

"Nicotinic Enhancement of Cognitive Remediation Training in People with Schizophrenia"

NCT02069392

Date of last IRB approval: July 5th 2018



UNIVERSITY of MARYLAND
BALTIMORE



University of Maryland, Baltimore
Institutional Review Board (IRB)
Phone: (410) 706-5037
Fax: (410) 706-4189
Email: hrpo@umaryland.edu

APPROVAL OF RESEARCH NOTIFICATION

Date: July 5, 2018

To: Britta Hahn
RE: HCR-HP-00058233-5
Type of Submission: Continuing Review
Type of IRB Review: Expedited

Approval for this project is valid from 7/5/2018 to 7/4/2019

This is to certify that the University of Maryland, Baltimore (UMB) Institutional Review Board (IRB) approved the continuing review report for the above referenced protocol entitled, “*Nicotinic Enhancement of Cognitive Remediation Training in Schizophrenia*”.

The IRB has determined that this protocol qualifies for expedited review pursuant to Federal regulations 45 CFR 46.110, 21 CFR 56.110, & 38 CFR 16.110 category(ies):

(8)(c) - Continuing review of research previously approved by the convened IRB where the remaining research activities are limited to data analysis. (For a multi-center protocol, an expedited review procedure may be used by the IRB at a particular site whenever these conditions are satisfied for that site.)

The IRB made the following determinations regarding this submission:

- Written informed consent is required. Only the valid IRB-approved informed consent form(s) in CICERO can be used.
- A waiver of HIPAA authorization for release of the PHI identified in the CICERO application has been reviewed and approved for recruitment purposes only.

This study is approved to enroll 70 local participants.

This study is approved to enroll 70 worldwide participants.

Below is a list of the documents attached to your application that have been approved:

Consent form
Eligibility Checklist for HP-00058233_1 v6-9-2014-1402319276253
Grant Application
Certificate of Confidentiality
HIPAA form
UMB - DHHM MOU
Package insert
Quality of Life Scale
Scale for the Assessment of Negative Symptoms

Structured Clinical Interview for DSM
Calgary Depression Scale
Evaluation to Sign Consent
Brief Psychiatric Rating Scale
Cognitive Assessment Interview
Addiction Severity Index
Nicotine Use Questionnaire
Side-Effects Checklist
Non-Psychiatric Medication Form
State-Trait Anxiety Inventory - State version
Sleep-Smoke-Caffeine Questionnaire
State-Trait Anxiety Inventory - Trait version
Medical history pre-screen
Nicotine Dependence Questionnaire
Reasons for Smoking Questionnaire
Treatment Group Guess
Psychiatric Medication Form
MATRICS Hopkins BVMT Delay
MATRICS Wechsler Memory Scale - 3 Spatial Span
MATRICS Hopkins BVMT
MATRICS WTAR scoring form
Ishihara test score form
WASI matrix reasoning subtest
MATRICS Hopkins Delay Form 1
MATRICS BACS
MATRICS Trailmaking A
MATRICS Hopkins Immediate Form 1
Visual Acuity scoring form
MATRICS Mazes
MATRICS MSCEIT Sections D and H
WASI vocabulary subtest
MATRICS Letter Number Span
Cogstate Terms of Use
DSMB Minutes 2014

In conducting this research you are required to follow the requirements listed in the INVESTIGATOR MANUAL. Investigators are reminded that the IRB must be notified of any changes in the study. In addition, the PI is responsible for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject (45 CFR 46.103(4)(iii)). The PI must also inform the IRB of any new and significant information that may impact a research participants' safety or willingness to continue in the study and any unanticipated problems involving risks to participants or others.

DHHS regulations at 45 CFR 46.109 (e) require that **continuing review** of research be conducted by the IRB at intervals appropriate to the degree of risk and **not less than once per year**. The regulations make **no provision for any grace period extending the conduct of the research beyond 7/4/2019**. You will receive continuing review email reminder notices prior to this date; however, it is your responsibility to submit your continuing review report in a timely manner to allow adequate time for substantive and meaningful IRB review and assure that this study is not conducted beyond **7/4/2019**. Investigators should submit continuing review reports in the electronic system at least six weeks prior to this date.

Research activity in which the VA Maryland Healthcare System (VAMHCS) is a recruitment site or in which VA resources (i.e., space, equipment, personnel, funding, data) are otherwise involved, must also be approved by the VAMHCS Research and Development Committee prior to initiation at the VAMHCS. Contact the VA Research Office at 410-605-7000 ext. 6568 for assistance.

The UMB IRB is organized and operated according to guidelines of the International Council on Harmonization, the United States Office for Human Research Protections and the United States Code of Federal Regulations and operates under Federal Wide Assurance No. FWA00007145.

If you have any questions about this review or questions, concerns, and/or suggestions regarding the Human Research Protection Program (HRPP), please do not hesitate to contact the Human Research Protections Office (HRPO) at (410) 706-5037 or HRPO@umaryland.edu.



Date: Tuesday, March 5, 2019 2:04:26 PM

[Print](#)[Close](#)

View: v2_Introduction Page

Introduction Page

- 1 * Abbreviated Title:
Nicotinic Enhancement of Cognitive Training

- 2 * Full Title:
Nicotinic Enhancement of Cognitive Remediation Training in Schizophrenia

3

- * Select Type of Submission:
IRB Application

Note: The Type of Submission cannot be changed after this application has been submitted for review.

- 4 Original Version #:

ID: VIEW4DF8709A33C00
Name: v2_Introduction Page

View: v2_Research Team Information

Research Team Information

- 1 * Principal Investigator - Who is the PI for this study (person must have faculty status)? **Faculty status is defined as being a full-time (>51% effort) faculty member holding one of the following titles at UM: Professor; Associate Professor; Assistant Professor.**
Britta Hahn

- 1.1 * Does the Principal Investigator have a financial interest related to this research?
 Yes No

- 2 Point of Contact - Who is the alternative point of contact for the PI? This person can be a study coordinator or any other study team member. In case the IRB cannot contact the PI, this person is a secondary person to contact:
Jacqueline Kiwanuka

- 2.1 Does the Point of Contact have a financial interest related to this research?
 Yes No

- 3 Other Team Members - list all additional members of the research team for this study. DO NOT include the PI or POC in this list:

Name	Edit Submission	cc on Email	Research Role	Has SFI?
Franklin Blatt	no	no	Research Team Member	no
Ann Kearns	yes	no	Other	no
James Gold	yes	yes	Sub-Investigator	no
Marie Yuille	no	no	Research Team Member	no
Robert Buchanan	yes	no	Sub-Investigator	no

IMPORTANT NOTE: All research team members (including PI) must have current CITI and HIPAA training completed.

View: v2_Resources

Resources

If this study is a collaborative UM/VA study, please clarify which resources are being used at each institution.

- 1 * **Describe the time that the Principal Investigator will devote to conducting and completing the research:**
Approximately 30% of her time.
- 2 * **Describe the facilities where research procedures are conducted:**
The study is conducted primarily at the Maryland Psychiatric Research Center (MPRC) which is located on the grounds of the Spring Grove Hospital Center. The facility includes an inpatient unit and several outpatient programs which are spread across two buildings on campus. The MPRC facilities have a large range of office space which is used for patient examination, interviews and completion of research procedures.
The PI and Sub-Investigators are based at the ORP, which houses a nurse's station equipped for performing blood draws, ECGs, vital signs, and physical exams in a private exam area. The ORP has its own pharmacy run by a part-time pharmacist whose effort is fully dedicated to supporting research studies. The research and clinical staff at the ORP have existed as a joint venture for over 20 years.
- 3 * **Describe the availability of medical and/or psychological resources that subjects might need as a result of anticipated consequences of the human research:**
A study nurse will be on site, and a physician familiar with the study will be on call, when a nicotine lozenge is first administered, and for subsequent repeat-exposures if side effects occurred upon first exposure that did not disqualify the participant. The availability of medical equipment is as described above. In the case of a severe adverse reaction to the lozenge, emergency medical services would be called and the participant transferred to a hospital.
The cognitive training sessions will be administered by a clinical research assistant who will be encouraging the participant and arrange for breaks as needed. Should the training cause any distress, the PI and Sub-Investigators (Dr. Gold is a Clinical Psychologist, Dr. Buchanan is a psychiatrist) can be reached by phone if training is performed off-site, or they can talk to the participant in person if training is performed at the MPRC.
- 4 * **Describe the process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions:**
As part of protocol implementation, a Study Manual will be distributed to all persons involved, detailing Standard Operating Procedures for each person's role in the study, procedures to be followed in the case of an adverse event, and emergency contact numbers. Prior to recruitment, all persons involved will meet, and the Principal Investigator will describe all procedures and sequences of events and answer any questions.

ID: VIEW4DF83CB976400
Name: v2_Resources

View: v2_Sites Where Research Activities Will Be Conducted

Sites Where Research Activities Will Be Conducted

- 1 * **Is this study a:**
 Multi-Site
 Single Site
- 2 * **Are you relying on an external IRB (not UM) to be the IRB of Record for this study?**
 Yes No
- 3 * **Are any other institutions/organizations relying on UM to be the IRB of Record for this study?**
 Yes No
- 3.1 Attach the applicable regulatory documents here (i.e., IRB Authorization Agreement (IAA), FWA, local ethics approval, other IRB approvals, etc.). Final UM approval will be contingent upon final execution of all required regulatory approvals:

Name	Created	Modified Date
UMB - DHMH MOU	12/10/2013 12:19 PM	12/10/2013 12:19 PM
- 4 * **Is UM the Coordinating Center for this study? (Applicable for multi-site studies. A Coordinating Center is responsible for overall data management, monitoring and communication among all sites, and general oversight of conduct of the project.)**
 Yes No
- 5 **Is VA the Coordinating Center for this study? (Applicable for Collaborative studies between the VA, UM and other sites. A Coordinating Center is responsible for overall data management, monitoring and communication among all sites, and general oversight of conduct of the project)**
 Yes No
- 6 * **Institution(s) where the research activities will be performed:**
Maryland Psychiatric Research Center (MPRC)
Community Mental Health Centers
Department of Health and Mental Hygiene (DHMH)

Other Sites

ID: VIEW4DF870DF2C000
 Name: v2_Sites Where Research Activities Will Be Conducted

View: v2 UM Coordinating Center

UM Coordinating Center

You indicated that UM is the Coordinating Center for this multi-site study.

2.1 *Describe the processes to ensure communication among sites.

