs). They will ensure that this information is captured in a comprehensive manner and reported according to Good Clinical Practice (GCP). The Principal Investigators, Study Physician, and the research staff will oversee and complete the monitoring process. Monitoring will be performed on an ongoing basis in accordance with the University of Pennsylvania Sponsor-Investigator Standard Operating Procedure PM 504.

The Principal Investigators are responsible for:

1. Obtaining IRB review and approval of a clinical investigation before the investigation is initiated and ensuring continuing review of the study by the IRB in accordance with 21 CFR Part 56;
2. Obtaining informed consent in accordance with 21 CFR Part 50; and
3. Assuring that all staff and subjects understand and accept the obligations incurred in undertaking this 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. Ashare) and Study Physician will work together to confirm eligibility criteria. The Study Physician and PI (Dr. Ashare) will review charts for each subject on an ongoing basis and will document reviews by initialing and dating each chart, case report forms that contain blood pressure and heart rate measurements, 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.

Anita Hole, Ph.D. is responsible for both staff training and continuing review of completed MINI and C-SSRS interviews.

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 50 subjects complete all study requirements. On average, 2-3 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 504 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 an adverse event.

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

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

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

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

Severity Grading Scale for Adverse Events
Many disease specific groups have developed toxicity grading scales. For example, most cancer clinical trials use the Common Terminology Criteria for Adverse Events (CTCAE) developed by the NCI. The CTCAE provides a descriptive terminology which is utilized for adverse event reporting. A grading (severity) scale is provided for each adverse event term (http://ctep.info.nih.gov). If no guidelines exist, then the following scale can be used:
• Mild: Noticeable to the subject, does not interfere with the subject's daily activities, usually does not require additional therapy, dose reduction, or discontinuation of the study.
• Moderate: Interferes with the subject's daily activities, possibly requires additional therapy, but does not require discontinuation of the study.
• Severe: Severely limits the subject's daily activities and may require discontinuation of the study. This would include all adverse events defined as "serious adverse events".

Attribution/Association with the Drug or Intervention:
An assessment of the relationship between the adverse event and the drug/intervention will be made for each occurrence by the Principal Investigator.

Adverse Event Attribution Categories:
• Unrelated - The AE is clearly NOT related to the intervention
• Unlikely - The AE is doubtfully related to the intervention
• Possible - The AE may be related to the intervention

• Probable - The AE is likely related to the intervention
• Definite - 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 ramelteon or TN treatment. These items will be rated by participants on a 0 (none) to 3 (severe) scale, and can be summed to provide an overall side effects index.

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

Research staff are trained to inquire (time of onset, nature of issue reported, possible relation to ramelteon/TN 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 Principal Investigator 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 ramelteon/TN and is qualified to manage possible side effects.

Based on published reports using the 8mg dose of ramelteon and 21mg dose of TN 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 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 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

This section describes the requirements for safety reporting by investigators who are Penn faculty, affiliated with a Penn research site, or otherwise responsible for safety reporting to the Penn IRB. The University of Pennsylvania IRB (Penn IRB) requires expedited reporting of those events related to study participation that are unforeseen and

indicate that participants or others are at increased risk of harm. The Penn IRB will not acknowledge safety reports or bulk adverse event submissions that do not meet the criteria outlined below. The Penn IRB requires researchers to submit reports of the following problems within 10 working days from the time the investigator becomes aware of the event:

- Any adverse event (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after the research study, which in the opinion of the principal investigator is:

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

  AND

  Related to the research procedures (An event is "related to the research procedures" if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.)

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

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

Reporting Deaths: more rapid reporting requirements
Concerning deaths that occur during the course of a research study, the following describes the more rapid reporting requirement of the Penn IRB for specific situations:

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

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

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

Other Reportable events:

- For clinical drug trials, the following events are also reportable to the Penn IRB:
- Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).
- Any adverse event that would cause the sponsor to modify the investigators brochure, protocol or informed consent form, or would prompt other action by the IRB to assure protection of human subjects.

- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency. For example:
    - An interim analysis indicates that participants have a lower rate of response to treatment than initially expected.
    - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
    - A paper is published from another study that shows that an arm of your research study is of no therapeutic value.
    - Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
    - Breach of confidentiality
    - Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain in the study.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- **Exception**: A one time, intentional action or process that departs from the IRB and CTSRMC approved study protocol, intended for one occurrence. If the action disrupts the study progress, such that the study design or outcome (endpoints) may be compromised, or the action compromises the safety and welfare of study subjects, advance documented IRB approval is required.
- For exceptions on Industry or Cooperative group sponsored protocols, written approval must be obtained from the Sponsor prior to submitting your exception request to the IRB.
- For in-house studies with a Medical Monitor or Safety Monitoring Committee (not DSMB), approval must be obtained from the Medical Monitor or Safety Monitoring Committee prior to submitting your exception request to the IRB.
- **Deviation:** A one time, unintentional action or process that departs from the IRB approved study protocol, involving one incident and identified retrospectively, after the event occurred. If the impact on the protocol disrupts the study design, may affect the outcome (endpoints) or compromises the safety and welfare of the subjects, the deviation must be reported to the IRB within 10 business days.

