PARTNERS HUMAN RESEARCH COMMITTEE
PROTOCOL SUMMARY

Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.

PRINCIPAL/OVERALL INVESTIGATOR
Kevin P. Hill, M.D., M.H.S.

PROTOCOL TITLE
D-cycloserine (DCS) Pretreatment + Cognitive Behavioral Therapy and Nicotine Replacement Therapy for Smoking Cessation

FUNDING
American Lung Association Clinical Patient Care Research Grant.

VERSION DATE
9/10/15

SPECIFIC AIMS

Concisely state the objectives of the study and the hypothesis being tested.

A. Compare the relative efficacy of ten weeks of once weekly 250 mg DCS vs. placebo (both in conjunction with CBT and NRT) on reducing cigarette smoking in treatment-seeking nicotine-dependent outpatients.

B. Compare the relative efficacy of ten weeks of once weekly 250 mg DCS vs. placebo on the process of extinction and the memory encoding processes.

BACKGROUND AND SIGNIFICANCE

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

Smoking remains an enormous public health problem. Despite advances in available medications and behavioral interventions, it remains difficult to quit. At the completion of this exploratory, proof-of-concept study, we hope to have improved our understanding of the relationship of DCS to smoking cessation as well as have gained a better understanding of the relationship of DCS, extinction, and the memory encoding process. The addition of DCS to a CBT and NRT program may improve the efficacy of CBT and NRT for smoking cessation and may also provide additional evidence supporting a similar combination treatment for other substance use disorders. This study may be translatable to other disorders because it targets a learning process as opposed to a specific receptor. If tests of neuropsychological performance provide information about how DCS may affect smoking cessation treatment, further work could help to predict characteristics that would make certain smokers more likely to respond to a particular treatment. This would help move the field of substance abuse treatment toward greater treatment individuation. Thus, with this proposal, we hope to take steps

toward developing an integrative treatment for nicotine dependence, an important public health problem that affects millions of Americans.

RESEARCH DESIGN AND METHODS

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site restrictions, for example, "Enrollment at Partners will be limited to adults although the sponsor's protocol is open to both children and adults."

a. Overview

We will conduct a Stage 1 pilot feasibility study at McLean Hospital to develop a medication to treat nicotine dependence. (FIGURE 1) In a randomized, double-blind, placebo-controlled trial, 40 nicotine-dependent participants ages 18-65 will receive cognitive behavioral therapy (CBT) and nicotine replacement therapy (NRT) over a 10-week period, with half receiving D-cycloserine (DCS) pretreatment and half receiving placebo. Participants will receive either 250 mg DCS or placebo prior to weekly CBT sessions in addition to NRT over a 10-week treatment period. We also aim to determine the effects of DCS on performance on neuropsychological tests. A 10-week treatment period will be followed by follow-up assessments including neuropsychological tests at 1 and 3 months post-treatment. Primary outcomes will include smoking as measured by carbon monoxide levels and self-report measurements.

b. Source of subjects and recruitment methods

Forty participants ages 18-65 with DSM-IV diagnosis of nicotine dependence will be recruited from McLean Hospital outpatient programs and from the Boston area via newspaper advertisements, flyers, Craigslist online ads, clinician referrals, and word-of-mouth.

Briefly describe study procedures. Include any local site restrictions, for example, "Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study." Describe study endpoints.

a. Recruitment and Intake

Interested individuals will respond to advertisements by leaving a message (first name and call back number only) in the BPRL recruiting voice mailbox. Research assistants will call them back with 24 to 48 hours and conduct an initial phone screen that takes about 15 minutes. It will cover basic inclusion and exclusion criteria, as well as a brief description of the study to determine if the person is interested in participating. If the volunteer is appropriate and agrees to participate, they will be invited to come to the BPRL for a physical and psychiatric evaluation (SCID). Treatment alternatives will also be offered to the prospective participant if they decide not to participate or are not eligible for participation.