Things to consider including in the communication plan:

- all sites have the most current version of the protocol, consent document, etc.
- all required approvals have been obtained at each site (including approval by the site's IRB of record).
- all modifications have been communicated to sites, and approved (including approval by the site's IRB of record) before the modification is implemented.
- all engaged participating sites will safeguard data as required by local information security policies.
- all local site investigators conduct the study appropriately.
- all non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.

The involvement of sites other than the MPRC (community day centers) will consist of an MPRC investigator (usually clinical research assistant) visiting the site with a laptop and testing material and taking the participant to a separate room for the training (and sometimes testing) intervention. If the local site has nursing or other medical staff who are willing to administer a lozenge that may contain nicotine, they may give the lozenge to the participant twice/week (usually Mon and Thur) prior to the cognitive training. Doctor's Orders will be provided for this by an MPRC physician on the protocol (Drs. Buchanan, Keller, or Fischer). Beyond this, there is no involvement of local site investigators/staff beyond facilitating the work of the MPRC investigator visiting daily. The MPRC investigator will coordinate the time of their daily visits with the availability of the participant and day room. Local site investigators/staff may assist with this.

Despite this limited involvement, local site investigators/staff will be in possession of the most current version of the IRB protocol and consent document. The PI will also meet with local site staff and explain the study and associated procedures in person. All site staff will have the PI's contact information and vice versa.

If the site has an IRB (such as community day centers associated with the Sheppard Pratt Healthcare System), separate IRB approval will be obtained. All protocol modifications will also be submitted to the local IRB prior to implementation at that site. All changes relevant to this site will also be communicated to the local site investigators/staff.

No data will be stored at any of the non-MPRC sites.

All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy, irrespective of at which site it occurred.

2.2 *Describe the method for communicating to engaged participating sites including:

- reportable new information.
- problems.
- interim results.
- the closure of a study.

Reportable new information, problems, and the closure of the study will be communicated to participating site investigators and staff via e-mail. No interim analysis will be performed.

ID: VIEW4DF737D4C2800
 Name: v2 UM Coordinating Center

View: v2 Other Sites Where Research Activities Will Be Conducted

Other Sites Where Research Activities Will Be Conducted

You selected "Other Sites," "Private Practice," "Community Mental Health Centers," and/or "Nursing Homes in Maryland" as a site where research will be conducted.

3.1 *Specify the name of the site(s):

1) MOSAIC Community Services, Sheppard Pratt Health System; 2) Humanim Inc.

3.2 *Contact Person(s) for Other Site:

1) Raymond Hoffman; 2) Kara Zoolakis

3.3 *Phone (if no phone available, input "none"):

1) none; 2) none

3.4 *Email Address (if no email available, input "none"):

1) Raymond.Hoffman@mosaicinc.org; 2) kzoolakis@humanim.com

ID: VIEW4DF8712DB5800
 Name: v2 Other Sites Where Research Activities Will Be Conducted

View: v2 DHMH

DHMH

You selected "Maryland Psychiatric Research Center" or "DHMH" as a research site. Answer the following questions to determine if Department of Health and Mental Hygiene (DHMH) review is needed.

3.1 *Does this protocol require DHMH IRB review?

Yes No

- 3.2 If Yes, will the DHMH IRB rely on UM IRB as the IRB of record for review of this protocol?

Yes No

ID: VIEW4DF86705BB800
Name: v2_DHMH

[View: v2_Funding Information](#)

Funding Information

- 1 * Indicate who is funding the study:

Federal

- 2 * What portion of the research is being funded? (Choose all that apply)

Drug
Staff
Participant Compensation

- 3 Please discuss any additional information regarding funding below:

ID: VIEW4DF85DF452400
Name: v2_Funding Information

[View: v2_DHHS Funded Study](#)

DHHS Funded Study

You indicated that this is a Federally funded study.

- 1 * Is this study sponsored by a Department of Health and Human Services (DHHS) agency?

Yes No

- 2 You may upload any grant documents here:

Name	Created	Modified Date
Grant Application	12/10/2013 2:46 PM	12/10/2013 2:46 PM

ID: VIEW4DF87B9560800
Name: v2_DHHS Funded Study

[View: v2_Federal Agency Sponsor Information](#)

Federal Agency Sponsor Contact Information

You indicated that this is a Federally funded study.

- 1 * Agency Name:

NIH - National Institute of Mental Health

- * Address 1:

9000 Rockville Pike

Address 2:

- * City:

Bethesda

- * State:

MD

- * Zip Code:

20892

- * Contact Person:

Michael J. Kozak

- * Phone Number:

301-443-6471

Grant Number 1 (if applicable):

1R21MH095824-01A1- OR - Check here if Grant 1 is not assigned a number.

If Grant 1 has no number, please provide the following information:

Title of Grant 1:

PI of Grant 1:

Britta Hahn

Grant Number 2 (if applicable):

- OR - Check here if Grant 2 is not assigned a number.

If Grant 2 has no number, please provide the following information:

Title of Grant 2:

PI of Grant 2:

Grant Number 3 (if applicable):

- OR - Check here if Grant 3 is not assigned a number.

If Grant 3 has no number, please provide the following information:

Title of Grant 3:

PI of Grant 3:

Grant Number 4 (if applicable):

- OR - Check here if Grant 4 is not assigned a number.

If Grant 4 has no number, please provide the following information:

Title of Grant 4:

PI of Grant 4:

ID: VIEW4DF8584874400
Name: v2_Federal Agency Sponsor Information

[View: v2_Research Protocol](#)

Research Protocol

1 * Do you have a research protocol to upload?

No, I do not have a research protocol and will use the CICERO application to enter my study information

2 If Yes, upload the research protocol:

Name

Created

Modified Date

There are no items to display

ID: VIEW4E00563F8D000
Name: v2_Research Protocol

[View: v2_Risk Level](#)

Risk Level

What is the risk level of your study? (Ultimately, the IRB will determine the appropriate risk level and your designation is subject to change.)

* Choose One:

Greater Than Minimal - Does not meet the definition of Minimal Risk.

ID: VIEW4E02805225800
Name: v2_Risk Level

[View: v2_Type of Research](#)

Type of Research

1 * Indicate ALL of the types of research procedures involved in this study (Choose all that apply):

Use of unapproved drug(s)/biologic(s) or approved drug(s)/biologic(s) whose use is specified in the protocol.

Psychological/Behavioral/Educational Method or Procedure (i.e., survey, questionnaires, interviews, focus groups, educational tests).
Sample (Specimen) Collection and/or Analysis (including genetic analysis).

- 2 * Is this study a clinical trial OR will this study be registered at ClinicalTrials.gov?
A clinical trial is a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

Yes No

ID: VIEW4E0280569E000
Name: v2_Type of Research

View: v2_Lay Summary

Lay Summary

- 1 * Provide a summary of the background and purpose of the study in language that can be understood by a person without a medical degree.

Schizophrenia is marked by problems in attention, memory and problem solving. These deficits predict long-term functional outcome such as the ability to live independently and maintain employment, but they are not ameliorated by currently available medications. Cognitive training improves these functions to some degree, but this approach is very time- and resource-intensive. The current project aims at enhancing and accelerating the benefits that people with schizophrenia derive from cognitive training by administering nicotine during some of the training sessions. This would provide the proof of principle for a treatment intervention that can improve cognitive symptoms of schizophrenia.

ID: VIEW4E02805CF7000
Name: v2_Lay Summary

View: v2_Justification, Objective, & Research Design

Justification, Objective, & Research Design

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

- 1 * Describe the purpose, specific aims, or objectives of this research. State the hypothesis to be tested:

The current project aims at determining whether the intermittent presence of nicotine during cognitive training exercises in people with schizophrenia will shorten the training period necessary to induce significant and clinically relevant improvement and enhance the improvement seen after a training period of specified length. Hypothesis 1a: Nicotine administration during training will increase the size of all measured effects of the training intervention, and will accelerate the time course of performance enhancement on the MCCB and training exercise progression parameters.

Hypothesis 1b: The larger training effects in the Nicotine Group will persist beyond the end of the intervention.

Hypothesis 2a: Within-session progress on the training exercises will be larger in the presence of nicotine than in the presence of placebo.

Hypothesis 2b: These acute nicotine-induced performance elevations will persist beyond the presence of nicotine through subsequent non-drug training sessions, giving evidence of an acute facilitation of learning processes.

- 2 * Discuss the research design including but not limited to such issues as: probability of group assignment, potential for subject to be randomized to placebo group, use of control subjects, etc.:

Volunteers with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder will be recruited, screened, and allocated in a double-blind manner to either the Nicotine Group or the Placebo Group. All participants will be asked to perform 10 weeks of cognitive remediation training (Posit Science, Duncan, SC), with daily training sessions Monday through Friday. On Mondays and Thursdays, all participants receive a lozenge 20 min prior to the training. In the Nicotine Group, the lozenge will contain 2 or 4 mg of nicotine, depending on smoking status. In the Placebo Group, the lozenge will be a matched placebo.

Outcome measures (OCMs) are assessed on Wednesdays in week 0 (day before training starts), weeks 4, 7 and 10 (after the training session), and week 14 (four weeks after training ends). OCMs are assessed on a non-drug day (Wed) because we are not studying the acute effects of nicotine but nicotine-induced enhancement of longer-term training effects.

- 3 * Describe the relevant prior experience and gaps in current knowledge. Describe any relevant preliminary data:

Schizophrenia is marked by pervasive neurocognitive deficits that predict much better than psychotic symptoms long-term community outcome such as social functioning and employment (70-80% of patients are un- or underemployed)(1)(2-4). First- and second-generation antipsychotics are minimally effective in improving cognitive symptoms of schizophrenia(5), and there are no current FDA-approved treatments targeting these symptoms. nAChR agonists such as nicotine acutely enhance early sensory, attentional and memory processes in schizophrenia(6-14), mimicking its effects in healthy subjects and laboratory animals. These effects tend to be small, and chronic administration of nicotine is undesirable because it is addictive and withdrawal causes deficits in the very functions nicotine enhances acutely(12;15;16). However, nicotine's facilitation of sensory information processing, alertness, attention, and mnemonic processes confer an ideal effects profile for promoting learning and enhancing effects of behavioral training(17). Thus, nicotine exposure coupled with a targeted training intervention may produce long-lasting cognitive benefits. This may be especially true in conditions marked by nAChR hypofunction, such as schizophrenia(18;19).

