

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

**Version 17, 06/23/2017**

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**PROTOCOL TITLE**

**1. Full Title**

Repurposing cholinesterase inhibitors for smoking cessation.

**2. Brief Title**

Effect of galantamine on short-term abstinence

**STUDY SPONSORSHIP**

**1. Funding Sponsor**

National Cancer Institute P50 Center for Interdisciplinary Research on Nicotine Addiction CA143187  
National Institute on Drug Abuse (K23 DA035295)

**2. Primary Sponsor**

Caryn Lerman, Ph.D., Director, CIRNA

**PROTOCOL ABSTRACT**

Nicotine dependence is a major public health problem and currently available treatments are ineffective for the majority of smokers. Thus, there is an urgent need to develop and test new medications to aid in smoking cessation. Recent evidence from a genetic study of prospective smoking cessation conducted at the CIRNA suggests that smoking cessation may be influenced by variation in acetylcholine levels. The proposed proof-of-concept study is a randomized, double-blind, placebo-controlled, parallel arm pilot study of the effects of the acetylcholinesterase inhibitor, galantamine (vs. placebo), on short-term abstinence among 80 treatment-seeking smokers. The primary outcome is the number of days abstinent during a 7-day quit attempt. Secondary outcomes include: smoking rate during the run-up and monitored abstinence phase, medication adherence, side effects, cognition, and smoking urges and other withdrawal symptoms. The data generated will be used to support an NIH grant application by a new investigator to evaluate whether acetylcholinesterase inhibitors could be effective smoking cessation medications.

**OBJECTIVES**

**1. Overall Objectives**

The objective of this proof-of-concept pilot study is to evaluate galantamine hydrobromide extended-release (ER) 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 7-day quit attempt.

**3. Secondary Outcome Variable(s)**

a. Smoking rate (cigarettes/day) during the 2-week drug run-up phase and during the monitored abstinence period.

b. Self-report symptoms of withdrawal, craving, subjective effects of smoking, and objectively measured cognitive function (e.g., working memory and attention).

## BACKGROUND

There is a critical need for novel smoking cessation treatments. Cigarette smoking continues to be the greatest preventable cause of morbidity and mortality in the U.S. and worldwide. Aside from nicotine replacement therapy (NRT), there are only two FDA-approved non-nicotine pharmacological treatments for smoking cessation. Clearly, there is a need to identify novel medications to help more smokers maintain abstinence. Repurposing medications that have been “de-risked” through phase I-III testing and target nicotine withdrawal symptoms provides a practical approach by reducing the time and cost burden of traditional drug development strategies (Collins, 2011; Oprea et al., 2011).

Most smokers relapse during the first week of abstinence. Of the 40% of smokers who try to quit each year, 50-75% relapse within the first week (Garvey, Bliss, Hitchcock, Heinold, & Rosner, 1992; Hughes, Keely, & Naud, 2004). Thus, it is essential to identify the factors that contribute to relapse during this early withdrawal period. Human laboratory paradigms of short-term smoking abstinence provide a clinically valid mechanism for understanding the processes that underlie relapse during this vulnerable period and for screening new smoking cessation medications (Perkins et al., 2010; Perkins et al., 2008).

Cognitive impairment during abstinence is a promising therapeutic target. Cognitive impairment is a common nicotine withdrawal symptom, reported by nearly 50% of smokers (Hughes, 2007b). These deficits peak during the first week of a quit attempt (Shiffman & Jarvik, 1980) and encompass a range of cognitive processes in animals and humans including attention (Myers, Taylor, Moolchan, & Heishman, 2008; Shoib & Bizarro, 2005), working memory (Jacobsen et al., 2005; Levin et al., 1990), and response inhibition (Ashare & Hawk, 2012; Harrison, Coppola, & McKee, 2009). Critically, withdrawal-related cognitive impairment predicts relapse to smoking (Krishnan-Sarin et al., 2007; Patterson et al., 2010; Rukstalis, Jepson, Patterson, & Lerman, 2005).

Acetylcholinesterase inhibitors (ACHEIs) represent a potential therapeutic target. The neurotransmitter acetylcholine (ACh) contributes to the rewarding effects of nicotine by binding to nicotinic receptors (nAChR) in the brain and stimulating dopamine release (Schilstrom, Ivanov, Wiker, & Svensson, 2006). ACh is synthesized by the choline acetyltransferase (ChAT) enzyme and polymorphisms on the *ChAT* gene demonstrated significant associations with smoking cessation and nicotine dependence in a recent study in our lab (Ray et al., 2010) and in an independent follow-up study (Wei et al., 2010), highlighting the importance of the endogenous cholinergic system in smoking behavior. Acetylcholinesterase inhibitors (ACHEIs), which increase ACh levels (Delrieu, Piau, Caillaud, Voisin, & Vellas, 2011), are FDA-approved treatments for Alzheimer’s disease (AD), which is marked by cognitive impairment, loss of cholinergic neurons, and decreased ACh levels (Foldi, White, & Schaefer, 2005; Koontz & Baskys, 2005; Terry & Buccafusco, 2003). Unlike other ACHEIs, galantamine acts as a positive allosteric modulator of  $\alpha 7$  and  $\alpha 4\beta 2$  nAChRs, which may partially account for its cognitive enhancing effects (Ago, Koda, Takuma, & Matsuda, 2011; Kuryatov, Onksen, & Lindstrom, 2008; Pandya & Yakel, 2011).

A few recent studies have begun to explore the effects of ACHEIs on smoking behavior. However, none have focused on the general population of smokers (Diehl et al., 2006; Diehl, Nakovics, Mutschler, Hermann, & Kiefer, 2009; Kelly et al., 2008). In our recent pilot study of 18 non-treatment seeking smokers (IRB # 812346), 4 weeks of treatment with the ACHEI, donepezil, modestly improved cognition (e.g., working memory and attention) and was well-tolerated, but had no effect on smoking behavior. Because smokers in the prior study were not interested in quitting, the question remains: Will ACHEIs increase abstinence among treatment-seeking smokers? Using this proof-of-concept study, we propose to examine whether galantamine can enhance a smoker’s ability to maintain short-term abstinence and whether it does so by ameliorating withdrawal-related cognitive deficits.

The primary objective of the proposed proof-of-concept study is to test the effects of galantamine, compared to placebo, on ability to quit smoking. Specifically, we will utilize a validated procedure for medication screening to test the effects of galantamine on short-term abstinence in 80 treatment-seeking smokers during a 23-day human laboratory study. As in prior studies (Scharre, Shiovitz, Zhu, & Amatniek, 2008; Sofuoglu & Carroll, 2011), following an initial 1-week drug run-up phase (8mg q.d galantamine), medication dose will be increased to 16 mg q.d. galantamine for the remainder of the medication period (through Day 23). On Day 16, smokers will undergo a mandatory 24-h abstinence period, which will be followed by a programmed smoking lapse. Smokers will then be

instructed to abstain for the following 7 days (observed abstinence), with small monetary incentives for abstinence and biochemical verification. The primary outcome is the total number of days abstinent out of seven. We will obtain self-report measures of side effects and smoking behavior, as well as objective measures of cognitive performance at regular intervals through the study.