The 75-minute initial assessment interview will be done by a research assistant and

study physician. Once participants have given informed consent, they will undergo a comprehensive evaluation that includes medical, psychiatric, and drug use histories as well as physical, psychiatric, and laboratory examinations and the following screening procedures: a) Detailed history of cigarette use; b) Review of DSM-IV criteria for nicotine dependence; c) Medical history and concomitant medication record; d) Physical examination; e) Laboratory screen that includes CBC, electrolytes, and BUN/creatinine; f) Expired CO level; g) Urinalysis; h) Urine pregnancy test for women; and i) 12 -lead electrocardiograph (ECG). The study physician will make the final decision to enroll.

b. Informed consent

Eligible participants will complete standard consent documentation. Prior to the participant being asked any question about his/her health, the participant will be given a consent form to read. The research assistant will go over it in detail with the participant and answer any questions the participant may have concerning the study. A study physician will then also review the study procedures and ask the subject to provide his/her informed consent. If enrolled in the study, consent to communicate with their other clinicians will be obtained as well. Clinicians will be notified of their patients' enrollment in the study, thus allowing them to carefully monitor for changes in mood while in they are undergoing treatment to stop use of nicotine. Treatment alternatives will be offered to the prospective participants if they decide not to participate or are not eligible for participation.

c. Randomization

Study participants will be randomized to receive either DCS or placebo and stratified according to baseline expired CO level (10-20 ppm and >20 ppm).

a.1. Availability and Flow of Subjects into Treatment

After approximately 240 telephone screens, we plan to conduct in-person screens of 40 individuals in the course of 18 months to achieve our desired sample size. Based our prior smoking-related studies, we estimate that there will be approximately 16 potentially eligible participants per month from treatment programs at McLean Hospital and the other Boston area recruitment methods and an adequate flow of participants to meet our target of 2.5 participants per month.

a.2. Study Visits and Participant Payments. Each weekly visit over 10 weeks will include a 50-minute CBT session and dispensing of pills. Research assessments will take place at 4 and 10 weeks of treatment and 4 and 12 weeks post-treatment. See Table D.1, Schedule of Measures. Participants will earn $50 for the initial screen, $20 for each of the 10 Actiwatch/Diary visits, a $10 gift card for the completion of additional neuropsychological assessments at week 3, $50 for each of the 4 Follow-Up Interviews, and a bonus $50 for diary completion, for a total of $510. Medication and therapy will be provided at no cost.

a.3. Clinical Emergencies. If a participant is intoxicated, the participant will be evaluated medically, sent home in a taxi when safe, and the appointment re-scheduled. If a participant experiences a problem that requires clinical

intervention during the course of the study (e.g., mania, suicidal ideation, or dangerous intoxication), we will evaluate the situation medically, make an appropriate recommendation, and help the participant to implement this plan. This could involve hospitalization at McLean, referral to the hospital's outpatient program, or other medical or psychiatric treatment, as clinically appropriate.

b. Drugs to be used
b.1. D-cycloserine. D-cycloserine (DCS)(Seromycin®, The Chao Center, West Lafayette, IN) is an FDA-approved broad spectrum antibiotic for the treatment of tuberculosis.
Participants will be randomized to receive either placebo or DCS 250 mg, given 1 hour prior to weekly CBT sessions. The McLean Research Pharmacy will randomize the participants and dispense medication or placebo weekly to the study physician, who

will deliver a prescription to the pharmacy days in advance of the CBT session. The medication will be purchased from McKesson by the PI. The dose is based upon prior clinical trials of patients with psychiatric disorders (Norberg et al. 2008). Norberg et al. (2008) showed that timing of the dose significantly predicted effect size; their meta-analysis found that the greatest enhancement of animal extinction or human exposure therapy was seen when DCS was given immediately prior to or after extinction/exposure.
Participants will be assessed for side effects prior to each medication administration. If side effects preclude a participant from continuing study medication, the medication will be discontinued, but the participant will continue to be followed for follow-up assessment visits. While our group recognizes the importance of medication adherence in substance use disorder patients, the once-weekly dosing of DCS mitigates many adherence issues.

b.2. Nicotine Replacement Therapy. Transdermal nicotine patches delivering 21-, 14-, and 7-mg/24 hours will be purchased from CVS by the PI. Nicotine patches will be distributed to volunteers at the initial assessment session and at the 6- and 8-week follow-up sessions. Participants smoking 15 of more cigarettes per day will start with a 21-mg patch and those smoking 10-15 cigarettes per day or who cannot tolerate a 21-mg patch will start with a 14-mg patch. Participants starting with a 21-mg nicotine patch will use it daily for 6 weeks, followed by a taper to a 14-mg nicotine patch daily for 2 weeks and, finally, a 7-mg nicotine patch daily for 2 weeks. The others will start with a 14-mg patch used daily for 8 weeks followed by a 7-mg patch used daily for 2 weeks. We will discuss possible side effects of nicotine with volunteers and ask them to report these symptoms or any others they experience. Adverse event forms will document any side effects experienced while using the patch.