- 4 * Provide the scientific or scholarly background, rationale, and significance of the research and how it will add to existing knowledge:

Several cognitive training approaches have been tested in people with schizophrenia (PSZ). Interventions ranged from environmental aids, compensation strategies and techniques to enhance executive function and social cognition to repetitive drill-like exercises that tax sensory information processing, attention and memory. Training-related improvements in neurocognitive tests varied greatly between studies but tended to reflect low to medium effect sizes, with some limited generalization to outcomes such as psychosocial functioning, employment and symptoms(20-23). A recent training program places particular emphasis on early sensory processing. In PSZ, deficits in different stages of auditory stimulus and speech processing have been described(24-28), and these appear to contribute to higher-order cognitive deficits(29-31). A computerized training approach that successfully improved auditory processing and oral language abilities in dyslexia(32) (Posit Science, Duncan, SC) has been adapted for use in PSZ. Effect sizes on verbal learning, memory and working memory subscales of the MCCB were moderate to large, with limited generalization to non-verbal measures(33). The addition of an analogous visual processing training further enhanced and broadened outcome(34). Effects persisted at 6 months follow-up and were associated with positive changes in the Quality of Life Scale(34). However, this intervention involves 50-100 hours of training over 10-20 weeks, which limits its clinical applicability. A pharmacological means of enhancing and speeding the effects of cognitive remediation training could advance this technique into a feasible effective treatment of the cognitive symptoms of schizophrenia that can be broadly applied. The acute effects of nicotine during cognitive training are expected to enhance long-lasting cognitive enhancement derived from the training. For a training challenge based on a bottom-up approach as described above, sensory processing facilitation by nicotine may be of particular importance.

The current project aims at determining whether the intermittent presence of nicotine during the cognitive training exercises will shorten the training period necessary to induce significant and clinically relevant improvement and enhance the improvement seen after a training period of specified length. The significance of such findings would be twofold. First, it would provide proof of concept for a treatment intervention that can markedly improve some of the most debilitating and as of yet

untreatable symptoms of schizophrenia. Given early in the disease course, this intervention may slow or prevent the development of psychosocial problems; later on it may alleviate problems that have developed, in part by enhancing the effectiveness of other rehabilitative interventions. Second, our results may redefine the target outcome of drug development efforts for this symptom group. Rather than seeking pharmacological agents capable of improving cognitive functions *per se*, our results may provide the proof of principle to direct efforts onto agents capable of enhancing the beneficial effects of training challenges. Such agents may include other, more subtype-selective nAChR agonists, or compounds from other drug classes.

ID: VIEW4E02805EA0C00
Name: v2_Justification, Objective, & Research Design

View: v2_Supporting Literature

Supporting Literature

- 1 * Provide a summary of current literature related to the research: **If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer box below.**

A literature review is provided under "Justification, Objective, Research Design", sections 3 and 4. The References cited are:

1. Lehman AF. Improving treatment for persons with schizophrenia. *Psychiatr Q.* 1999;70:259-272.
2. Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? *Am J Psychiatry.* 1996;153:321-330.
3. Green MF, Kern RS, Heaton RK. Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. *Schizophr Res.* 2004;72:41-51.
4. Tan BL. Profile of cognitive problems in schizophrenia and implications for vocational functioning. *Aust Occup Ther J.* 2009;56:220-228.
5. Tandon R, Nasrallah HA, Keshavan MS. Schizophrenia, "just the facts" 5. Treatment and prevention. Past, present, and future. *Schizophr Res.* 2010;122:1-23.
6. Depatie L, O'Driscoll GA, Holahan AL, Atkinson V, Thavundayil JX, Kin NN, Lal S. Nicotine and behavioral markers of risk for schizophrenia: a double-blind, placebo-controlled, cross-over study. *Neuropsychopharmacology.* 2002;27:1056-1070.
7. Larrison-Faucher AL, Matorin AA, Sereno AB. Nicotine reduces antisaccade errors in task impaired schizophrenic subjects. *Prog Neuropsychopharmacol Biol Psychiatry.* 2004;28:505-516.
8. Myers CS, Robles O, Kakoyannis AN, Sherr JD, Avila MT, Blaxton TA, Thaker GK. Nicotine improves delayed recognition in schizophrenic patients. *Psychopharmacology (Berl).* 2004;174:334-340.
9. Smith RC, Warner-Cohen J, Matute M, Butler E, Kelly E, Vaidhyanathaswamy S, Khan A. Effects of nicotine nasal spray on cognitive function in schizophrenia. *Neuropsychopharmacology.* 2006;31:637-643.
10. Barr RS, Culhane MA, Jubelt LE, Mufit RS, Dyer MA, Weiss AP, Deckersbach T, Kelly JF, Freudenreich O, Goff DC, Evins AE. The effects of transdermal nicotine on cognition in nonsmokers with schizophrenia and nonpsychiatric controls. *Neuropsychopharmacology.* 2008;33:480-490.
11. Jubelt LE, Barr RS, Goff DC, Logvinenko T, Weiss AP, Evins AE. Effects of transdermal nicotine on episodic memory in non-smokers with and without schizophrenia. *Psychopharmacology (Berl).* 2008;199:89-98.
12. AhnAllen CG, Nestor PG, Shenton ME, McCarley RW, Niznikiewicz MA. Early nicotine withdrawal and transdermal nicotine effects on neurocognitive performance in schizophrenia. *Schizophr Res.* 2008;100:261-269.
13. Freedman R, Olincy A, Buchanan RW, Harris JG, Gold JM, Johnson L, Allensworth D, Guzman-Bonilla A, Clement B, Ball MP, Kutnick J, Pender V, Martin LF, Stevens KE, Wagner BD, Zerbe GO, Sotil F, Kern WR. Initial phase 2 trial of a nicotinic agonist in schizophrenia. *Am J Psychiatry.* 2008;165:1040-1047. <http://ajp.psychiatryonline.org/cgi/reprint/165/8/1040>
14. Wozniak AA, Sacco KA, George TP. Prepulse inhibition deficits in schizophrenia are modified by smoking status. *Schizophr Res.* 2009;112:86-90.
15. George TP, Vessicchio JC, Termine A, Sahady DM, Head CA, Pepper WT, Kosten TR, Wexler BE. Effects of smoking abstinence on visuospatial working memory function in schizophrenia. *Neuropsychopharmacology.* 2002;26:75-85.
16. Sacco KA, Termine A, Seyal A, Dudas MM, Vessicchio JC, Krishnan-Sarin S, Jatlow PI, Wexler BE, George TP. Effects of cigarette smoking on spatial working memory and attentional deficits in schizophrenia: involvement of nicotinic receptor mechanisms. *Arch Gen Psychiatry.* 2005;62:649-659.
17. Kenney JW, Gould TJ. Modulation of hippocampus-dependent learning and synaptic plasticity by nicotine. *Mol Neurobiol.* 2008;38:101-121.
18. Dalack GW, Healy DJ, Meador-Woodruff JH. Nicotine dependence in schizophrenia: clinical phenomena and laboratory findings. *Am J Psychiatry.* 1998;155:1490-1501.
19. Adams CE, Stevens KE. Evidence for a role of nicotinic acetylcholine receptors in schizophrenia. *Front Biosci.* 2007;12:4755-4772.
20. Twamley EW, Jeste DV, Bellack AS. A review of cognitive training in schizophrenia. *Schizophr Bull.* 2003;29:359-382.
21. Velligan DI, Kern RS, Gold JM. Cognitive rehabilitation for schizophrenia and the putative role of motivation and expectancies. *Schizophr Bull.* 2006;32:474-485. [PMC2632243](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2632243/)
22. McGurk SR, Twamley EW, Sitzer DI, McHugo GJ, Mueser KT. A meta-analysis of cognitive remediation in schizophrenia. *Am J Psychiatry.* 2007;164:1791-1802.
23. Medalia A, Choi J. Cognitive remediation in schizophrenia. *Neuropsychol Rev.* 2009;19:353-364.
24. Jonsson CO, Stjordet A. Auditory perception in schizophrenia: a second study of the Intonation test. *Acta Psychiatr Scand.* 1973;49:588-600.
25. Kugler BT, Caudrey DJ. Phoneme discrimination in schizophrenia. *Br J Psychiatry.* 1983;142:53-59.
26. Javitt DC. Intracortical mechanisms of mismatch negativity dysfunction in schizophrenia. *Audiol Neurotol.* 2000;5:207-215.
27. Vercammen A, de Haan EH, Aleman A. Hearing a voice in the noise: auditory hallucinations and speech perception. *Psychol Med.* 2008;38:1177-1184.
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33. Fisher M, Holland C, Merzenich MM, Vinogradov S. Using neuroplasticity-based auditory training to improve verbal memory in schizophrenia. *Am J Psychiatry.* 2009;166:805-811.
34. Fisher M, Holland C, Subramaniam K, Vinogradov S. Neuroplasticity-based cognitive training in schizophrenia: an interim report on the effects 6 months later. *Schizophr Bull.* 2010;36:869-879.

- 2 If available, upload your applicable literature search:

Name	Created	Modified Date
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There are no items to display

- 3 * Provide a list of 3 keywords or search terms (1 per line) relevant to your research that would help potential participants find your study using search engines:

Keyword 1: schizophrenia

Keyword 2: cognitive remediation training

Keyword 3: nicotine

ID: VIEW4E02805A7E400
Name: v2_Supporting Literature

View: v2_Study Procedures

Study Procedures

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below. (If this study is a collaborative UM/VA study please list each procedure that is being conducted and the locations where it is being conducted.)