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

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

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

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 ramelteon and TN. Research staff will monitor subjects closely during their participation. Data from this project will serve as preliminary data to formally test ramelteon as an adjunct behavioral component to smoking cessation treatment.

SUBJECT COMPENSATION

Participants will receive compensation at each session they attend and can receive up to $592 for completing all study requirements (including travel reimbursement). Compensation distribution is shown in the table below.

Study Visit	Visit Compensation	Travel	Armband Incentive	Quit Incentive	Total
Intake*	$20	$10			$30
Week 1 Baseline Session (Mon)	$10	$10			$20
Week 1 Baseline Session (Wed)	$10	$10			$20
Week 1 Baseline Session (Fri)	$20	$10	$16		$46
Week 2 Quit Assess. (Mon)	$10	$10		$10+	$30
Week 2 Quit Assess. (Tues)	$10	$10		$10+	$30
Week 2 Quit Assess. (Wed)	$10	$10		$10+	$30
Week 2 Quit Assess. (Thurs)	$10	$10		$10+	$30
Week 2 Quit Assess. (Fri)	$10	$10	$20	$10+	$50
Week 5 Baseline Session (Mon)	$10	$10			$20
Week 5 Baseline Session (Wed)	$10	$10			$20
Week 5 Baseline Session (Fri)	$20	$10	$16		$46
Week 6 Quit Assess. (Mon)	$10	$10		$10+	$30
Week 6 Quit Assess. (Tues)	$10	$10		$10+	$30
Week 6 Quit Assess. (Wed)	$10	$10		$10+	$30
Week 6 Quit Assess. (Thurs)	$10	$10		$10+	$30
Week 6 Quit Assess. (Fri)	$10	$10	$20+$50[a]	$10+	$100
TOTAL	$200	$170	$122	$100	
Grand Total:					**$592**

***** Participants who test positive for study prohibited drugs will not be eligible to receive visit or travel compensation.

+ Participants will receive $10/day (in cash) for each day of self-reported abstinence that is biochemically-confirmed

[a] Participants will be provided $4/day for each day they wear the armband and complete the sleep diary plus $50 if they provide at least 18 of 22 days of data (85%)

INFORMED CONSENT

1. Consent Process

At the Intake (Day 0), participants will provide written study consent and HIPAA documents (combined) before completing additional survey measures and undergoing any study related activities. A member of the research staff will explain the study procedures before the start of the Intake visit and ask each participant if they have any further questions and provide answers or any clarifications and written consent will be obtained. All individuals obtaining consent will have completed the University of Pennsylvania human subject certification and will be fully trained in the informed consent process. Individuals can elect not to participate and may withdraw at any time without penalty. Participants will receive a copy of the combined consent/HIPAA form. Hard copies of Intake data and a copy of the signed combined consent/HIPAA forms will be stored in a subject's study folder. The original signed combined consents/HIPAA will be centrally stored in Regulatory Consent Binders.

2. Waiver of Authorization

Not applicable as we will be operating under FDA regulations.

RESOURCES NECESSARY FOR HUMAN RESEARCH PROTECTION

1. Research Staff

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

- Rebecca Ashare, Ph.D., Principal Investigator
- David Dinges, Ph.D., Co-Investigator
- Janet Audrain-McGovern, Ph.D., Co-Investigator
- Frank Leone, M.D., Study Physician
- Paul Wileyto, Ph.D., Statistician

- Susan Ware, B.S. Database Manager
- Paul Sanborn, Samples Manager
- Molly Ruben, MPH, Project Manager
- Anita Hole, Ph.D. MINI review
- Leah La Prate, Study Support Staff
- Janice Biddle, CRNP, Study Support Staff
- Chan To, Study Support Staff
- Erin Logue, Study Support Staff
- Victoria McLaughlin, Study Support Staff
- Zoe Rosoff-Verbit, Study Support Staff
- Katrina Serrano, Study Support Staff
- Morgan Thompson, Study Support Staff

2. Staff Training

Dr. Ashare 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.

3. 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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