c. Devices to be used
N/A.

d. Research Measures: Data to be collected
d.1. Diagnostic Assessment of Smoking. To make the diagnosis of nicotine dependence, the Structured Clinical Interview for DSM-IV (SCID) (First et al. 1996) will be used.

d.2. Self-Report of Smoking. Participants will receive a packet of 1 page, self-addressed, prepaid postage Daily Diary pages. The diary consists of questions about smoking and other drug use as well as eating and sleeping habits. We have had excellent compliance with these diaries in the past. During the weekly visits, we plan to collect cigarette use data using the Timeline Follow Back (TLFB) (Sobell and Sobell, 1992) protocol.

d.3. Alveolar carbon monoxide (CO). End-expiratory CO will be measured after a 10-second breath-hold using a P.K. Morgan CO analyzer (Chatham, Kent, UK) at baseline, each CBT session, and each follow-up visit. Abstinence from cigarettes will be verified by an expired air CO concentration ≤10 ppm.

d.4. Other Assessments. We developed the self-administered Drug and Alcohol Use Questionnaire (Weiss et al. 1988), a baseline measure that addresses the context of lifetime and recent drug and alcohol use, as well as sociodemographic data. Function in multiple spheres of the participants' lives will be obtained at baseline and monthly using the LIFE functional assessment (Keller et al. 1987). HIV risk behaviors will be assessed at baseline and weeks 10, 14, and 22 with the Risk Assessment Battery (Metzger 1992). To assess treatment services outside the study that patients use, we will administer the Treatment Services Review (TSR) (McLellan et al. 1992) at baseline and monthly. The Client Satisfaction Questionnaire (CSQ-8) is an 8-item self-report scale will assess satisfaction with treatment. The Quick Inventory of Depressive Symptomatology (QIDS-SR) is a short self-report questionnaire for depressive symptoms used successfully in the STAR*D project. At baseline and week 3, several standard self-report questionnaires will be used to assess cigarette craving: Tiffany QUS Brief form, nicotine withdrawal: Wisconsin Smoking Withdrawal Scale, and affect: Positive and negative affect scales (PANAS). Menstrual cycle phase information also will be collected in women.

d.5. Neuropsychological Assessment. (see Appendix for description of assessments) We will use a brief battery of standard, well-known neuropsychological tests designed primarily to evaluate general intellectual capacity and executive/attentional functions. All test scoring will be completed blind to participants' clinical ratings. The WASI 4-subtest version (Vocabulary, Similarities, Block Design and Matrix Reasoning) is a reliable, brief assessment used to obtain IQ estimates (Weschler 1981). The Rey Auditory Verbal Learning Test (RAVLT) assesses immediate memory span, new learning, susceptibility to interference, and recognition memory (Lezak et al. 2004). The Stroop Color Word Task challenges the ability to inhibit inappropriate responses and resist interference (Bush et al. 2003). The Multi-Source Interference Task (MSIT) has been shown to reliably and robustly activate cingulo-frontal-parietal circuitry associated with cognitive/attentional pathways (Bush and Shin, 2006). The Go/No Go Task is a task of inhibitory control (Menon et al. 2001).

Table D.1 Schedule of Measures

Baseline only
Physical examination
Structured Clinical Interview for DSM-IV
Menstrual Cycle Info. (Women only)
Drug and Alcohol Use Questionnaire
Wechsler Abbreviated Scale of Intelligence
Tiffany QUS Brief form
Wisconsin Smoking Withdrawal Scale
Positive and Negative Affect Scales (PANAS)

Baseline and week 3
Tiffany QUS Brief form
Wisconsin Smoking Withdrawal Scale
Positive and Negative Affect Scales (PANAS)
Menstrual Cycle Info. (Women Only)

Baseline, weeks 10, 14, and 22
ECG
Laboratory tests[a]
Rey Auditory Verbal Learning Test
Stroop Color Word Test
Multi-Source Interference Task
Timeline Followback Functional Assessment (from the LIFE)
Risk Assessment Battery
Quick Inventory of Depressive Symptomatology
Fagerstrom Test for Nicotine Dependence
Client Satisfaction Questionnaire-8

[a]Tests include urinalysis, electrolytes, complete blood count, & blood chemistries

Baseline and weekly
Daily Diary
Adverse Events & Side Effects
Alveolar Carbon Monoxide (CO)