- 1 * Describe all procedures being performed for research purposes only (these procedures would not be done if individuals were not in the study) and when they are performed, including procedures being performed to monitor subjects for safety or to minimize risks:

Volunteers who provide Informed Consent will be screened for all Inclusion/Exclusion criteria. SCREENING will include: - Verification of age. - The SCID, to determine the presence/absence of current psychiatric conditions. For most patients, a SCID will have already been obtained and does not need to be repeated. - Medical history targeted at the cardiovascular, neurological, cognitive and other exclusion criteria. - Blood pressure and heart-rate reading. - ECG (12-lead with 3-5 minute rhythm strip). Exclusionary conditions documented on ECG include: Wolfe Parkinson White syndrome Myocardial ischemia and infarction Complete left bundle branch block PR interval <120 ms or >200 ms Prolonged QT interval (corrected) >500 ms Cardiac arrhythmias as defined by PACs >3 per min or PVCs >1 per min - Urine drug test, as a possible indication for substance abuse or dependence (may be repeated at any time during the study if intoxication is suspected) - Alcohol breathalyzer test, as a possible indication for alcohol abuse or dependence (may be repeated at any time during the study if intoxication is suspected) - Urine pregnancy test for females (also performed at the beginning of the cognitive training phase, and every two weeks thereafter) - Targeted questions about smoking history and motivation to stop smoking - Breath CO reading, as an indicator of smoking status and frequency - Listing of all currently taken medication - Vision test - The Addiction Severity Index - Drug and Alcohol Use subscale as an indicator for substance abuse or dependence. - The Wechsler Abbreviated Scale of Intelligence (WASI), as an indicator for possible mental retardation. Volunteers who pass the screening will be randomized to either the nicotine group or the placebo group. Randomization will be performed by the MPRC's biostatistician, Dr. Robert McMahon, upon receiving a randomization request from the research assistant coordinating the study or a study investigator. Participants are then scheduled for a first NICOTINE EXPOSURE SESSION. In this session, participants will consume a nicotine lozenge (2 mg for non-smokers, 4 mg for smokers) if they have been randomized to the nicotine group and a placebo lozenge if they have been randomized to the placebo group. The number of smokers will be counterbalanced between the nicotine and placebo group. Participants will be instructed not to eat or drink within 15 min prior to or while consuming the lozenge. Participants are asked to report any adverse effects as soon as noted and to rate their subjective state immediately before the lozenge and every 30 min thereafter (see Side-Effects Checklist under "Additional Documents"). At this time, an investigator will also take their blood pressure and heart rate. The adverse effects of nicotine develop rapid tolerance. If any adverse effects are observed that are greater than "mild" and were not present pre-lozenge, the participant will undergo another lozenge exposure session on a separate day before starting the study. This may be repeated up to 4 times. Once both the participant and the investigator judge that any untoward effects of the lozenge are mild and tolerable and will not interfere with the cognitive training, the first outcome measurement session is scheduled, and the daily training sessions will commence the day after. A smoker who cannot tolerate the 4-mg lozenge may be dosed with a 2-mg lozenge in the cognitive training phase (the study would be single-blind for this subject). A participant who cannot tolerate the 2-mg lozenge even after repeated attempts will be excluded from the study. Participants who with the 2 mg lozenge display a rise in blood pressure by >20 mm Hg relative to pre-lozenge, a rise in HR to >120, or vomiting, will also be excluded from the study. OUTCOME MEASUREMENTS will be performed before the training begins, and approximately every 4 weeks after that until 4 weeks after the training ends. During the training phase, the outcome measurements will be performed AFTER completion of the daily cognitive training session. We will always schedule at least 1 hour between training and the outcome measurement, during which the participant can rest or have lunch. Outcome assessments are: a) The MATRICS Consensus Cognitive Battery (MCCB), an FDA-approved assessment tool for trials of cognition-enhancing treatments in PSZ. The battery measures 7 domains: speed of processing, attention/vigilance, working memory (verbal, nonverbal), verbal learning, reasoning, problem solving, and social cognition. b) The progression in training exercise parameters since the last outcome measurement time point (see below). c) Symptom assessments: the Brief Psychiatric Rating Scale, Scale for Assessment of Negative Symptoms, and Calgary Depression Scale. d) The state version of the State-Trait Anxiety Inventory. e) The Cogstate computerized assessment battery. Further outcome measures taken only pre- and post-training (week 0 and 10): a) Working Memory capacity (K) derived from a computerized change localization task. Two to four colored squares are shown for 100 ms. After a delay, they reappear and the task is to click on the one square that has changed color. b) The UCSD Performance-Based Skills Assessment, measuring ability to perform real-life tasks by standardized role-play. c) Quality of Life Scale, measuring functional outcome and quality of life in PSZ. d) The trait version of the State-Trait Anxiety Inventory. e) The Cognitive Assessment Interview (CAI), a brief interview-based measure of daily life cognitive functioning, administered to both the PSZ and a close relative or caretaker. The CAI was developed based on two longer scales and assesses 10 items related to working memory, attention/vigilance, learning/memory, problem solving, processing speed, and social cognition, with little or no repetition effects. f) Questionnaire asking each participant to guess their treatment group (nicotine or placebo; post-training only). g) A 5-ml venous blood sample will be taken, centrifuged, and frozen. At the completion of the study, the samples will be analyzed for TNF alpha, and potentially other inflammatory markers, to test whether repeated nicotine exposure may have anti-inflammatory effects that may be related to any effects on cognitive outcome measures. If a participant declines to have their blood drawn but are otherwise eligible for the study, they may participate without the blood draws. COGNITIVE REMEDIATION TRAINING PROCEDURE Prior to each daily training session, participants will complete a brief checklist about their caffeine and cigarette consumption today (how much/how many), when they last smoked/drank a caffeinated beverage, how many hours of sleep they got the previous night, when they last drank alcohol and how much. Prior to each session, smokers also provide a CO breathalyzer reading. Each training session will include ~30 min of auditory and ~30 min of visual training exercises by Posit Science, in a counterbalanced manner. The auditory training consists of six exercises: fast and accurate discrimination of (1) sound frequencies, (2) phonemes and (3) syllables, and recall of syllables, (4) sequences of syllables, (5) multi-element verbal instructions, and (6) details of a narrative. The visual training consists of five exercises designed to (1) improve visual precision, (2) increase capacity to divide visual attention, (3) improve visual memory, (4) expand field of view, and (5) increase visual processing speed. The programs train the fine-tuned and differentiated processing of sensory input and engage attention, working memory and/or executive processes. To induce the right level of challenge and promote engagement and motivation, task difficulty adjusts continuously to user performance to maintain ~85% correct responses (which are rewarded by auditory and visual feedback). Adjustable parameters include presentation time, interstimulus interval, physical similarity between stimuli, stimulus eccentricity, number of stimuli, and information complexity. Some exercises provide a progress summary of these parameters after each session. These values will be recorded on all training days. Other exercises provide a separate assessment tool to monitor progress. These assessments will be performed every 4 weeks with other outcome measurements. Every Monday and Thursday, a nicotine or placebo lozenge, encapsulated in gelatin, will be administered 20 minutes prior to the beginning of the training. Nicotine lozenges are mint-flavored "mini" lozenges, placebo lozenges are size-matched breath mints. Smokers in the Nicotine Group will receive a 4-mg lozenge. Plasma concentrations after this dose resemble the "nicotine boost" typically seen in dependent smokers by smoking a single cigarette (~1 ng/ml). Non-smokers in the Nicotine Group will receive a 2-mg lozenge because 4 mg in nicotine-naïve individuals would likely result in low tolerability. Participants will be instructed not to eat or drink within 15 min prior to or while consuming their lozenge. Participants may perform the training sessions at the Maryland Psychiatric Research Center (MPRC), or, in a separate room, at their day program or inpatient unit if applicable (a research associate would visit daily with laptop, lozenge or assessment instruments). The lozenge would be administered by a local nurse or other medical professional if possible, else these sessions would be performed at the MPRC. Participants who are unable to come to the MPRC or day program to complete the training (e.g., because they work or live too far away) may perform the exercises at home if they have internet access and their clinician or study staff considers them capable of doing so reliably. The CO measurement would be omitted on home-training days, and participants would be given the questionnaire about how much they slept and how much caffeine or alcohol they consumed to complete by themselves at home. On the two weekly lozenge days, they would be scheduled to perform the training at the MPRC. Under select circumstances, when the patient is unable to come to the MPRC on those days, too, they would be instructed to take the lozenge at home, following doctor's orders. A study team member would call them at home and

remind them to take the lozenge 20 min before the training. The participant would be allowed to keep up to two lozenges at home, for the event that they meet unexpected obstacles to coming to the MPRC on a lozenge day. Their performance would be monitored and recorded via an internet portal maintained by Posit Science Inc. Participants may take breaks but are encouraged to first complete the current exercise. We allow some flexibility in the above training and testing schedule because it will be unavoidable that some participants will be unavailable on some days. In general, if one lozenge session is missed, the lozenge will be given on the following day. If an outcome measurement day is missed, outcome measurements will be performed on either Tuesday or Friday of the same week (thus avoiding lozenge days), or if not feasible, in the preceding or following week. If an entire week of training is omitted by an otherwise reliable participant, the following weeks of the schedule will be moved back by one week.

- 2 * Describe all procedures already being performed for diagnostic or treatment purposes (if not applicable to the study, enter "N/A"):

N/A

- 3 * Describe the duration of an individual participant's participation in the study:

The cognitive training intervention will take 10 weeks. A follow-up outcome assessment session will be scheduled 4 weeks following training completion, but we will allow up to 10 weeks before a participant is labeled as "lost to follow-up". We will allow up to 3 months between consent and the next study session; after this, a participant would have to be re-consented. We will allow up to 3 months between the last nicotine exposure session and the beginning of the cognitive training. Thus, the maximum duration of participation is 12 months. If more than 3 months elapsed between the screening and the beginning of the training procedure, we would repeat most of the screening procedures prior to the start. A study physician would determine which procedure need to be repeated.

- 4 * Describe the duration of the entire study:

We anticipate that data collection will be completed in two years. Data analyses and preparation for publication may continue thereafter.

- 5 * Describe any additional participant requirements:

None.

ID: VIEW4E0280585B400

Name: v2_Study Procedures

View: v2_Sample Size and Data Analysis

Sample Size and Data Analysis

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

- 1 * Provide the rationale and sample size calculations for the proposed target population:

Statistical and power analyses: Hypothesis 1a (larger or faster improvement in Nicotine than Placebo Group): Assuming training effects are linear with time, we will conduct an intention to treat (ITT) analysis by fitting the mixed model regression for repeated measures OCM= time+ treatment+ treatment x time, with time as a continuous measure. The treatment x time interaction estimates the difference between treatment groups in OCM rate of change (slope). Although we will include subjects with partial data, the effect size detectable was estimated conservatively⁷⁸ by: $d = [2(z_a + z_b)2(1-r)/bnVar(t)]/2$, where d = (difference in slopes)/SD(OCM), r = within-subject correlation of OCM, $b=4$ visits per subject, n = number of completers per group, $Var(t)=0.185$ is the within-subject variance of the visit times, and $z_a=1.96$ and $z_b=0.84$ for two-sided $\alpha=0.05$ and power=0.80. With $n=20$ completers per group, $d=0.56$ (a medium effect size) will be detectable for $r=0.7$ consistent with the high ICC of the MCCB, the primary OCM. To explore differences in treatment effects between MCCB domains, we will employ the mixed model for repeated measures: T-score= domain+ treatment+ time+ interactions. In particular, the domain x treatment x time interaction assesses variation among domains in the magnitude of the treatment effects on change slopes in OCM scores. In secondary analyses to guide the design of future studies, we will fit a model in which time is treated as a categorical measure unconstrained by a linear fit to explore different learning scenarios such as a more rapid initial acquisition but similar ceiling. In this model, we will add week 14 data to examine Hypothesis 1b (persistence of improvements after training ends), comparing treatment groups on the difference between week 14 and 10. Other exploratory analyses: 1) Smoking status (smoker, never-smoker) is added as an exploratory between-subject factor. 2) A further regression will explore differences between treatment groups in two compliance measures, the cumulative percentage of missed training sessions and lozenge administrations until each OCM time point. If treatment groups differ on compliance, we would include time-dependent compliance as a mediator of treatment effects. A descriptive analysis to support Hypothesis 1a will compare the percentage of participants in each group that achieves clinically significant improvement in MCCB composite scores (6 points from baseline adjusted for practice effects, see above) at each OCM time point.