## **CHARACTERISTICS OF THE STUDY POPULATION**

### **1. Target Population**

Eighty adult, treatment-seeking smokers, between the ages of 18-60, 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**

Two hundred and fifty smokers will be enrolled in order to have 80 smokers (40 per group) complete all sessions, accounting conservatively for 25% attrition. Participants will first be screened over the phone and then complete an in-person Intake to ensure final eligibility. Enrolled participants will complete a Baseline session and be randomized to receive galantamine or placebo. Participants will be told that this is a practice quit attempt with an FDA-approved medication that is being tested as a possible new treatment for smoking cessation.

### **3. Key Inclusion Criteria**

Smokers ages 18-60, 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 6 months. Using a scale from 0 to 100, they must rate their confidence that they will make a quit attempt in the next 6 months a 50 or higher. Following the current study, participants will be referred to a free smoking cessation program in our Center. 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. Daily use of chewing tobacco, snuff, and/or snus.
2. 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 month.
3. Provide a carbon monoxide (CO) breath sample reading less than 10 parts per million (ppm) at Intake.

#### Alcohol/Drugs:

1. History of substance abuse in the past 6 months and/or currently receiving treatment for substance abuse (e.g., alcohol, opioids, cocaine, marijuana, or stimulants) as determined by self-report during the phone screen and/or through the MINI during the Intake. Subjects reporting a history of substance abuse must be in remission at least 6 months or greater.
2. Current alcohol consumption that exceeds 25 standard drinks/week over the past 6 months.
3. Providing a breath alcohol concentration (BrAC) reading of greater than or equal to 0.01 at Intake, Baseline, or Testing Days.
4. A positive urine drug screen for cocaine, amphetamines, methamphetamines, benzodiazepines, PCP, methadone, barbiturates, and opiates at the Intake, Baseline, or Testing days.

#### Medical:

1. Women who are pregnant, planning a pregnancy in the next 3 months, or 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 Baseline and Testing days for all female subjects of child-bearing potential.
2. Diagnosis of Alzheimer's Disease or dementia.
3. Current treatment of cancer or diagnosed with cancer (except basal cell carcinoma) in the past 6 months.
4. Liver/kidney failure, peptic ulcer disease, benign prostate hypertrophy.
5. Asthma or chronic obstructive pulmonary disease (COPD).



6. History (last 6 months) of abnormal heart rhythms, tachycardia and/or cardiovascular disease (stroke, angina, heart attack). These conditions will be evaluated on a case by case basis by the Study Physician/Health Care Provider.
7. Serious or unstable disease within the past 6 months, as determined by the Study Physician/Health Care Provider.
8. Clinically significant abnormalities within physical examination and vital signs at Intake. Abnormalities will be assessed by the Study Physician/Health Care Provider and eligibility will be determined on a case-by-case basis.
9. Any impairment (physical and/or neurological) including visual or other impairment preventing cognitive task performance.
10. Uncontrolled high blood pressure (SBP>160 or DBP>100).
11. Hearing impairment, significant hearing loss (more than 20% in either ear), cochlear implants, or bi-lateral hearing aids.
12. History of brain injury.
13. History of epilepsy or a seizure disorder.
14. Color Blindness.
15. Low or borderline intellectual functioning – determined by receiving a score of less than 90 on the Shipley Institute of Living Scale (SILS) which correlates with the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Estimated IQ Test (administered at Intake).

Psychiatric Exclusion (as determined by self-report on phone screen and/or through MINI during Intake):

1. Current diagnosis of major depression. Persons with a history of major depression, in remission for 6 months or longer, are eligible, provided they are not excluded based on medications (below).
2. Suicide risk score on MINI greater than 1.
3. History or current diagnosis of schizophrenia, psychosis, and/or bipolar disorder.
4. Current or past hypomanic/manic episode.
5. Current or history of a diagnosis of Attention-Deficit/Hyperactivity Disorder (ADHD).

Medication:

1. Current use, recent discontinuation (within the last month) of any form of smoking cessation medications (i.e., Zyban, Wellbutrin, Wellbutrin SR, Chantix, nicotine replacement therapy);
2. Current use or recent discontinuation (within the last 60 days) of:
  - a. Anti-anxiety or panic disorder medications.
  - b. Anti-psychotic medications.
  - c. Mood-stabilizers (e.g., Lithium, Lamictal/lamotrigine, Neurontin/gabapentin, Topamax/topiramate, valproic acid, Tegretol/carbamazepine).
  - d. Anti-depressants (e.g., Wellbutrin, MAOIs, SSRIs, tricyclic antidepressants).
  - e. Prescription stimulants (e.g., Provigil, Ritalin, Adderall).
  - f. Systemic Steroids (e.g., Prednisone).
  - g. Alzheimer's disease medications (e.g., Acetylcholinesterase inhibitors (ACIs), Aricept/donepezil, Exelon/rivastigmine, Tacrine, or memantine).
  - h. Parkinson's disease medications (e.g., Cogentin/benzotropine).
  - i. Irritable bowel syndrome medication (e.g., Dicylomine/Bentyl).
  - j. Heart medications (e.g., quinidine or Procardia/nifedipine).
  - k. Peptic ulcer disease medication (e.g, Zantac/ranitidine).
  - l. Muscle relaxants (e.g., Soma/carisoprodol, Anectine/succinylcholine).
  - m. Anti-fungal medication (e.g., Nizoral/ketoconazole).
  - n. Anti-seizure medications (e.g., Ativan, Banzel, Carbatrol, Dilantin, Lamictal, Gabitril, Lyrica, Neurontin, Tegretol, Topomax).
  - o. COPD medication (e.g., Atrovent/Ipratropium Bromide).
  - p. Urinary retention medications (e.g., Duvoid/bethanechol, Proscar/finasteride, Avodart/dutasteride, Dibenzylamine/phenoxybenzamine, Regitine/phentolamine).
  - q. Eye medication (e.g., Atropine).
3. Daily use of:
  - a. Opiate-containing medications for chronic pain (Duragesic/fentanyl patches, Percocet, Oxycontin).
  - b. Medication for asthma (albuterol, Serevent, Combivent, Advair, Flovent, Azmacort, Symbicort).

4. Known allergy to study medication.

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. Any medical condition, illness, disorder, or concomitant medication that could compromise participant safety or treatment, as determined by the Principal Investigator and/or Study Physician.
4. Inability to provide informed consent or complete any of the study tasks as determined by the Principal Investigator.
5. Completion of neurocognitive assessments and/or use of study medication(s) at the CIRNA in the past month that could influence performance on study tasks as determined by the Principal Investigator.
6. Not able to effectively communicate in English (reading, writing, speaking).
7. Missing 2 or more consecutive sessions, or 3 or more sessions during the medication period.
8. Missing 2 or more consecutive doses during the medication period.
9. Missing 3 or more doses throughout the medication period.

**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 may be exposed to these advertisements and choose to respond. 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 advertising (i.e., Craigslist, flyers, newspaper, social media, or radio ads) will be used to invite smokers from the general population.