Baseline and monthly
LIFE
Urine pregnancy test
Treatment Services Review

8.2. Data Analysis.

a. For the main outcome measures acquired during treatment and post-treatment follow-up, the analytical approach will address the nature of the outcome (e.g., categorical vs. quantitative outcomes), as well as accommodate the within-individual correlation due to repeated assessments. In addition, the results from the given approach will be assessed for sensitivity to drop outs or missing data. The primary data analysis will be an intent-to-treat analysis, which includes all randomized participants. Of note, every attempt will be made to continue assessing participants even if they drop out of treatment. In addition, we will replicate all analyses with the completers only. The primary and secondary outcome variables are intended to explore various aspects of response to therapy and

to help define a clinically meaningful response. The primary outcome measures, 7-day point prevalence of abstinence, and expired CO, have been chosen for their ability to indicate daily use of cigarettes by relying on self-report of use.
Specifically, for assessing the effect of DCS on smoking patterns, we propose to use the generalized estimating equations (GEE) approach to longitudinal analysis, appropriately accounting for the positive correlation among the post-baseline repeated binary measures of 7-day abstinence within the same individual. The GEE approach incorporates all of the repeated assessments on an individual and provides a more powerful statistical analysis than does a cross-sectional analysis that focuses only on a single summary index. Specifically, we will fit logistic regression models for the repeated post-randomization binary measures of 7-day abstinence of the following form:logit(p) = β0 + β1*trt, where trt (treatment)=1 if randomized to DCS and trt=0 otherwise, and p denotes the probability of 7-day abstinence.

The logistic regression model will be fit using the GEE approach (as implemented in PROC GENMOD in SAS) to account for correlation among repeated assessments of the same individual. The logistic regression analyses will also adjust for the stratification factor used in the randomization of patients. The GEE analysis accounts for this within-subject correlation, and the resulting estimated β1, when exponentiated, provides an estimate of the treatment effect expressed as an odds ratio, comparing the DCS group to the placebo group. The effect of DCS on 7 -day abstinence will be assessed by testing Ho: β1=0.
A relatively similar analytic approach will be used to assess the effect of DCS on changes in expired CO assessments. A linear mixed effects model will be used to assess changes in CO during treatment and at post-treatment follow-up. The linear mixed effects model will include the effects of treatment group, time and the baseline measure of CO; the inclusion of random effects accounts for the correlation among the 12 post-baseline CO measurements (1-per week during 10 weeks of treatment, plus week 14 and 22). We will adjust for the dose of NRT by including dose as an additional covariate in the linear mixed effects model analysis of the treatment comparison (DCS vs. placebo). The linear mixed effects model includes random intercepts and random slopes for time to appropriately account for correlation among repeated measures of CO and heterogeneity of variance over time; the model will be fit using PROC MIXED in SAS.

Analyses of secondary outcomes will focus on assessing the effect of DCS on neuropsychological assessments. For example, linear mixed effects models will also be used to analyze quantitative/continuous neuropsychological outcomes (e.g., MSIT response accuracy and times), with appropriate transformation (e.g., log transformation) of the outcome as necessary. To examine the effect of DCS on changes in neuropsychological performance during treatment, the linear mixed effects model will include the effects of treatment condition and the baseline measure of the neuropsychological outcome. Additional analyses of secondary outcomes will focus on the number of days of cigarette smoking during treatment and post-treatment follow-up. Frequency of days of cigarette use will be analyzed via a log-linear (or Poisson) regression model, controlling for pre-treatment frequency of days of cigarette use. Although log-linear regression methods are considered appropriate for the analysis of count or frequency data, in many biomedical applications, count data have variability that far exceeds that predicted by the Poisson distribution; we expect that days of cigarette use will not be an exception. This phenomenon, known as overdispersion, will be accounted for in the planned regression analysis through the inclusion of a

dispersion parameter. The log-linear regression analyses will be fit using PROC GENMOD in SAS.

b. Missing Data and Dropout. With repeated assessments, missing data are inevitable. Incomplete data pose 2 concerns for inference: bias and efficiency. We will use statistical methods (GEE and linear mixed effects models) that incorporate partially observed data on participants who drop out. We will provide detailed descriptions of the patterns of missing data and assess the sensitivity of results to different assumptions about the mechanism by which data are missing. For example, pattern-mixture models can be used to assess the sensitivity of results to informative dropout or missing data. Dr. Garrett Fitzmaurice, our biostatistician consultant, is an expert in handling missing data in longitudinal studies (Fitzmaurice et al. 2004).

c. Sample Size and Power. We plan to randomize 20 participants per group for a total of 40 subjects. This sample size will provide a reasonable estimate regarding the effect size for a subsequent larger trial. With a total of 40 participants, and assuming a Type-I error level (alpha-level) of 0.05 (two-sided), a 7-day abstinence prevalence of 25% in the placebo group, the study would have approximately 80% power to detect medium effect sizes, corresponding to risk ratios of 2.3-2.6 (as the within-participant correlations ranges from 0.3-0.7). For example, with moderate within-participant correlation (ρ=0.5), the study would have 80% power to detect a risk ratio of 2.48.