Hypothesis 2a (training progress within nicotine vs. placebo sessions): For those adaptive exercise parameters for which progress is stated at the end of each session, we will compare nicotine - placebo differences on within-session progress, averaged over 20 lozenge-sessions, between treatment groups using a t-test. Power is estimated from the formula⁷⁸ $d = [2(z_a + z_b)2(1-(b-1)r)/bn]$, where d = (difference in average change)/SD(change within 1 session), $b=20$ visits per subject, and other terms are defined as above. For $n=20$ completers per group, we would have power=0.80 at two-sided $\alpha=0.05$ to detect $d=0.51$ (a medium effect size) for $r=0.3$. r is estimated based on each exercise being short and of potentially low reliability. To test Hypothesis 2b (persistence of nicotine-induced improvements beyond the presence of nicotine), we will analyze within-session progress on no-lozenge sessions. If progress made in the nicotine sessions does not persist, we would expect a performance decrement in subsequent no-lozenge sessions (Tue, Fri), whose difficulty levels begin where the previous session left off. If progress made under nicotine does persist, we would expect no decrement and progress comparable to no-lozenge sessions in the placebo group.

To achieve 20 completers per group, we expect having to enroll 25 subjects per group into the training and having to screen approximately 70 subjects in total.

Please note that screening is part of the study protocol. Thus, we expect to consent 70 subjects.

- 2 * Provide the plan for data analysis. Include in the description the types of comparisons that are planned (e.g., comparison of means, comparison of proportions, regressions, analysis of variance, etc.), which is the primary comparison/analysis, and how the analyses proposed will relate to the primary purposes of the study:

Please see above. The sample size calculation is closely related to the planned analyses.

ID: VIEW4E02806052800

Name: v2_Sample Size and Data Analysis

View: v2_Sharing of Results

Sharing of Results

- 1 * Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how it will be shared:

If significant abnormalities are identified during screening, these test results would be given to the subject, together with a recommendation regarding the appropriate type of follow-up (e.g., see family doctor or specialist).

The overall trial outcome would not be shared with individual participants or their providers but will be made accessible via scientific publication. Furthermore, data

obtained with the CogState test battery will be provided to Cogstate Ltd upon completion of the trial for their own research and development. No subject identifiers will be given to Cogstate Ltd. We may include age in years and gender.

ID: VIEW4E02808CBD800
Name: v2_Sharing of Results

View: v2_Research with Drugs or Biologics

Research with Drugs or Biologics

You indicated on the "Type of Research" page that your study involves use of unapproved drug(s)/biologic(s) or approved drug(s)/biologic(s) whose use is specified in the protocol AND/OR evaluation of food(s) or dietary supplement(s) to diagnose, cure, treat, or mitigate a disease or condition.

- 1 * List all drugs/biologics to be administered in this study. Be sure to list each drug/biologic with its generic name only.

Drug Name	FDA Approved	IND Number	PI IND Holder
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View: Nicotine polacrilex lozenge

yes

- 2 * Attach the drug package insert or investigational drug brochure for the drugs being administered in this study:
Package insert 12/10/2013 3:14 PM 12/10/2013 3:14 PM

- 3 If more than one drug is administered, discuss the risk implications of drug/therapy interactions:

- 4 * Will you be using Investigational Drug Services?

Yes No

ID: VIEW4E0916E6E1400

Name: v2_Research with Drugs or Biologics

View: v2_Drug or Biologic Storage and Handling

Drug or Biologic Storage and Handling

- 4.1 * Do you have a plan regarding access controls for essential and appropriate research personnel?

Yes No

- 4.2 * Will you have procedures for verifying physical access to the drug(s)?

Yes No

- 4.3 * Will you label the drug(s) so that it is (they are) used appropriately for the study?

Yes No

- 4.4 * Will there be an establishment of a drug transfer process both into and out of the research site?

Yes No

- 4.5 * Will the storage of the drug(s) be in a secure environment and include locks on doors and controlled access?

Yes No

- 4.6 * Do you have a plan for only allowing trained personnel to administer the drug(s)?

Yes No

- 4.7 If applicable, will the storage of the drug(s) be at the appropriate temperature, with a storage and temperature log?

Yes No

ID: VIEW4E1D85CC57C00

Name: v2_Drug or Biologic Storage and Handling

View: v2_Placebos

Placebos

- 1 * Is this study placebo controlled?

Yes No

ID: VIEW4E0514EECCC00
Name: v2_Placebos

View: v2_Placebo Use

Placebo Use

You indicated that this study is placebo-controlled.

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section

and page numbers from that document in the answer box below.

- 1.1 * **Justify the use of the placebo study design and how the benefit to society outweighs the risks to the participants:**
 All participants will receive 10 weeks of cognitive remediation training as part of the study, but only half of the participants will receive a nicotine lozenge biweekly prior to the training session. The other half will receive a placebo lozenge matched for looks and taste. There is no risk associated with receiving placebo instead of nicotine lozenges. If nicotine enhances the training effects, as hypothesized, then the placebo group on average will derive less benefit from the training. This remains to be shown, and it could not be shown without the placebo group. If it was shown to be true, this would provide the proof-of-principle for a mechanism that may help alleviate one of the most debilitating symptoms of schizophrenia.
- 1.2 * **Is the placebo being used in place of standard therapy?**
 Yes No
- 1.3 * **Is the standard treatment considered effective?**
 Yes No

ID: VIEW4E0514D79B400
 Name: v2_Placebo Use

View: v2_Psychological/Behavioral/Educational Methods and Procedures

Psychological/Behavioral/Educational Methods & Procedures

You indicated on the "Type of Research" page that your study involves a psychological/behavioral/educational method or procedure such as a survey, questionnaire, interview, or focus group.

- 1 * **Select all behavioral methods and procedures which apply to this study:**

Surveys/questionnaires
 Key informant or semi-structured individual interviews
 Individual or group behavioral observations
 Psychosocial or behavioral interventions
 Neuropsychological or psychophysiological testing

ID: VIEW4E09416F57800

Name: v2_Psychological/Behavioral/Educational Methods and Procedures

View: v2_Surveys/Questionnaires

Surveys/Questionnaires

You indicated that this study involves surveys and/or questionnaires.

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

- 1 * **List all questionnaires/surveys to be used in the study, including both standardized and non-standardized assessments:**
 Questionnaire asking about hours of sleep, caffeine and cigarette consumption today, to be used on each training day.
 Psychiatric and non-psychiatric medication forms, to record all currently taken medication
 Side-effects checklist to be used in the nicotine exposure session(s)
 The state- and the trait-version of the State-Trait Anxiety Inventory
 The Reasons for Smoking questionnaire
 The Nicotine Use Questionnaire
 The Nicotine Dependence Questionnaire
 A questionnaire recording the participant's guess as to whether or not their lozenges contained nicotine (Treatment Group Guess), to be completed with the outcome measurement immediately following training completion.
 A medical history pre-screening questionnaire, to be performed by a research assistant prior to the Medical History by the physician.

- 2 * **Upload a copy of all questionnaires/surveys:**

Name	Created	Modified Date
Medical history pre-screen	12/12/2013 3:22 PM	12/12/2013 3:31 PM
Treatment Group Guess	12/10/2013 4:15 PM	12/10/2013 4:15 PM
Nicotine Dependence Questionnaire	12/10/2013 4:02 PM	12/10/2013 4:02 PM
Nicotine Use Questionnaire	12/10/2013 4:01 PM	12/10/2013 4:01 PM
Reasons for Smoking Questionnaire	12/10/2013 4:01 PM	12/10/2013 4:01 PM
State-Trait Anxiety Inventory - Trait version	12/10/2013 4:00 PM	12/10/2013 4:00 PM
State-Trait Anxiety Inventory - State version	12/10/2013 4:00 PM	12/10/2013 4:00 PM
Side-Effects Checklist	12/10/2013 3:58 PM	12/10/2013 3:58 PM
Non-Psychiatric Medication Form	12/10/2013 3:57 PM	12/10/2013 3:57 PM
Psychiatric Medication Form	12/10/2013 3:56 PM	12/10/2013 3:56 PM
Sleep-Smoke-Caffeine Questionnaire	12/10/2013 3:44 PM	12/10/2013 3:44 PM

3 * What is the total length of time that each survey is expected to take?

Sleep-Smoke-Caffeine Questionnaire: 3 min

Medication forms: 10 min

Side Effects Checklist: 5 min

STAI - State: 4 min

STAI - Trait: 4 min

Reasons for Smoking Questionnaire: 3 min

Nicotine Use Questionnaire: 5 min

Nicotine Dependence Questionnaire: 5 min

Treatment Group Guess: 2 min

Medical history pre-screen: 5 min

4 * Are any of the questions likely to cause discomfort in participants or cause harm if their confidentiality were breached? (i.e., Illegal activities)

 Yes No

5 * Do any questions elicit information related to the potential for harm to self or others?

 Yes No

5.1 If Yes, what procedures are in place to assure safety?

ID: VIEW4E09460F5EC00

Name: v2_Surveys/Questionnaires

View: v2_Interviews

Interviews

You indicated that this study involves key informant or semi-structured individual interviews.

1 * Are any of the questions likely to cause discomfort in participants or cause harm if their confidentiality were breached? (i.e., Illegal activities)

 Yes No

2 * Upload a copy of the interview script or guide that will be used to guide the interviews:

Name	Created	Modified Date
Cognitive Assessment Interview	12/13/2013 11:32 AM	12/13/2013 11:32 AM
Quality of Life Scale	12/11/2013 9:53 AM	12/11/2013 9:53 AM
Addiction Severity Index	12/11/2013 9:53 AM	12/11/2013 9:53 AM
Calgary Depression Scale	12/11/2013 9:52 AM	12/11/2013 9:52 AM
Scale for the Assessment of Negative Symptoms	12/11/2013 9:52 AM	12/11/2013 9:52 AM
Brief Psychiatric Rating Scale	12/11/2013 9:51 AM	12/11/2013 9:51 AM
Evaluation to Sign Consent	12/11/2013 9:51 AM	12/11/2013 9:51 AM
Structured Clinical Interview for DSM	12/11/2013 9:51 AM	12/11/2013 9:51 AM

3 * What is the individual duration of each interview and what is the entire duration of the interviews?