**STUDY DESIGN**

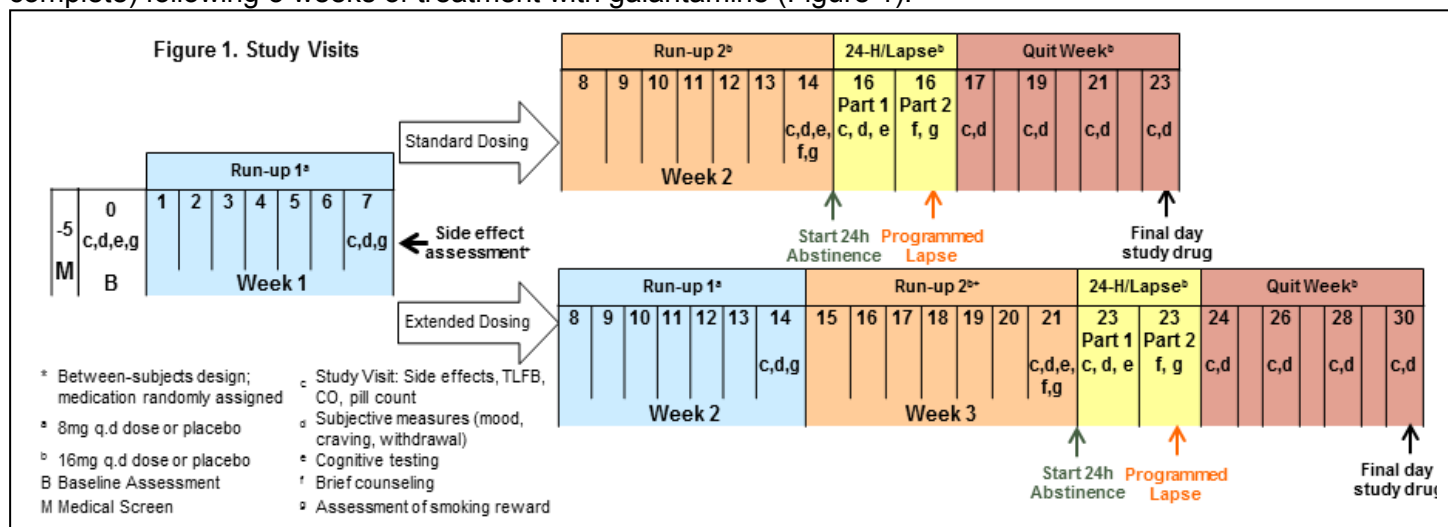
**1. Phase**

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

**2. Design**



We propose to conduct a between-subject, randomized, double-blind, placebo-controlled trial to assess smoking behavior, adherence, side effects, and cognition among treatment-seeking smokers (n=200 to have n=80 complete) following 3 weeks of treatment with galantamine (Figure 1).



### 3. Study Duration

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

Enrollment will start in July 2012 (after IRB approval is received). We estimate that we will need to telephone screen 1000 smokers to enroll 250 smokers into the study (accounting for 20% eligibility). We expect approximately 50% of those who attend Intake to be eligible and a drop-out rate of 25% based on prior experience and expect to have 80 (40 per group) participants complete the study. We estimate enrolling 2-3 smokers per month.

#### Length of a subject's participation time in study

We estimate it will take a minimum of 5 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 start of medication (Day 1), or dosing modification. Thus, although the maximum period of time that participants will take study medication is 4.5 weeks (30 days for those who follow the "Extended Dosing" schedule; 23 days for those who follow the "Standard Dosing" schedule; See Figure 1), the maximum duration a participant can be in the study is 8 weeks.

#### Projected date of completion of the proposed study

We estimate that 80 people will have completed the study by April 2018, and that analyses and reporting will be complete by September 2018.

### DRUGS OR DEVICES

The study will be performed using the 8mg and 16mg doses of galantamine hydrobromide-ER, which is currently marketed for the treatment of Alzheimer's disease. The dosing regimen will be an initial 1 week of drug run-up at the lowest 8mg q.d. dose (see Figure 1) followed by an assessment at the end of week 1. Unless there are moderate to severe adverse events (see definitions below), the dose will be increased to 16mg q.d. ("Standard Dosing"; see Figure 1). If moderate to severe adverse events are reported, participants will remain at the 8mg dose for one more week before titrating to 16mg ("Extended Dosing"). All participants will begin the 24-H abstinence period after one week on 16mg (end of week 2 for Standard Dosing and end of week 3 for Extended Dosing). All participants will continue to take the 16mg q.d. during the mandatory 24-h quit period, programmed lapse day, and 7-day quit week.

The dosing regimen is documented to be safe and well tolerated in prior clinical studies (Scharre, et al., 2008; Sofuoglu & Carroll, 2011). There does not appear to be a significant decrease in medication efficacy compared to the 24 mg dose, thus decreasing the risk for participants in our study (Aronson, Van Baelen, Kavanagh, &

Schwalen, 2009). Galantamine will be purchased and packaged into blister packs by the Investigational Drug Service at the University of Pennsylvania. Participants will be instructed to take one 8mg or 16mg pill (galantamine-ER) every morning, preferably with food, for 23 days. Those following the Extended Dosing schedule will take study medication for 30 days. However, based on initial data, we anticipate that this will be rare.

Though galantamine has been administered to non-Alzheimer's healthy volunteers in multiple studies (Beglinger et al., 2004; Chuah & Chee, 2008; Chuah et al., 2009; Gron, Kirstein, Thielscher, Riepe, & Spitzer, 2005; Nathan et al., 2001; Silver, Shenhav, & D'Esposito, 2008), our pilot study (IRB#814947) was the first study to administer galantamine-ER to a population of treatment-seeking smokers. Therefore, an Investigational New Drug (IND) exemption has been submitted to OHR for this protocol. Such an exemption was received in our prior study of the ACI donepezil and galantamine in smokers (IRB #s 812346 and 814947).

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

Galantamine-ER 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. Galantamine 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 to treatment, 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 one week of 8mg galantamine (or placebo) and 16 days of 16mg (or placebo). In case moderate or severe adverse events are reported at the end of the first week, all medication kits will include one extra week of 8mg galantamine (or placebo), which will be labeled as the alternate blister pack for the Extended Dosing schedule. If no moderate or severe adverse events are reported at the end of the first week, we will proceed with the default blister pack (see Figure 1). If moderate or severe adverse events are reported during the first week, the study physician will be consulted and a decision will be made as to whether to proceed with the default or provide the alternative blister pack, in which case participants will remain in the study for one extra week. 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.

### **SUICIDAL IDEATION AND BEHAVIOR**

Suicide risk is assessed via MINI during the Intake Visit. Participants with a suicide risk score greater than 0 will be deemed ineligible at the Intake Visit.