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

The standard of care for nicotine dependence is psychotherapy and/or medication; our treatment attempts to strengthen the best available treatment by enhancing the behavioral intervention.

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

Care will be taken to minimize risk. In addition to carefully screening prior to enrollment, we have weekly visits during which we will carefully monitor response to medication or placebo with respect to side effects and changes in mood.

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

Safety Monitoring.
D-cycloserine has been shown to have a favorable safety profile in studies; it has been well-tolerated in several clinical trials and no adverse events have been reported (Santa Ana et al. 2009; Storch et al. 2010; Evans and Drobes, 2008; Goff et al. 2008). Nonetheless, we will monitor safety through standardized methods. Presence and severity of side effects will be obtained through a standard Adverse Events Checklist as well as the "Frequency and Intensity of Side Effects Rating/Global Report of Side

Effects Burden" (Weiss, 2004), a 2-minute questionnaire that assesses the frequency, intensity, and level of burden of side effects. We will have a low threshold for obtaining additional medical workup during the study if the participant reports medical symptoms. Based on the literature on the effects of DCS, we anticipate few adverse events (Norberg et al. 2008). However, if a participant has a clinically significant laboratory or other medical abnormality that cannot be attributed to another cause, the participant's medication will be discontinued and the participant will be followed for follow-up assessment visits only. If a participant is intoxicated, he/she will be evaluated medically, sent home in a taxi when safe, and the appointment rescheduled. If a participant experiences a problem that requires clinical intervention during the course of the study (e.g., mania, suicidal ideation, or dangerous intoxication), we will evaluate the situation medically, make an appropriate recommendation, and help the participant to implement this plan. This could involve hospitalization at McLean, referral to the hospital's outpatient program, or other medical or psychiatric treatment, as clinically appropriate.

FORESEEABLE RISKS AND DISCOMFORTS

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/performed solely for research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

a. Drug side effects and toxicities

D-cycloserine has been shown to have a favorable safety profile in studies; it has been well-tolerated in several clinical trials and no adverse events have been reported in these studies (Santa Ana et al. 2009; Storch et al. 2010; Evans and Drobes, 2008; Goff et al. 2008). Most adverse reactions occurring during therapy with D-cycloserine involve the nervous system or are manifestations of drug hypersensitivity (Seromycin package insert). Nervous system side effects appear to be related to higher doses (500 mg daily or above) and include drowsiness, headache, tremor, psychoses, and hyperirritability. Sudden development of congestive heart failure has been reported in patients receiving 1 to 1.5 g of D-cycloserine daily. Nicotine can cause headache and skin irritation.

b. Psychosocial risks

There is a low likelihood that participants previously screened for significant psychiatric disorders will be triggered by content of therapy sessions. As mood may be affected, we will monitor mood and suicidal ideation weekly with the Columbia Suicide Severity Scale.

EXPECTED BENEFITS

Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, for example, "It is hoped that the treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects." Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, e.g., through increased knowledge of human physiology or behavior, improved safety, or technological advances.

a. Potential benefits to participating individuals

Participants may be able to stop or reduce their smoking, which would have enormous health and financial benefit to them.

b. Potential benefit to society

Smoking remains an enormous public health problem. Despite advances in available medications and behavioral interventions, it remains difficult to quit. At the completion of this exploratory, proof-of-concept study, we hope to have improved our understanding of the relationship of DCS to smoking cessation as well as have gained a better understanding of the relationship of DCS, extinction, and the memory encoding process. The addition of DCS to a CBT and NRT program may improve the efficacy of CBT and NRT for smoking cessation and may also provide additional evidence supporting a similar combination treatment for other substance use disorders. This study may be translatable to other disorders because it targets a learning process as opposed to a specific receptor. If tests of neuropsychological performance provide information about how DCS may affect smoking cessation treatment, further work could help to predict characteristics that would make certain smokers more likely to respond to a particular treatment. This would help move the field of substance abuse treatment toward greater treatment individuation. Thus, with this proposal, we hope to take steps toward developing an integrative treatment for nicotine dependence, an important public health problem that affects millions of Americans.