Cognitive Assessment Interview: ~30 min

Addiction Severity Index (Drug and Alcohol subsection): ~10 min

Quality of Life Scale: ~40 min

Calgary Depression Scale: ~15 min

Scale for the Assessment of Negative Symptoms: ~15 min

Brief Psychiatric Rating scale: ~15 min

Evaluation to Sign Consent: ~3 min

Structured Clinical Interview for DSM: 25-60 min

4 * How will the interview responses be recorded and by whom?

The responses will be recorded by the rater on assessment forms (attached) labeled by subject ID code, date, study number and rater ID. who is either a clinical psychologist or a clinical research assistant at the MPRC, or a therapist/social worker (for the symptom assessment scales). All of these individuals are listed on the current protocol. The data are then entered into a secure database.

5 * Do any questions elicit information related to the potential for harm to self or others?

 Yes No

5.1 If Yes, what procedures are in place to assure safety?

If a participant were to disclose his or her intent to harm him- or herself or others, the participant will be escorted to a psychiatrist, to a social worker, or to another clinician in our outpatient psychiatric clinic for an immediate evaluation. These clinicians will then determine appropriate action and follow-up depending on the circumstances.

ID: VIEW4E0947A633C00
Name: v2_Interviews

Observation

You indicated that this study involves individual or group behavioral observations.

- 1 * Are any of the observations likely to cause harm if confidentiality were breached? (i.e., Illegal activities)
- Yes No

- 2 * How will individuals identities be protected?

Standardized role-play will be done with an investigator as part of the UCSD Performance-Based Skills Assessment, measuring ability to perform real-life tasks. The 35-45 min assessment will be done in a private room. No audio or video recordings will be taken.

- 3 * How will observations be recorded?

Observations will be recorded on a score sheet labeled by subject ID code, study number, date, and rater ID.

ID: VIEW4E0BBF1EF0400
Name: v2_Observation

View: v2_Behavioral Interventions

Behavioral Intervention

You indicated that this study involves psychosocial or behavioral interventions.

- 1 * Describe the intervention (duration, number of sessions, focus, etc.):

Participants will be asked to perform 10 weeks of computerized cognitive remediation training (Posit Science, Duncan, SC), with daily 80-min training sessions Monday through Friday, usually in the presence of a research assistant. Each cognitive remediation training session will include ~30 min of auditory and ~30 min of visual training exercises by Posit Science, in a counterbalanced manner. Both programs posit that the quality and quantity of processed sensory information form the basis for higher cognitive functions by affecting, e.g., processing speed and the availability of attentional resources. The auditory training consists of six exercises: fast and accurate discrimination of (1) sound frequencies, (2) phonemes and (3) syllables, and recall of syllables, (4) sequences of syllables, (5) multi-element verbal instructions, and (6) details of a narrative. The visual training consists of five exercises designed to (1) improve visual precision, (2) increase capacity to divide visual attention, (3) improve visual memory, (4) expand field of view, and (5) increase visual processing speed. Participants will perform ~15 min of an exercise at a time and complete five exercises per session. The aim is to complete each exercise twice/week and on at least one lozenge-day/week (Mon or Thur). Within these restrictions, we will aim at completing the sound frequency discrimination almost daily.

The programs train the fine-tuned and differentiated processing of sensory input and engage attention, working memory and/or executive processes. To induce the right level of challenge and promote engagement and motivation, task difficulty adjusts continuously to performance to maintain ~85% correct responses (rewarded by auditory and visual feedback). Adjustable parameters are presentation time, interstimulus interval, stimulus similarity, stimulus eccentricity, number of stimuli, and information complexity.

ID: VIEW4E0BC12A9F800
Name: v2_Behavioral Interventions

View: v2_Testing

Testing

You indicated that this study involves neuropsychological or psychophysiological testing.

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

- 1 * List all of the tests to be used in the study, including both standardized and non-standardized assessments:

The cognitive status of patients and controls will be assessed by the following tests:

- The WASI Vocabulary and Matrix Reasoning subtests to assess intellectual competence
- The MATRICS battery
- Visual Acuity Test to test inclusion criterion of normal vision
- Ishihara's Test for Color Deficiency
- Change localization task, to test working memory capacity
- Tests to assess progress on the Posit Science cognitive remediation training exercises
- Cogstate computerized assessment battery

- 2 * Describe procedures related to all testing:

-The WASI subtests are paper and pencil tests and will be administered by an investigator during one of the first three visits (screening, nicotine exposure session prior to lozenge administration, or first outcome measurement session). The setting is a private room, seated at a table.

-The MATRICS battery is a collection of co-normed measures of verbal and visual episodic and working memory, processing speed, problem solving, sustained attention, and social cognition. Most tests are paper and pencil tests done in interaction with the investigator. One subscale involves performing a ~10-min Continuing Performance Task on a computer. The MATRICS battery will be performed every four weeks in each outcome measurement session.

-The Visual Acuity Test consists of reading a sequence of letters with one eye covered at a certain distance from the chart. Performed during screening.

-The Ishihara Test consists of reading green numbers against a red background or vice versa, or finger-tracing a line. Performed during screening.

-The Change localization task is performed at a computer. One or four colored squares are presented for ~200 ms, and after a ~1-s delay, they reappear. The task is to identify the square that has changed color. Performed on outcome measurement days just before and just after the cognitive training (weeks 0 and 10).

-The Posit Science exercises are performed on a computer. Some exercises provide a progress summary of these parameters after each session, which will be recorded. Other exercises provide a separate assessment tool to monitor progress, which will be performed on outcome measurement days every three to four weeks, together with other outcome measurements (see "Study Procedures").

- The Cogstate battery is performed on a computer and comprises tests of processing speed, attention, learning and memory, and higher cognitive functions.

- 3 * Upload relevant testing materials:

Name	Created	Modified Date
Visual Acuity scoring form	12/11/2013 11:01 AM	12/11/2013 11:01 AM
Ishihara test score form	12/11/2013 10:58 AM	12/11/2013 10:58 AM
MATRICS BACS	12/11/2013 10:58 AM	12/11/2013 10:58 AM
MATRICS Hopkins BVMT	12/11/2013 10:55 AM	12/11/2013 10:55 AM
MATRICS Hopkins BVMT Delay	12/11/2013 10:55 AM	12/11/2013 10:55 AM
MATRICS Hopkins Delay Form 1	12/11/2013 10:54 AM	12/11/2013 10:54 AM
MATRICS Hopkins Immediate Form 1	12/11/2013 10:54 AM	12/11/2013 10:54 AM
MATRICS Mazes	12/11/2013 10:53 AM	12/11/2013 10:53 AM
MATRICS MSCEIT Sections D and H	12/11/2013 10:53 AM	12/11/2013 10:53 AM
MATRICS Trailmaking A	12/11/2013 10:52 AM	12/11/2013 10:52 AM
MATRICS Letter Number Span	12/11/2013 10:51 AM	12/11/2013 10:51 AM
MATRICS Wechsler Memory Scale - 3 Spatial Span	12/11/2013 10:51 AM	12/11/2013 10:51 AM
MATRICS WTAR scoring form	12/11/2013 10:50 AM	12/11/2013 10:50 AM
WASI matrix reasoning subtest	12/11/2013 10:49 AM	12/11/2013 10:49 AM
WASI vocabulary subtest	12/11/2013 10:48 AM	12/11/2013 10:48 AM

- 4 * What is the individual duration of each test and what is the entire duration of all tests?

WASI subtests: 15-30 min

MATRICS battery: 65-75 min

Ishihara test: 3 min

Visual Acuity test: 4 min

Change Localization task: ~10 min

Cognitive training exercise progression tests: ~20 min

Cogstate battery: ~35 min

- 5 * Are any of the questions likely to cause discomfort in participants or cause harm if their confidentiality were breached? (i.e., Illegal activities)

Yes No

- 6 * Do any questions elicit information related to the potential for harm to self or others?

Yes No

- 6.1 If Yes, what procedures are in place to assure safety?

ID: VIEW4E0BC1E3C2800
Name: v2_Testing

View: v2_Sample Collection/Analysis

Sample Collection/Analysis

You indicated on the "Type of Research" page that your study involves a sample (specimen) collection and/or analysis.

- 1 * What type of samples will be involved in this study? (Check all that apply)

Prospective (will be collected)

- 2 * Will genetic analysis/testing be done on any of the samples?

Yes No

- 3 * Will this study involve banking of samples (storing for future research use)?

Yes No

- 4 * What is the purpose of the sample collection and/or analysis?

1) A urine sample will be obtained during screening to perform a urine drug test and a pregnancy test. A urine sample will also be collected from female participants at the beginning of the nicotine exposure session, and every two weeks during the cognitive remediation training, to perform a pregnancy test. A urine sample for a drug test may be requested from any participant at any time should acute or recent intoxication be suspected. The sample will be discarded immediately after the drug and/or pregnancy test has been performed.

2) A 5-ml venous blood sample will be collected before and after the cognitive training intervention. These samples will be analyzed for TNF alpha and potentially other inflammatory markers, to test whether repeated nicotine exposure may modulate inflammatory processes which may be related to cognitive effects.

- 5 * Is there the possibility that cell lines will be developed with any of the samples?
 Yes No

- 6 * Will the samples be released to anyone not listed as an investigator on the protocol?
 Yes No

6.1 If Yes, give name(s) and affiliation(s):

The blood samples will be sent to the University of Maryland Cytokines Core Laboratory (Bressler Research Building) for analysis.

- 7 * Will the sample material be sold or given to any third parties?
 Yes No

7.1 If Yes, give name(s) and address(es):

ID: VIEW4E0E1A4B80000
 Name: v2_Sample Collection/Analysis

View: v2_Prospective Samples

Prospective Samples

You indicated that the study involves collection of prospective samples (specimens).

- 1 * What type of sample will be collected? (Check all that apply)

Blood
Urine

1.1 If Other, specify:

- 2 For blood draws, specify the amount drawn, in teaspoons, at each visit and across the course of the subject's entire participation time:

One teaspoon of blood will be drawn before the cognitive training intervention, and one teaspoon after the intervention, for a total of two teaspoons over the duration of the study.