### **STUDY PROCEDURES**

#### **1. Procedures**

This is a randomized placebo-controlled study of the effects of galantamine, 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. Fifty four will be randomized to receive galantamine and 54 will be randomized to receive placebo to have 80 smokers (40 per group) complete the study. All study visits

will be completed at the CIRNA. Participants will complete a Baseline, 2 Observation Days, and a Pre-quit (counseling) Testing Day (Day 14). Beginning on Day 15, smokers will undergo a mandatory 24-h abstinence period. On Day 16 (part 1), following confirmation of abstinence, abstinence-induced cognitive deficits will be tested and subjective assessments will be collected in-Center. Subsequently, there will be a programmed smoking lapse, after which the subjective rewarding value of the programmed lapse cigarette will be assessed (Day 16 part 2). Smokers will receive another 20-minute coaching session and be instructed to try to remain abstinent from 10 P.M. that evening until after the final Observation Visit (7 days observed abstinence), with small monetary incentives for abstinence and biochemical verification. During the 7-day quit attempt, participants will complete 4 Observation Days (Days 17, 19, 21, and 23) (Figure 1). NOTE: Days refer to the Standard Dosing schedule. Please see Figure 1 for Extended Dosing schedule.

## 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 visits dates' and times. Method of preference will be collected over the phone.
- Intake (Day -5). 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 and a psychological interview (MINI) (Description under Screening/Covariate Measures)
  8. Receive a physical examination by the Nurse Practitioner
  9. Have height and weight measured (led by study staff)
  10. Complete the Shipley Institute of Living Scale. Participants with a Wechsler Adult Intelligence Scale-Revised (WAIS-R) Estimated IQ Test score less than 90 will be ineligible to participate

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:

11. Complete questionnaires (demographics, nicotine dependence, smoking rate, withdrawal, and smoking urges)
12. Provide one 5ml saliva sample to test for cotinine.
13. Finalize their study schedule and their Baseline Session

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.





Once final eligibility is confirmed, the Study Physician (Dr. Leone) will sign the prescription blank to assign the participant to a treatment group.

- Baseline Session (Day 0). Participants will complete a 1.5 hour Baseline session before starting study medication. The Baseline session can be scheduled within 2 days of the Intake but no more than 30 days can elapse between Intake and Baseline. At the Baseline session 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 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 withdrawn from the study.
  3. Provide a blood pressure sample (See Blood Pressure Procedures under Screening/covariate measures)
  4. Provide 2ml saliva sample for DNA collection and genotyping (Oragene™) (note- collection of saliva for DNA is optional)
  5. Complete questionnaires (smoking rate, concomitant medication review, withdrawal, smoking urges, mood, attention, subjective effects, and side effects)
  6. Complete a 60-minute battery of cognitive tasks assessing working memory (n-back), attention (continuous performance task; XO reaction time task), response inhibition (stop-signal task, Stroop test)
  7. Receive their study medication and be given instructions as when to start taking study medication

This session can be scheduled any time of day. However the timing of this session will influence when the Day 14 and Day 16 testing appointments are scheduled. Ideally, the subsequent testing sessions would be at the same time of day, but can be scheduled up to 1 hour earlier or later than the Baseline session. However, the sessions may go beyond 1 hour as determined by PI discretion.

- Observation Day 7. Participants 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:
  - Blood pressure (See Blood Pressure Procedures under Screening/covariate measures)
  - CO breath sample
  - BrAC sample
  - Smoking rate (timeline followback; TLFB)
  - Medication adherence/pill count
  - Side effects and concomitant medication review
    - If no moderate to severe adverse events are reported, participants will be given the default blister pack for week 2 (i.e., 16mg galantamine or placebo)
    - 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 default or provide the alternative blister pack (i.e., 8mg or placebo) for one more week before titrating to 16mg. Thus, participants who follow this schedule will remain in the study for one extra week (i.e., 30 days instead of 23 days).
  - Mood, smoking urges, withdrawal symptoms, attention, subjective effects

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

- Pre-Quit Testing Day (Day 14). Participants will be asked to bring their study medication to this visit. During this 2-hour visit, participants will complete the same activities they completed at the Baseline Session except that they will complete additional measures of pill count and receive pre-target quit date (TQD) counseling. TQD counseling will involve meeting with a smoking cessation counselor and taking part in a brief 20-minute coaching session to prepare them for the 24-h abstinence period. This session will focus on management of smoking triggers and a plan to prevent and manage smoking relapse.

Ideally, this session will be scheduled at the same time the Baseline Session was achieved but it can be scheduled for up to 1 hour earlier or later than the Baseline time. However, the sessions may go beyond 1 hour as determined by PI discretion. Day 14 must occur on the target date.

- Mandatory 24-h Abstinence Period (Day 15/Day 16 Part 1). On Day 15, participants will receive a telephone call to remind them to begin their practice quit attempt approximately 24 hours before their scheduled visit on 24-H Testing Day 16. Participants will also be reminded that in order to remain eligible for the study, they must remain abstinent during this 24 period.
- 24-H Testing Day (Day 16). The 24-h Testing Day occurs after approximately 24 hours of abstinence from nicotine. The Testing Day Visit takes about 2 hours to complete and is split into two parts. Ideally, this session will be scheduled at the same time the Pre-Quit Testing Session was achieved but it can be scheduled for up to 1 hour earlier or later than the Pre-Quit Testing session time. However, the sessions may go beyond 1 hour as determined by PI discretion. The procedures participants will complete within each part of the Testing Day Visit are as follows:
  - 24-H Testing Day Part 1  
On Day 16 part 1, participants will provide:
    1. A CO sample to verify abstinence. Mandatory abstinence will be biochemically confirmed by a CO reading of less than 10 ppm. If the CO reading is not less than 10 ppm, but there is a 50% reduction from the CO collected at the Baseline Visit, this will be considered sufficient and the participant may continue as scheduled. If a participant smokes (self-reported or biochemically confirmed) during the mandatory abstinence period, they may be withdrawn from the study.
    2. A breath alcohol (BrAC) sample. Participants with a BrAC greater than 0.00 will be ineligible.
    3. A urine sample for a urine drug screen and pregnancy test. If urine drug screen or pregnancy test is positive, participants will be withdrawn from the study.
    4. Blood pressure (See Blood Pressure Procedures under Screening/covariate measures)
    5. Medication adherence/pill count
    6. Side effects and concomitant medication review
    7. Mood, smoking urges, attention, and withdrawal symptoms
    8. Complete a 60-minute battery of cognitive tasks assessing working memory (n-back), attention (continuous performance task; XO reaction time task), response inhibition (stop-signal task, Stroop test)
  - 24-H Testing Day Part 2 (Programmed Lapse)
    1. Participants will be instructed to smoke one of their own cigarettes in the CIRNA Smoking Laboratory.
    2. Following the programmed lapse, participants will complete the assessments of the subjective and rewarding effects of the 'programmed lapse' cigarette (Table 1).
    3. Participants will complete a brief smoking cessation counseling session (~15 minutes) during which they will review strategies to try to remain abstinent during the 7-day monitored abstinence/observation phase. Participants will be permitted to return to their normal smoking practices after they leave the Center until 10 P.M. that evening.
- 7-Day Quit Attempt (Days 17-23). During this 7-day period, participants will be given instructions to remain abstinent from smoking from 10 P.M. the evening of Day 16 until after they complete their final Observation Visit. On Days 17, 19, 21, and 23, all participants will be asked to come to the CIRNA for brief 20-minute visits to complete the following:
  - Complete CO, smoking rate (TLFB), and concomitant medication assessment.
    - To increase abstinence motivation, participants will receive \$15/day (in cash) for each day for self-reported abstinence that is biochemically-confirmed. On Day 17, a CO reading of less than 10ppm or less than 50% of CO breath sample taken at Baseline visit will be sufficient as biochemically-confirmed abstinence. On Days 19, 21, and 23, a CO reading less than 8 ppm will be considered as biochemically-confirmed abstinence.