EQUITABLE SELECTION OF SUBJECTS

The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, for example, men, women, pregnant women, children, and minorities, should be categorically excluded from the research without a good scientific or ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

Men, women, and minorities will all be recruited. Pregnant women and children will be excluded in part due to the lack of data on the safety of D-cycloserine in these groups.

When people who do not speak English are excluded from participation in the research, provide the scientific rationale for doing so. Individuals who do not speak English should not be denied participation in research simply because it is inconvenient to translate the consent form in different languages and to have an interpreter present.

Proficiency in English is necessary for a long-term treatment study that includes 10 CBT sessions and ensures that the participants can properly convey any subtle side effects that relate to their safe participation in this study.

For guidance, refer to the following Partners policy:
Obtaining and Documenting Informed Consent of Subjects who do not Speak English
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Non-English_Speaking_Subjects.1.10.pdf

RECRUITMENT PROCEDURES

Explain in detail the specific methodology that will be used to recruit subjects. Specifically address how, when, where and by whom subjects will be identified and approached about participation. Include any specific recruitment methods used to enhance recruitment of women and minorities.

a. Inclusion Criteria. 1) Age range 18-65 years; 2) DSM-IV diagnosis of nicotine dependence, based on the Structured Clinical Interview for DSM-IV (SCID) (First et al. 1996); 3) express a desire to quit cigarette smoking within the next 30 days; 4) smokes greater than or equal to 10 cigarettes per day and less than or equal to 20 cigarettes per day; 5) an expired carbon monoxide (CO) determination greater than or equal to 10 ppm over ambient values; 6) for women of childbearing age, a negative pregnancy test at screening with agreement to use adequate contraception to prevent pregnancy and multiple subsequent pregnancy tests; 7) consent for us to communicate with their prescribing clinician; 8) furnish the names of 2 locators, who would assist study staff in locating them during the study period; 9) live close enough to McLean Hospital to attend study visits; 10) plan to remain in the Boston area for the next 4 months; and 11) are willing and able to sign informed consent.

Exclusion Criteria. 1) Current diagnosis of other drug or alcohol dependence (other than nicotine and opioid dependent participants on agonist or antagonist pharmacotherapy); 2) significant cardiac disease; 3) current serious psychiatric illness or history of psychosis, schizophrenia, bipolar type I disorder (taking psychiatric medications, aside from wellbutrin, is not an exclusionary criterion); 4) have a current medical condition (including significant laboratory abnormalities, such as liver function tests >5 times the upper limit of normal range) that could prevent regular study attendance; 5) have mental retardation or organic mental disorder; 6) exhibit acutel y dangerous or suicidal behavior; 7) are pregnant, nursing, or, if a woman of childbearing potential, not using a form of birth control judged by the Principal Investigator to be effective; 8) current NRT or other smoking cessation treatment; 9) current CBT for smoking cessation; 10) current smokeless tobacco use; 11) inability to read or write in English; 12) has epilepsy.

b. Source of subjects and recruitment methods

Forty participants ages 18-65 with DSM-IV diagnosis of nicotine dependence will be recruited from McLean Hospital outpatient programs and from the Boston area via newspaper advertisements, flyers, Craigslist online ads, clinician referrals, and word-of-mouth.

Provide details of remuneration, when applicable. Even when subjects may derive medical benefit from participation, it is often the case that extra hospital visits, meals at the hospital, parking fees or other inconveniences will result in additional out-of-pocket expenses related to study participation. Investigators may wish to consider providing reimbursement for such expenses when funding is available

Subject Payments. Participants will earn $50 for the initial screen, $20 for each of the 10 Actiwatch/Diary visits, a $10 gift card for the completion of the additional neuropsychological assessments at week 3, $50 for each of the 4 Follow-Up Interviews,

and a bonus $50 for diary completion, for a total of $510. Medication and therapy will be provided at no cost.

For guidance, refer to the following Partners policies:

Recruitment of Research Subjects
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Recruitment_Of_Research_Subjects.pdf

Guidelines for Advertisements for Recruiting Subjects
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Guidelines_For_Advertisements.1.11.pdf

Remuneration for Research Subjects
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Remuneration_for_Research_Subjects.pdf

CONSENT PROCEDURES

Explain in detail how, when, where, and by whom consent is obtained, and the timing of consent (i.e., how long subjects will be given to consider participation). For most studies involving more than minimal risk and all studies involving investigational drugs/devices, a licensed physician investigator must obtain informed consent. When subjects are to be enrolled from among the investigators' own patients, describe how the potential for coercion will be avoided.