- 3 * What type of samples will be collected? (Check all that apply)

Samples obtained specifically for research purposes-obtained via a separate collection procedure done solely for the purposes of the study

3.1 If Other, specify:

- 4 * How are these samples labeled? For example, do they contain name, initials, dates, Social Security number, medical record number, or other unique code?

1) The urine test(s) will be performed immediately upon receipt of the urine sample from the participant. Therefore, samples will not be labeled.
 2) The blood samples will be labeled with MPRC ID, study ID, date, sample type, and initials of person collecting the sample.

- 5 * Will sample(s) be made available to the research subject (or his/her medical doctor) for other testing?

Yes No

- 6 * If a participant withdraws from the study, will that participant have the option to get the remaining portion of their sample(s) back?

Yes No

- 7 * If the participant withdraws, explain how their sample(s) will be handled (For example, will sample(s) be destroyed, anonymized, etc.):

1) Urine samples will be discarded immediately after the drug and/or pregnancy test.
 2) Blood samples already obtained will be retained and analyzed even if a participant withdraws.

- 8 * Will the samples be destroyed after the study is over?

Yes No

8.1 If No, describe how the samples will be stored, where they will be stored, and for how long.

ID: VIEW4E0E257D60C00
 Name: v2_Prospective Samples

View: v2_Clinical Trial Registration

Clinical Trial Registration

You indicated on the "Type of Research" page that your study is a clinical trial.

- 1 * Does the UM Clinical Trials Registry policy require registration of this trial?
 Yes No

2 * Has this trial been registered?

Yes No

ID: VIEW4E093BF078C00
Name: v2_Clinical Trial Registration

[View: v2_Clinical Trial Registration Information](#)

Clinical Trial Registration Information

You indicated that this clinical trial has been registered.

1 * Was this trial registered at www.clinicaltrials.gov?

Yes No

2 If no, was this trial registered on a site other than clinicaltrials.gov?

Yes No

2.1 If Yes, specify the name of the other site:

2.2 Provide justification for registering this trial on this site:

3 * Registration Number

NCT02069392

ID: VIEW4E093BF1D0800
Name: v2_Participant Selection

[View: v2_Participant Selection](#)

Participant Selection

1 * How many local potential participants (or specimens/charts) do you anticipate will be screened for this study? **Screening includes determining potential participants' initial eligibility for and/or interest in a study.**

300

2 * How many participants (or specimens, or charts) will be enrolled/used for this study? **A local prospective participant is considered enrolled in the study when a UM-approved Informed Consent Document (not including separate screening consent forms) is signed.**

Local - the number being enrolled at this site:

70

Worldwide - the number being enrolled total at all sites (including local enrollment):

70

3 * Gender:

Male
Female

4 * Age(s):

18 years and older (Adult)

5 * Race/Ethnicity:

All Races Included

6 * Language(s):

English

6.1 Specify Other:

7 * Are you excluding a specific population, sub-group, or class?

Yes No

7.1 If Yes, indicate your justification for excluding a specific population, sub-group, class, etc.:

Pregnant or lactating women will be excluded from participation because nicotine crosses the placenta and is secreted in breast milk. Former smokers will be excluded because nicotine administered as part of the study may act as a priming cue and reinstate smoking.

ID: VIEW4E0E519C1D000
Name: v2_Participant Selection

[View: v2_Vulnerable Populations](#)

Vulnerable Populations

- 1 * Will you be including ANY of the following Vulnerable Populations? (Select all that apply)
Students

You may not include any members of the above populations as subjects in your research unless you indicate this here.

ID: VIEW4E0E519917800
Name: v2_Vulnerable Populations

View: v2_Vulnerable Populations - Students

Vulnerable Populations - Students

You indicated that students are included in this study.

- 1 * Describe the types of students that are included in this study:

Any individual who meets the inclusion/exclusion criteria will be allowed to participate in the study - regardless of whether or not they have student status at any school or university.

- 2 * Describe how you will prevent undue influence.

No special effort is made to recruit students, nor is there any special effort to eliminate them from the eligible pool of subjects. In order to protect the confidentiality of this group as well as of all subjects in this protocol, numbers rather than names will appear on charts, files, and digital data. The code linking the names with the number will be locked with limited access. Records will be kept confidential, with access granted only to those medical and research professionals directly involved with the study. No information that could be linked to any single participant will be reported in publications and presentations. Confidentiality will be protected to the fullest extent permitted by law. Participation of students in the University of Maryland System in research at the MPRC will not in any way affect educational plans or social relationship with the hospital/academic opportunity. The monetary incentive is not coercive. The Informed Consent process will be as outlined below and will not differ from that of other volunteers.

ID: VIEW4E0E519F32000
Name: v2_Vulnerable Populations - Students

View: v2_Eligibility

Eligibility

- 1 * Do you have an existing Eligibility checklist(s) for this study?

Yes No

- 1.1 If Yes, upload here. If you need a template, you can download it by clicking **HERE**. The checklists you upload will also be available under the Documents tab of this application.

Name **Created** **Modified Date**

There are no items to display

- 1.2 If No, create an eligibility checklist below:

List inclusion criteria (List each Inclusion Criteria individually, using the ADD button):

Number Criteria

View 1	Aged 18-60 years.
View 2	DSM diagnosis of schizophrenia or schizoaffective disorder.
View 3	Ability to give written informed consent.
View 4	Either currently smoking and not attempting to quit, or having smoked no more than 80 cigarettes, cigarillos or cigars in lifetime and not at all within the last year.
View 5	Normal or corrected to normal vision (at least 20/50).
View 6	Four weeks of stable pharmacological treatment (same psychiatric medication at same dose) and no foreseeable changes at enrollment.

List exclusion criteria (List each Exclusion Criteria individually, using the ADD button):

Number Criteria

View 1	Alcohol or substance abuse or dependence other than nicotine within the last 12 months.
View 2	Uncontrolled hypertension (resting systolic blood pressure above 150 or diastolic above 90 mm Hg).
View 3	History of myocardial infarction, heart failure, angina, stroke or severe arrhythmias.
View 4	ECG abnormalities (Wolfe Parkinson White syndrome; Myocardial ischemia and infarction; Complete left bundle branch block; PR interval <120 ms or >200 ms; Prolonged QT interval (corrected) >500 ms; Cardiac arrhythmias as defined by PACs >3/min or PVCs >1/min).
View 5	History of neurological conditions such as stroke, seizures, dementia or organic brain syndrome.
View 6	Mental retardation.

Number Criteria

View	7	Pregnant, verified by urine pregnancy test for females.
View	8	Breast-feeding.

After entering the inclusion and exclusion criteria above, click the Save link. CICERO will automatically generate a printable Eligibility Checklist for you to use in your research. To review the checklist, click on the resulting link below. This checklist is also available under the Documents tab of this application.

Eligibility Checklist for HP-00058233_1 v6-9-2014-1402319276253(0.01)

ID: VIEW4E0E5185F9000
Name: v2_Eligibility

View: v2_Recruitment

Recruitment

- 1 * **Describe plans for recruitment, including the identification of potential participants (or acquisition of charts/records/samples) and initial interactions with them: (If this study involves the VA please list all sites at which recruitment will take place.):**

Patients will be recruited from the MPRC and other local clinics. Potential subjects will first be identified by their primary clinicians who are aware of study entry criteria and who will be asked to identify clinically stable subjects who may be interested in participation. An investigator will then individually approach subjects in order to explain the study. Should they express interest in the project, they will be given a copy of the Informed Consent form for review. If they express interest in participating, an appointment will be arranged with the investigator for further explanation of the study/procedures. At this time, agreement to participate will be documented on the Informed Consent form.

- 2 * **Describe measures that will be implemented to avoid participant coercion or undue influence (if not applicable to the study, enter "N/A"):**

During initial contact, potential participants are asked in a non-suggestive manner whether they are interested in learning more about this study. The consent form stresses that the study is voluntary and that there will be no adverse consequences for declining to participate or for ending participation early. Volunteers are not asked to sign the consent form until adequate understanding of the study is formally demonstrated using an evaluation-to-sign-consent procedure developed at the MPRC (uploaded under "Interviews"). After reviewing the consent form, patients are asked to demonstrate their understanding of the study in response to probes that cover the nature of study procedure, the risks that are involved in the study, what they should do if they find study participation upsetting or stressful, and the actions they should take if they wish to end study participation. Participants are required to score at least 10 out of a possible 12 in order to participate in the protocol. Treatment is in no way affected by study participation, and this is stressed on the consent and HIPAA form and by the investigator. The study remuneration is well within norms.

- 3 * **Who will recruit participants (or acquire charts/records/samples) for this study? (Check all that apply)**

PI
Study Staff

- 3.1 If you are using a third party, specify Third Party Recruiters:

- 4 Upload any recruitment tools such as screening/telephone scripts and introductory letters (do not upload advertisements here):

Name	Created	Modified Date
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There are no items to display

ID: VIEW4E0BCAA0A6C00
Name: v2_Advertising

View: v2_Advertising

Advertising

- 1 * **Will you be using advertisements to recruit potential participants?**

Yes No

ID: VIEW4E0BCCFB11000
Name: v2_Advertising

View: v2_Research Related Risks

Research Related Risks

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer box below.

- 1 * **Individually list each research-related risk, using a separate line for each. Next to each risk, delineate the likelihood/seriousness of the risk, and the provisions for minimizing the risk:**

a)

Possible adverse events (AEs) related to the nicotine lozenge administration include:

- Abdominal Pain. This is a relatively unlikely and minor risk.
- Chest pain. This is a moderately serious but unlikely risk.
- Coughing. This is a relatively likely but non-serious risk.
- Diaphoresis. This is a relatively likely but non-serious risk.
- Dizziness. This is a moderately serious but relatively unlikely risk.
- Dry mouth. This is a relatively unlikely and minor risk.

- Headache. This is a moderately likely but relatively minor risk.
- Nausea. This is a moderately likely but relatively minor risk.
- Vomiting. This is a moderately serious but relatively unlikely risk.
- Palpitations. This is a moderately likely but minor risk.
- Injury to mouth, teeth or dental work from consuming lozenges. This is a moderately serious but unlikely risk. This side effect is particularly unlikely in the present study because participants only consume 2 lozenges/week, as opposed to several/day when used for smoking cessation.
- Mild jaw muscle ache. This is an unlikely and minor risk. This side effect is particularly unlikely in the present study because participants only consume 2 lozenges/week, as opposed to several/day when used for smoking cessation.
- Restlessness. This is a relatively unlikely and minor risk.
- Sleepiness. This is a relatively unlikely and minor risk.
- Sore mouth or throat. This is a moderately likely but relatively minor risk.
- Temporary mood changes. This is a relatively unlikely and minor risk.