- Take scheduled dose of study medication under supervision of the research staff.
- Provide a blood pressure sample.
- Complete measures of side effects, pill count, smoking urges, attention, withdrawal, and mood (Table 1).
- On Day 23:

**Table 1. Study Measures**

State	Intake	Baseline	Smoking as Usual*	Abstain 24 hr	Programmed Lapse	7-Day Quit Attempt
<b>Study Visit Days</b>	<b>-5</b>	<b>0</b>	<b>7, 14</b>	<b>16 Part 1</b>	<b>16 Part 2</b>	<b>17, 19, 21, 23</b>
<b>Screening Variables/Covariates</b>						
Demographics	X					
Nicotine Dependence (FTND/Cigarette Brand)	X					
Smoking/ETOH History	X					
Medical History, Height/Weight	X					
Blood Pressure	X	X	X	X		X
Psychiatric History (MINI)	X					
Saliva for DNA		X				
Shipley Institute of Living Scale	X					
Urine Drug Screen/Pregnancy	X	X	X (Day 14)	X		
Breath Alcohol Content (BrAC)	X	X	X	X		X
Carbon Monoxide (CO)	X	X	X	X		X
Brief Counseling			X (Day 14)		X	
<b>Primary Outcomes</b>						
Cigarette Consumption (TLFB)		X	X	X		X
Saliva Cotinine	X					X (Day 23)
Neurocognitive Test Battery		X	X (Day 14)	X		
<b>Secondary Outcomes</b>						
Craving (QSU-B); Withdrawal (MNWS-R)		X	X (week)	X (24hr)	X (now)	X
Current ADHD Symptoms (BAARS-IV)		X	X(week)	X (24hr)		X (24hr)
Mood (PANAS)		X	X (week)	X (24hr)	X (now)	X
Subjective Effects, Cigarette Ratings (CES, SQ)		X	X		X	
<b>Medication Measures</b>						
Concomitant Medication Review		X	X	X		X
Medication Side Effects		X	X	X		X
Pill Count			X	X		X

\* Participants on the Extended Dosing Schedule will have one additional observation visit. The 24-H/Lapse visit will occur on Day 23.

- Participants will return any unused study medication.
- Participants reporting not smoking (which was biochemically confirmed) for 7 days will also provide a saliva sample to assess cotinine levels.
- Participants will be offered information (i.e. flyer, brochure, etc.) about a smoking cessation research program. The participant's decision whether or not to receive this information will be documented.

### 3. Description of Measures and Variables

#### 3.1 Screening/Covariate Measures

**History and Physical Examination.** A medical history 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 and the physical examination will be conducted by the Nurse Practitioner/Health Care Provider.

Urine Drug Screen. The urine drug screen will be administered at the Intake, Baseline, Day 14, and Day 16 Part 1 visits. The urine drug screen requires about 30ml of urine and indicates whether the subject has recently taken any exclusionary drugs (cocaine, PCP, amphetamines, methamphetamines, tricyclic antidepressants, ecstasy, opiates, methadone, benzodiazepines, and barbiturates). Participants with a positive urine drug screen for any substance listed above other than THC 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, Intake, Baseline, Day 14, and Day 16 Part 1 visits, 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/ETOH History. 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 the Intake, Baseline, and/or Testing Days (Day 14, Day 16) indicates alcohol consumption within the last 14 hours and will result in the participant being withdrawn from the study. The ETOH history form will be administered at the Intake visit and will ask subjects about their alcohol consumption over the past 7 days.

Blood Pressure. At the Intake, participants presenting with elevated blood pressure (i.e., systolic blood pressure greater than 160 and/or diastolic blood pressure greater than 100) will have a second blood pressure reading taken after a ten minute period in which the participants will be instructed to sit comfortably. If, after the second reading, systolic blood pressure remains greater than 160 and/or diastolic remains greater than 100, the participant will be ineligible for the study.

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 160 and/or diastolic blood pressure greater than 100) at any subsequent visit, the staff will follow the same steps listed above. If, after the second reading, systolic blood pressure remains greater than 160 and/or diastolic remains greater than 100, the subject will be told to not take the next dose of study medication. 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.

Psychiatric History. Current major depression, lifetime prevalence of psychosis, bipolar disorder, schizophrenia, hypomanic/manic episodes, ADHD, and substance abuse will be determined via self-report during the phone screen and via semi-structured interview using the Mini International Neuropsychiatric Interview (MINI). The MINI is a 10-15 minute structured interview developed by the World Health Organization to assess major DSM-IV Axis 1 psychiatric diagnoses. This instrument permits both current (past 30 days) and lifetime assessments of psychiatric illness, and recent data support its reliability and validity (Sheehan et al., 1998). The MINI will be administered by a trained research staff member at the Intake visit. There will be 100% review of paper MINIs by Dr. Hole, a clinical psychologist with relevant training, to maintain quality control.

Shipley Institute of Living Scale. All participants will complete the Shipley Institute of Living Scale (SILS) at the Intake visit. The SILS is a self-administered test designed to assess general intellectual functioning in adults and adolescents and to aid in identifying cognitive impairments (Zachary, 2000). The scale consists of two subtests, a 40-item vocabulary test and a 20-item test of abstract thinking. The total administration time is 20 minutes (10 minutes per subtest). A trained member of the study staff will score the test. The SILS correlates with the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Estimated IQ Test; those participants earning less than an

estimated WAIS-R IQ of 90 will be ineligible. The SILS is considered a highly reliable assessment tool; with a good total score internal consistency (Cronbach's  $\alpha = .92$ ).

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 (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991). The FTND scale has satisfactory internal consistency (Cronbach's  $\alpha = .64$ ) and high test-retest reliability ( $r = .88$ ) (Pomerleau, Carton, Lutzke, Flessland, & Pomerleau, 1994).

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

Genotyping. The 2ml saliva sample, via the Oragene™ collection kit will be used to conduct exploratory analyses of associations of genes related to nicotine addiction and cognitive function. Because all genetic analyses are exploratory, participants will not be informed of their genetic test results. All samples and results will be kept confidential and secure. The saliva Oragene™ sample will be collected at the Intake. Participants who do not consent to providing a saliva sample for DNA testing will still be eligible to participate.

Brief counseling. These 20-minute sessions will occur during the 2-hour visit on Testing Day 14 and following the Programmed Lapse (Day 16 Part 2). This counseling session will be similar to previous studies in our center (IRB#811325). 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 Medication Measures**

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

Pill Count/Adherence. Medication adherence will be assessed by pill count at each study visit or telephone session after the Baseline visit (Ray et al., 2009).

Side Effects. A checklist of side effects based on the product insert will be administered to participants at all study visits after the Intake. 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 Outcome Variables**



Smoking Rate (TLFB). We will assess cigarettes smoked during the Baseline session (dating back to the Intake visit), and throughout the medication period. A standard timeline follow-back (TLFB) method will be used (Brown, Burgess, Sales, & Whiteley, 1998), as we have done previously (Lerman et al., 2004) to assess self-reported smoking rate.