Eligible participants will complete standard consent documentation. Prior to the participant being asked any question about his/her health, the participant will be given a consent form to read. The research assistant will go over it in detail with the participant. After answering any questions the participant may have concerning the study, he/she will be asked to provide their informed consent. If enrolled in the study, consent to communicate with their other clinicians will be obtained as well. Clinicians will be notified of their patients' enrollment in the study, thus allowing them to carefully monitor for changes in mood while in they are undergoing treatment to stop use of nicotine. Treatment alternatives will be offered to the prospective participants if they decide not to participate or are not eligible for participation.

NOTE: When subjects are unable to give consent due to age (minors) or impaired decision-making capacity, complete the forms for Research Involving Children as Subjects of Research and/or Research Involving Individuals with Impaired Decision-making Capacity, available on the New Submissions page on the PHRC website:
https://partnershealthcare.sharepoint.com/sites/phrmApply/aieipa/irb

For guidance, refer to the following Partners policy:
Informed Consent of Research Subjects:
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Informed_Consent_of_Research_Subjects.pdf

DATA AND SAFETY MONITORING

Describe the plan for monitoring the data to ensure the safety of subjects. The plan should include a brief description of (1) the safety and/or efficacy data that will be reviewed; (2) the planned frequency of review; and (3) who will be responsible for this review and for determining whether the research should be altered or stopped. Include a brief description of any stopping rules for the study, when appropriate. Depending upon the risk, size and complexity of the study, the investigator, an expert group, an independent Data and Safety Monitoring Board (DSMB) or others might be assigned primary responsibility for this monitoring activity.

NOTE: Regardless of data and safety monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for protecting the rights, safety, and welfare of subjects under his/her care.

Safety Monitoring.

D-cycloserine has been shown to have a favorable safety profile in studies; it has been well-tolerated in several clinical trials and no adverse events have been reported in these studies (Santa Ana et al. 2009; Storch et al. 2010; Evans and Drobes, 2008; Goff et al. 2008). Nonetheless, we will monitor safety through standardized methods. Nicotine can cause headache and skin irritation. Presence and severity of side effects will be obtained through a standard Adverse Events Checklist as well as the "Frequency and Intensity of Side Effects Rating/Global Report of Side Effects Burden" (Weiss,2004), a 2-minute questionnaire that assesses the frequency, intensity, and level of burden of side effects. We will have a low threshold for obtaining additional medical workup during the study if the participant reports medical symptoms. Based on the literature on the effects of DCS, we anticipate few adverse events (Norberg et al, 2008). However, if a participant has a clinically significant laboratory or other medical abnormality that cannot be attributed to another cause, the participant's medication will be discontinued and the participant will be followed for follow-up assessment visits only. If a participant is intoxicated, he/she will be evaluated medically, sent home in a taxi when safe, and the appointment rescheduled. If a participant experiences a problem that requires clinical intervention during the course of the study (e.g., mania, suicidal ideation, or dangerous intoxication), we will evaluate the situation medically, make an appropriate recommendation, and help the participant to implement this plan. This could involve hospitalization at McLean, referral to the hospital's outpatient program, or other medical or psychiatric treatment, as clinically appropriate.

Describe the plan to be followed by the Principal Investigator/study staff for review of adverse events experienced by subjects under his/her care, and when applicable, for review of sponsor safety reports and DSMB reports. Describe the plan for reporting adverse events to the sponsor and the Partners' IRB and, when applicable, for submitting sponsor safety reports and DSMB reports to the Partners' IRBs. When the investigator is also the sponsor of the IND/IDE, include the plan for reporting of adverse events to the FDA and, when applicable, to investigators at other sites.

NOTE: In addition to the adverse event reporting requirements of the sponsor, the principal investigator must follow the Partners Human Research Committee guidelines for Adverse Event Reporting

The Principal Investigator assumes responsibility for ensuring informed consent, data management, and the detection and reporting of adverse events. In general, the data to be reviewed will include screening data, baseline data, efficacy data, safety data, quality assurance data, accrual status including projections, and any other data that will help in the assessment of the effectiveness of the clinical trial.

The risk associated with participating in this study is moderate. D-cycloserine has been established as a safe treatment for tuberculosis. Consequently, serious side effects associated with this treatment are not expected. There will be on-call medical coverage to respond to any adverse events throughout the clinical trial.