Saliva samples. All participants will provide saliva samples during the Intake visit. For participants reporting abstinence (which is biochemically confirmed) during the 7-day quit week, a second saliva sample will be collected at the final study visit (Quit Observation 4) to test cotinine levels.

Withdrawal Symptoms. The “Minnesota Nicotine Withdrawal Scale - Revised version”(MNWS\_R) (Hughes, 2007c) captures the current state of nicotine withdrawal (Hughes, 2007a; Hughes & Hatsukami, 1986). The scale assesses eight DSM-IV items of nicotine withdrawal including: dysphoria or depressed mood, insomnia, irritability/frustration/anger, anxiety, decreased heart rate, difficulty concentrating, restlessness, and increased appetite/weight gain. Participants will rate the intensity of their symptoms on the following scale: 0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = severe and a summary score will be calculated. This will be administered at all study visits (except the Intake). Withdrawal will be assessed using a one-week time reference for the Baseline visit, all Pre-Quit Observation Days, and the Pre-Quit Testing Day. During the 24-h Abstinence Period and the 7-Day Quit Attempt, the reference point will be 24 hours. The afternoon visit of the Programmed Lapse will assess current withdrawal symptoms.

Smoking Urges. The 10-item brief QSU questionnaire on smoking urges (Cox, Tiffany, & Christen, 2001) will be used to assess craving for cigarettes during the medication run-up period. The QSU-B contains 2 subscales (anticipation of reward, relief from negative affect). Craving has also been related to long-term cessation outcome in many, but not all, clinical studies (Killen & Fortmann, 1997). This will be administered at all study visits (except the Intake). Similar to withdrawal symptoms, craving will be assessed using a one-week time reference for the Baseline visit, all Pre-Quit Observation Days, and the Pre-Quit Testing Day. During the 24-h Abstinence Period and the 7-Day Quit Attempt, the reference point will be 24 hours.

Barkley Adult ADHD Rating Scale-IV (BAARS-IV): The BAARS-IV will be used to assess current attention-deficit and hyperactive symptoms. The 27-item scale is divided into symptoms pertaining to inattention (e.g. “don’t listen when spoken to directly”) and hyperactive-impulse symptoms (e.g., “shift around excessively or feel restless”). Participants will rate the intensity of their symptoms using the following scale: 1= never or rarely, 2 = sometimes, 3 = often, or 4 = very often. ADHD symptoms have been associated with smoking behavior and likelihood to relapse in prior studies (Lerman et al., 2001; Rukstalis, et al., 2005). The BAARS-IV with a 1-week frame of reference will be assessed at the Baseline Visit, all Pre-Quit Observation Days, and the Pre-Quit Testing Day. The BAARS-IV with a past 24-hour frame of reference will be assessed on Day 16 part 1, and the 7-Day Quit Attempt Observation Visits.

Mood: Positive and Negative Affect. The Positive and Negative Affect Schedule (PANAS) (Watson , Clark, & Tellegen, 1988), a 20-item Likert-format self-report measure, will be used to assess Positive Affect (PA; 10 items, e.g., enthusiastic, strong) and Negative Affect (NA; 10 items, e.g., distressed, upset), two dominant and generally orthogonal dimensions of affect. PA and NA (PANAS) will be assessed at all study visits (except the Intake). PA and NA will be assessed using a one-week time reference for the Baseline visit, all Pre-Quit Observation Days, and the Pre-Quit Testing Day. During the 24-h Abstinence Period and the 7-Day Quit Attempt, the reference point will be “today”.

Cigarette Ratings and Subjective Effects. The Cigarette Evaluation Scale (CES), developed to assess subjective effects of smoking (Westman, Levin, & Rose, 1992), is an 11-item Likert-format measure. Questions include items for nausea and dizziness, craving relief, and enjoyment of airway sensations. The Rose Sensory Questionnaire (SQ), a 9-item Likert-format measure, will be used to assess how much they liked the cigarette smoked and how high in nicotine the cigarettes appeared to be. The questionnaire also includes a diagram of the respiratory tract and asks participants to rate the strength of the cigarette puffs on their tongue, nose, back of mouth and throat,

windpipe, and chest. The CES and SQ will be administered at the Baseline, Pre-Quit Observation Day 7, Testing Day 14, and following the programmed lapse cigarette (Day 16 part 2).

Neurocognitive Measures. Neuropsychological tests will be administered in a quiet laboratory testing room on a Dell® desktop computer running on Windows XP® at the CIRNA. Unless otherwise noted, all tasks will be administered via E-Prime 2.0 (Psychology Software Tools, Inc.). The computerized battery is administered in a random order using clickable icons. Total administration time is ~ 1 hour. The tasks are:

- Visual/Spatial-N-Back: 3-back version (VSNB3). The n-back is one of the most commonly used paradigms in neuroimaging studies investigating the neurological underpinnings associated with maintenance and retrieval of information in working memory (Owen, McMillan, Laird, & Bullmore, 2005). The current study employs a visuo-spatial working memory task that is based on the visuo-spatial n-back paradigms used in prior research (Ehlis, Bahne, Jacob, Herrmann, & Fallgatter, 2008; Green et al., 2005; Owen, et al., 2005). During the n-back, participants are instructed to remember the location of a stimulus, a grey circle that is approximately 5 cm in diameter, as it appears randomly in 8 possible locations around the perimeter of a computer screen. The stimulus will appear for 200 ms, followed by an interstimulus interval (ISI) of 2800 ms. A cross hair will remain visible during the stimulus presentation to cue participants to look at the center of the screen so that all stimuli appearing around the perimeter of the screen can be seen clearly. The n-back task includes 4 conditions of varying difficulty levels: the 0-back, 1-back, 2-back, and 3-back. Participants respond only to targets (30% of stimuli) by pressing the SPACEBAR. They are instructed to do nothing on other trials.

Each of the task conditions (0-, 1-, 2- & 3-back) will be administered in a pseudorandomized counterbalanced order. Each difficulty level will consist of 1 block of 50 trials, preceded by a practice block of 20 trials. During the 0-back, participants are instructed to press the SPACEBAR if the stimulus appears in a predetermined location (designated as the upper left corner of the computer screen. The 0-back serves as a baseline condition of the n-back, during which participants are engaged in a task that does not require storage or manipulation of information in working memory, but is otherwise analogous to the other n-back conditions. During the 1-back, participants are instructed to press the SPACEBAR whenever the stimulus appears in the same location as the stimulus that immediately preceded it and to do nothing if the stimulus appears in any other location. During the 2- and 3-back conditions, participants are instructed to press the SPACEBAR whenever the stimulus appears in same location as the stimulus that preceded it by 2 or 3 trials, respectively. The primary dependent variables for this task are total number of correct responses and reaction time. Time: approximately 16 min.

- Word Recognition Memory (WRM). This task is a computerized version of WRM tasks used in prior work (Peterson & Peterson, 1959). Ten target words are presented on a computer monitor via E-Prime 2.0 software. After a 16-min delay period (e.g., while participants are completing the n-back task), 10 words are presented on the monitor: 6 targets and 4 distractor words. Participants are asked whether the word on the screen appeared earlier in the session. The target words and distractor words are equated for frequency, length, concreteness and low imageability. Time (learning and recall combined): 5 min.
- Penn Continuous Performance Test - Number/Letter Version (PCPT-nl). The PCPT-nl is a measure of visual attention and vigilance based on the Penn CPT (Kurtz et al., 2001). In this task, a series of red vertical and horizontal lines (7-segment displays) flash in a digital numeric frame (resembling a digital clock). The participant must press the spacebar whenever these lines form complete numbers or complete letters. The task is divided in two parts, each lasting three minutes: in the first part the participant is requested to respond to numbers and in the second part the response is to letters. The participant practices both sets of trials before the task begins. Time: approximately 10 min with practice.
- Stop Signal Task. The Stop Signal Task (SST) is a measure of response inhibition, or the ability to inhibit a prepotent response and has been used in previous work with smokers (Ashare & Hawk, 2012). In this task, participants are instructed to press labeled keyboard keys as quickly and as accurately as possible to indicate the direction the arrow faced (“z” for left; “/” for right). Following a 32-trial practice, stop signals (an 800-Hz, 100-ms, 70-dB tone) are presented on 25% of trials for a 32-trial practice and three task blocks of 64 trials

each. The initial stop delay in each block is 250 ms and adjusts by 50 ms increments depending on whether the participant is able to successfully inhibit a response (Logan, Schachar, & Tannock, 1997). The adjusting stop delay allows the determination of the delay at which inhibition occurs on approximately 50% of trials. All trials consist of a 500-ms warning stimulus followed by a 1,000-ms go signal (left- and right-facing arrows) and 1,000-ms blank screen intertrial interval.

Mean RT for each block is calculated based on valid responses (i.e., RT > 200 ms), and only blocks with 20–80% inhibition and at least 80% accuracy are included in analyses. Stop signal reaction time (SSRT) is the primary dependent variable and is calculated by subtracting the mean stop delay from the mean RT on go-trials. Time: approximately 10 min.

- **Stroop test.** The Stroop test is a measure of interference control, or the ability to screen out distracting stimuli (Stroop, 1935). In this task, participants view a series of words on a computer monitor and using the keyboard, are asked to press the key associated with the color of the word rather than the word itself. Congruent trials are trials in which the word and color match (e.g., the word “green” appears in the color green). Incongruent trials are trials in which, the words are printed in colors that do not match the colors of the words (e.g., the word “red” might appear in green). The primary outcomes will be the number of correct trials and reaction time (RT) for congruent and incongruent trials. An interference score is also calculated (e.g., RT incongruent – RT congruent), which measures the ability to suppress a habitual response in favor of an unusual one, taking into account overall speed of naming. Time: approximately 5 min.
- **XO Reaction Time Task.** The XO reaction time task is a simple computerized letter discrimination task to assess intra-individual response distributions. Participants are asked to discriminate between an X and an O that appear on the screen by pressing one of two labeled buttons on the keyboard as quickly as possible while maintaining accuracy. The task consists of 10 practice trials followed by 200 task trials. Each letter is presented on the screen for 3000 ms separated by a 1000 ms inter-stimulus interval. Only responses during the 3000 ms stimulus presentation are recorded. An audible click occurs the first time a button is pressed during each trial. Task duration: ~10 minutes.

## 2. Statistical Analysis

**Sample size.** For all power analyses, effect sizes were derived from our previous work on the effects of the smoking cessation drug, varenicline, on days of abstinence; significance levels set at 0.05.

Aim 1, the effects of galantamine on the number of days abstinent, will be tested as a single degree of freedom between-subject main effect. In our prior varenicline study, there was a difference of 2.31 days of abstinence between varenicline and PLA [2]. With 40 subjects per group we have >80% power to detect an effect size  $d=1.7$  (2-tailed,  $\alpha=0.05$ ), which is a difference of 2.3 days of abstinence between GAL and PLA (using an SD of 1.32 drawn from a binomial sample of 7 days).

For Aim 2a, the effects of GAL on working memory correct RT, we calculated change from baseline on n-back median correct RT from our prior study [2]. With 40 subjects per group we have 80% power to detect an effect size of  $d=0.9$  for the group x time interaction. After adjusting the SD to account for an observed within-subject correlation of 0.88, this corresponds to an effect size difference of 48ms between the abstinence effects on GAL compared to PLA. Thus, we have sufficient power for both of our primary aims.

**Statistical Analysis.** For the primary outcome, a standard between-subject (GAL vs PLA) ANOVA model using SPSS GLM in SPSS will test the hypothesis for medication effects on number of days abstinent (out of 7).

The secondary outcome, medication effects on the primary cognitive outcome, n-back correct reaction time, will be tested with a repeated measures ANOVA with drug (GAL vs PLA) as a between-subjects factor and time (session) and n-back load level (0-, 1-, 2-, and 3-back) as within-subjects factors. Similar repeated measures ANOVAs will be used to conduct exploratory analyses for additional tasks including: the PCPT ( $d'$ , correct RT), n-back # correct, WRM # correct, SST (stop signal reaction time), Stroop reaction time, and XO (deviation from the

mode. Covariates (e.g., nicotine dependence, gender, and age) will be included in all models. Since this is a pilot study intended to generate data for a future grant submission none of the outcome variables will be adjusted for multiple comparisons.

### 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
- Date of birth
- Medical and drug use history
- E-mail address
- Last 4 digits of Social Security Number
- Results from all questionnaires, tests, or procedures
- Urine for drug screening/pregnancy test
- Saliva sample for testing nicotine metabolites
- Genetic information from saliva sample

### 6. Tissue Specimens

Urine. A urine sample will be required at the Intake, Baseline visits, and Testing days (Day 14 and 16) 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 will complete a pregnancy test at the Intake visit. Only females of child-bearing potential will complete urine pregnancy tests at the Baseline visits and Testing days to exclude pregnancy and ensure compliance with contraception through the study.

Saliva. A 2ml saliva sample will be collected for DNA extraction using the Oragene™ kit at the Intake visit for genetic analyses. Participants will provide a 5mL saliva sample at the Intake visit as a baseline measure of cotinine levels. If a participant reports not smoking (not even a puff of a cigarette) during the 7-day quit attempt



s/he will be asked to provide a 5ml saliva sample at the final study visit (Quit Observation 4) to assess cotinine levels and biochemically verify 7-day point prevalence abstinence.

## 7. Genetic Testing

All genetic information (as with all study information) will be kept strictly confidential using the procedures outlined in section 4, above. Results will not be revealed to study participants.

## RISK/BENEFIT ASSESSMENT

### 1. Potential Study Risks

Potential Risks of the Medication: The following are the common side effects that have been reported with galantamine treatment: nausea, diarrhea, vomiting, weight decrease, anorexia, and skin rash. All of these side effects have been mild and transient in nature. The incidence of side effects is lower with the 8mg and 16mg doses (as compared to the 24mg dose) which are the doses that have been selected in the proposed project.