The Principal Investigator will conduct a review of all adverse events and determine the attribution and grade of severity of the adverse event by using the following scales:

Attribution of Risk Categories:
Definite: Adverse event(s) will clearly be related to investigational agent(s) or other intervention
Probable: Adverse event(s) will likely be related to investigational agent(s)
Possible: Adverse event(s) may be related to investigational agent(s)
Unlikely: Adverse event(s) will doubtfully be related to investigational agent(s)
Unrelated: Adverse event(s) will clearly not be related to the investigational agents(s)

Grades of Risk:
0: No adverse event or within normal limits
1: Mild adverse event
2: Moderate adverse event
3: Severe adverse event resulting in hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect
4: Life-threatening or disabling adverse event
5: Fatal adverse event

Serious adverse events (SAEs) include any untoward medical occurrence that at any dose results in death or the immediate risk of death, hospitalization or the prolonging of an existing hospitalization, persistent or significant disability/incapacity or a congenital anomaly/birth defect. Participants will be terminated from participation if the investigator feels that participants' health or well-being may be threatened by continuation in the study. Serious unanticipated adverse events will be reported within 48 hours to the Partners IRB. The principal investigator will evaluate the adverse event and determine whether the adverse event affects the Risk/Benefit ratio of the study and whether modifications to the protocol are required. In addition, he will conduct a review of all adverse events at least semi-annually, and he will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

MONITORING AND QUALITY ASSURANCE

Describe the plan to be followed by the principal investigator/study staff to monitor and assure the validity and integrity of the data and adherence to the IRB-approved protocol. Specify who will be responsible for monitoring, and the planned frequency of monitoring. For example, specify who will review the accuracy and completeness of case report form entries, source documents, and informed consent.

NOTE: Regardless of monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for ensuring that the study is conducted at his/her investigative site in accordance with the IRB-approved protocol, and applicable regulations and requirements of the IRB.

The research assistants will be responsible for day-to-day monitoring of the validity and integrity of the data. Dr. Hill will meet with the research assistants to discuss data monitoring on a monthly basis and will sample participant data folders monthly as well.

For guidance, refer to the following Partners policies:

Data and Safety Monitoring Plans and Quality Assurance
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/DSMP_in_Human_Subjects_Research.pdf

Reporting Unanticipated Problems (including Adverse Events)
https://partnershealthcare-public.sharepoint.com/ClinicalResearch/Reporting_Unanticipated_Problems_including_Adverse_Events.pdf

PRIVACY AND CONFIDENTIALITY

Describe methods used to protect the privacy of subjects and maintain confidentiality of data collected. This typically includes such practices as substituting codes for names and/or medical record numbers; removing face sheets or other identifiers from completed surveys/questionnaires; proper disposal of printed computer data; limited access to study data; use of password-protected computer databases; training for research staff on the importance of confidentiality of data, and storing research records in a secure location.

NOTE: Additional measures, such as obtaining a Certificate of Confidentiality, should be considered and are strongly encouraged when the research involves the collection of sensitive data, such as sexual, criminal or illegal behaviors.

All data collected will be de-identified with participant ID numbers and used for research purposes only. Written records will be kept in a locked file cabinet in a locked office. They will be destroyed after 7 years. Computerized data files will also be de- identified with subject ID numbers and kept in a password protected file on a password protected computer.

SENDING SPECIMENS/DATA TO RESEARCH COLLABORATORS OUTSIDE PARTNERS

Specimens or data collected by Partners investigators will be sent to research collaborators outside Partners, indicate to whom specimens/data will be sent, what information will be sent, and whether the specimens/data will contain identifiers that could be used by the outside collaborators to link the specimens/data to individual subjects.

Not applicable.

Specifically address whether specimens/data will be stored at collaborating sites outside Partners for future use not described in the protocol. Include whether subjects can withdraw their specimens/data, and how they would do so. When appropriate, submit documentation of IRB approval from the recipient institution.

RECEIVING SPECIMENS/DATA FROM RESEARCH COLLABORATORS OUTSIDE PARTNERS

When specimens or data collected by research collaborators outside Partners will be sent to Partners investigators, indicate from where the specimens/data will be obtained and whether the specimens/data will contain identifiers that could be used by Partners investigators to link the specimens/data to individual subjects. When appropriate, submit documentation of IRB approval and a copy of the IRB-approved consent form from the institution where the specimens/data were collected.