In addition to the side effects mentioned above, other rare side effects reported with galantamine ER treatment are: headache, body pain (various locations), syncope, bradycardia, insomnia, somnolence, anemia, rhinitis, urinary tract infection, hematuria, constipation, agitation, confusion, anxiety, hallucination, injury, back pain, peripheral edema, asthenia, chest pain, urinary incontinence, upper respiratory tract infection, bronchitis, coughing, hypertension, fall, and purpura. All of these side effects shall be queried using a side effects checklist at the Baseline visit (to obtain a baseline estimate of any side effects prior to starting medication) as well as all subsequent visits (up to 9 times throughout the study).

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 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 Health Care Provider/Study Physician immediately for appropriate intervention. The Study Physician's emergency contact numbers shall be on the medication blister pack, the study consent form, as well on an emergency card all participants will be provided with once they enroll into the study.

Pregnancy: In a study in which pregnant rats were dosed from the beginning of organogenesis through day 21 post-partum pup weights were decreased at 8 and 16 mg/kg/day, but no adverse effects on other postnatal developmental parameters were seen. The doses causing the above effects in rats produced slight maternal toxicity. No major malformations were caused in rats given up to 16 mg/kg/day. No drug related teratogenic effects were observed in rabbits given up to 40 mg/kg/day (32 times the MRHD on a mg/m<sup>2</sup> basis) during the period of organogenesis. There are no adequate and well-controlled studies of galantamine hydrobromide ER in pregnant women. Thus, galantamine hydrobromide must not be used during pregnancy. All female participants of child bearing potential must have a negative pregnancy test at the Intake session, Baseline session, and Testing days; and must agree in writing to use an approved method of contraception through the study.

Genetic Testing: All genetic information (as with all study information) will be kept strictly confidential using the procedures outlined in section 4, above. Results will not be revealed to study participants.

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.

### 2. Potential Study Benefits

All participants who enroll in this study will receive brief behavioral counseling prior to the 7-day quit period to aid them in their effort to quit smoking. And, lastly, this study may eventually help better understand whether modulating the endogenous cholinergic tone affects smoking behavior and whether ACIs can be potential smoking cessation medications.



### 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, Project Manager, 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), Nurse Practitioner, 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. will review all completed MINIs on an ongoing basis and train and supervise smoking cessation counselors.

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 80 subjects complete all study requirements. On average, 3-4 subjects will be enrolled per month. During the course of the study, safety and data quality monitoring will be performed on an ongoing basis in accordance with the University of Pennsylvania Sponsor-Investigator Standard Operating Procedure PM 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.

### **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 galantamine-ER treatment (e.g., nausea, vomiting). 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 galantamine 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, Research Nurse/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 galantamine and is qualified to manage possible side effects.

Based on published reports using the 8mg and 16mg galantamine-ER doses we expect some side effects with galantamine-ER treatment; however 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 (Dr. Leone) 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. Dr. Leone will determine the relationship of toxicity of the study medication (galantamine-ER) as not related, possibly related, probably related, or definitely related using standard criteria.

All adverse events occurring during the 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) and the CTSRMC DSMC require 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 to the DSMC**



• 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 DSMC within 30 days. SAEs or SADR for Penn subjects regardless of attribution or expectedness will be submitted to the DSMC within 10 days. Reports will continue to be sent to the DSMC 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.

• IND Safety Updates/Alerts

IND Safety Updates/Alerts (sent by sponsors), that are specifically for the protocol open in the ACC, with a grade 3 or higher, regardless of attribution or expectedness will be submitted to the DSMC within 30 days. Events for studies using a novel agent, on any protocol in the Cancer Center, not specifically the protocol open in the ACC, shall be sent within 30 days. All other IND Safety Updates/Alerts shall be sent within 60 days of receipt. Once the study closes to accrual at Penn, reports shall be sent to the DSMC for 30 days from the date the last Penn subject was treated. Events for studies using a novel agent or agents manufactured on campus will be sent until the protocol terminates.

Reporting Events

All events will be entered into the ACC Clinical Trials Management System (CTMS) AE/SAE form.

**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 on 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 and DSMC 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 DSMC.



- 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 DSMC.
- **Deviation:** A one time, unintentional action or process that departs from the IRB and DSMC 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 DSMC within 5 business days and 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

**6. Risk/Benefit Assessment**

There is minimal risk for serious adverse events. The treatments and procedures used in this study have been shown to be relatively safe. Numerous clinical trials have demonstrated the safety and efficacy of acetylcholinesterase inhibitors, including galantamine in Alzheimer's disease patients, alcohol-dependent patients, and patients with schizophrenia. Research staff will monitor subjects closely during their participation. Data from this project will serve as preliminary data to formally test and develop an ACI as a potential smoking cessation medication for treatment-seeking smokers. Thus, the importance of this research outweighs the risks to subjects, which are minor.

**SUBJECT COMPENSATION**

Participants will receive compensation at each session they attend and can receive up to \$445 for completing all study requirements (including travel reimbursement). Compensation distribution is shown in the table below.

<b>Study Visit</b>	<b>Visit Compensation</b>	<b>Travel</b>	<b>Quit Incentive</b>	<b>Total</b>
Intake*	\$20	\$10		\$30
Baseline Session	\$30	\$10		\$40
Pre-Quit/Run-up period				
Observation Day 7	\$20	\$10		\$30
Testing Day 14	\$40	\$10		\$50
24-h Abstinence Period				
Day 16 Part 1 and 2	\$60	\$10		\$70
7-day Quit Period				
Observation Day 17	\$20	\$10	\$15 <sup>+</sup>	\$45
Observation Day 19	\$20	\$10	\$15 <sup>+</sup> (Day 18,19)	\$60
Observation Day 21	\$20	\$10	\$15 <sup>+</sup> (Day 20, 21)	\$60
Observation Day 23	\$20	\$10	\$15 <sup>+</sup> (Day 22, 23)	\$60
<b>TOTAL</b>	\$250	\$90	\$105	
<b>Grand Total:</b>				<b>\$445<sup>a</sup></b>
<p>* Participants who test positive for study prohibited drugs will not be eligible to receive visit or travel compensation.</p> <p>+ Participants will receive \$15/day (in cash) for each day of self-reported abstinence that is biochemically-confirmed.</p> <p><sup>a</sup> Participants following the Extended Dosing schedule will be able to earn up to \$475 for attending one extra Observation Day visit (\$20 visit compensation + \$10 travel).</p>				

## **INFORMED CONSENT**

### **1. Consent Process**

At the Intake (Day -5), 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
- Caryn Lerman, Ph.D., Faculty Sponsor
- Andrew Strasser, Ph.D., Co-Investigator
- Paul Wileyto, Ph.D., Statistician
- Frank Leone, MD, Study Physician
- Susan Ware, B.S. Database Manager
- Anita Hole, Ph.D. MINI review
- Leah Bernardo, B.A., Study Support Staff
- Dominique Spence, Research 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
- Jonnie Handschin, Study Support Staff

### **2. Staff Training**

Drs. Lerman and Ashare will oversee the development of protocols for laboratory related tasks (e.g., cognitive 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. Dr. Lerman will also oversee study progress as part of regular study meetings.

### **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.

The Translational Core Laboratory (TCL) will process and store blood samples for nicotine metabolite analysis.

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