Risk minimization for all of the above risks:

All effects are temporary and will dissipate spontaneously with the metabolism of nicotine (half-life: 2.3 hours for the lozenge). Only individuals who meet certain medical history criteria will be admitted into the study. Participants will consume at least one lozenge before the training program starts. Subjective and cardiovascular (blood pressure, heart rate) effects of the lozenge will be monitored for 3 hours. This will identify subjects prone to experiencing any greater than expected untoward effects, such as a rise in blood pressure by >20 mm Hg, a rise in HR to >120, or vomiting. Such subjects would be excluded from the trial. Participants with side effects less severe than the above, but which they perceive as disruptive, will receive a further lozenge on a separate day before the start of the training intervention. Due to rapid tolerance to the adverse effects of nicotine, this pre-exposure will reduce unpleasant effects of nicotine during training. Furthermore, participants are asked not to chew the lozenge or swallow it whole. The lozenges dissolve over 10 min, thus enforcing a relatively slow rise in nicotine blood levels.

- Another risk is related to nicotine being an addictive substance. Nicotine addiction would be a serious but very unlikely risk. The likelihood of any reinforcing properties of the nicotine lozenge leading to abuse liability is very low. The abuse liability of a drug depends on the kinetics of drug delivery, such that reinforcing properties are greater for delivery routes associated with faster absorption. Nicotine plasma levels peak approximately 1 hour following administration of a nicotine polacrilex lozenge, and the protracted absorption of nicotine has been shown to not produce subjectively reinforcing effects. There is however a concern that nicotine lozenges may trigger relapse in former regular smokers because the subjective effects, even if not reinforcing in themselves, may be associated with dependent cigarette smoking and dependence-related effects of cigarette-derived nicotine. Thus, lozenge-derived nicotine may act as a priming cue. Risk minimization: Former smokers will not be included in this study.

- Due to potential overlap of smoking-derived and lozenge-derived blood nicotine, some smokers may be exposed to more nicotine than they are used to. However, the slow rise of lozenge-derived blood nicotine will coincide with the metabolism of cigarette-derived nicotine, even if a cigarette was smoked immediately before the session. Thus, side effects due to this scenario are expected to be mild and rare. Risk minimization: Participants are asked not to chew the lozenge or swallow it whole. The lozenges dissolve over 10 min, thus enforcing a relatively slow rise in nicotine blood levels.

- Nicotine may be harmful to a born or unborn baby. It is secreted in breast milk and crosses the placenta. If nicotine was given to a pregnant or lactating female, this risk would be likely and relatively serious. Risk minimization: Pregnant or lactating females are excluded from study participation.

b) Participants may find the cognitive training exercises boring or tiring. This is a likely but non-serious risk.

Risk minimization: The exercises adjust their difficulty to maintain participants' performance at 85%, provide positive reinforcement for correct responses, and are perceptually engaging. Participants may take breaks.

c) Cognitive testing: Participants may find the MATRICS Battery, Change localization task, Posit Science evaluation programs, and other outcome assessments boring, difficult or frustrating. This is a relatively likely but minor risk.

Risk Minimization: Participant may take breaks as needed. If all assessments cannot be performed in one session, they may be completed on a separate day (usually after training on the following Friday, i.e. the next no-lozenge day). Furthermore, many assessments stop when a difficulty level is reached at which the participant's performance brakes off. The testers have extensive clinical experience, conduct assessment sessions in a highly supportive fashion and are accustomed to working with patients in more demanding protocols than the current one.

d) Questionnaires and Characterization Measures: Some of the questions asked may be perceived as embarrassing. This is a relatively likely but minor risk.

Risk Minimization: The confidentiality of all replies will be ensured and emphasized to participants. Participants will be advised during consenting that they may refuse to answer any questions that cause them discomfort.

e) Loss of confidentiality or privacy. This is a serious but unlikely risk.

Risk minimization: All data, including screening data, demographic details and experimental data, will be collected solely for research purposes and will not be shared with any third party except where indicated in the consent form and when instructed in writing by the participant. Strict subject confidentiality will be maintained throughout. Participants are assigned a code number, which will be used throughout the experiment and will be the only identifier on screening documents and on all outcome measures. The identity of participants will not be revealed to any unauthorized person or in any vehicle of public communication. ID codes will be maintained separate from the study data in a secure electronic database, to which only investigators have access.

Medical data will be stored at the MPRC in the ORP Clinical Database. All databases are handled via a local area network (LAN) maintained behind a Netscreen 5XP firewall with multiple layers of protection against unauthorized intrusion. Databases are maintained on the center's server and are additionally protected by a 5-tiered system involving restricted access at the desktop, directory, database, reporting and table levels. Data downloaded will be identified only by subject ID code. In addition, participants may be assigned a medical records folder to store paper copies of medical documents. These charts are kept in locked filing cabinets in a locked room, and access is limited to MPRC study investigators, nursing staff and clinicians. Research data are labeled by ID codes and study number only. This includes participants' PositScience training accounts, which will be created before the start of the intervention. Data from computer tests are backed up onto data drives that can be accessed only via password-protected computers. Hard copies of paper and pencil tests are stored in research folders in a locked cabinet. These data are also entered onto a password protected secured server. Identifiable research records, such as consent forms, are stored in locked cabinets in a locked room.

f) Screening: The EKG electrodes occasionally cause redness and itching. When they are removed, they can pull out hair. This is a moderately likely but minor risk.

Risk minimization: The nurse performing the EKG is experienced in the procedure and will take great care not to hurt the participant.

g) Blood draws:

1. Skin irritation is expected to be rare and of minor severity. Risk Minimization: Blood draws will only be performed by experienced medical or nursing staff.
2. Pain/discomfort is expected to be common but of minor severity. Risk Minimization: Blood draws will only be performed by experienced medical or nursing staff.
3. Weakness or light-headedness is expected to be rare and to dissipate quickly. Risk Minimization: Blood draws will only be performed by experienced medical or nursing staff. Participants will be asked to lie down if experiencing the onset of these symptoms.
4. Syncope is expected to be very rare but is of significant severity if it occurs. Risk Minimization: Blood draws will only be performed by experienced medical or nursing staff. Participants will be asked to lie down if experiencing weakness or light-headedness.
5. Bleeding is expected to be common but of minor severity. Risk Minimization: Blood draws will only be performed by experienced medical or nursing staff.
6. Swelling at the draw site is expected to be rare and of minor severity. Risk Minimization: Blood draws will only be performed by experienced medical or nursing staff.

Potential Benefits and Alternatives

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

1 *** Describe the potential direct benefit(s) to participants:**

There is a possibility that participants will profit from the cognitive remediation training, with or without added nicotine. Participants may experience an improved ability to concentrate or remember information.

2 *** Describe the importance of the knowledge expected to result from the study:**

The potential benefit of the proposed research consists of a proof of principle of a novel treatment approach to improving cognition in schizophrenia. This approach consists of potentiating the effects of cognitive remediation training on cognition, functional capacity and quality of life by intermittently pairing the training exercises with a nicotinic agonist. The benefits to both the individual and society of finding more effective treatments for the cognitive symptoms of schizophrenia would be large. A positive result would also motivate larger-scale studies aimed at optimizing the parameters for pharmacological enhancement of cognitive training interventions.

3 *** Describe how the potential risks to participants are reasonable in relationship to the potential benefits:**

The risks related to administration of nicotine, cognitive training and testing, questionnaire and interview administration, handling of private information, and blood draws will be minimized as outlined above. We consider these risks to be very low in comparison with the scientific and clinical merits to be gained, which may contribute to finding a treatment intervention that can alleviate some of the most debilitating symptoms of schizophrenia.

4 *** Describe the alternatives to participation in this study. If there are no alternatives, state that participation is voluntary and the alternative is not to participate. For intervention studies, describe appropriate alternative clinical procedures or courses of treatment available to subjects.**

Participation is voluntary, and the alternative is not to participate. There are currently no FDA-approved treatments for the cognitive deficits seen in schizophrenia.

ID: VIEW4E1B5251B0400

Name: v2_Potential Benefits and Alternatives

View: v2_Withdrawal of Participants

Withdrawal of Participants

If the questions below are not applicable to the research (i.e., chart review), enter "N/A".

1 *** Describe anticipated circumstances under which subjects will be withdrawn from the research without their agreement:**

Participants may be withdrawn if they display adverse effects of nicotine that would make their continued participation in the study unsafe (see "Study Procedures" for stop criteria), if they cannot or do not follow instructions (for example, will not engage in any of the cognitive exercises despite the individually adjusted difficulty levels), or if a participant is missing too many study days (see "Study Procedures" for criteria of study exclusion).

2 *** Describe procedures for orderly termination:**

Participants are informed that their study participation is terminated, and they are paid for their time up to this time point.

3 *** Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection:**

Withdrawal would end any procedures associated with the study. If participants withdraw or are withdrawn due to nicotine side effects, they will be asked to stay on at the MPRC for continued monitoring until symptoms have subsided and the study physician considers it safe for them to leave.

ID: VIEW4E1B52531F800

Name: v2_Withdrawal of Participants

View: v2_Privacy of Participants

Privacy of Participants

If the study does not involve interaction with participants, answer "N/A" to the questions below.

1 *** Describe how you will ensure the privacy of potential participants throughout the study (*privacy refers to persons and their interest in controlling access to themselves*):**

Informed consent will be obtained in a private room. Medical screening will be performed in the MPRC nursing station, which contains a private exam area. Outcome measurements (cognitive testing, tests and questionnaires of every-day functioning, symptom ratings) will be performed in a private room.

2 *** Describe the location where potential participants will receive research information and detail the specific actions the study team will take to ensure adequate privacy areas:**

Either a clinical caretaker or a study investigator will approach a potential volunteer. Investigators would usually first approach them in a non-private, e.g. waiting, area. If the potential volunteer expresses an interest in hearing about the study, a first description would be given in a separate room. If interested, the volunteer would be invited for the consent and screening session. A more detailed description of all study procedures would be provided during the Informed Consent process, in a private room. Sometimes, potential volunteers will be approached by telephone. The investigator first will ask whether they would like to hear about a study, and will offer to call back later if the call is currently inconvenient.

3 *** Describe potential environmental stressors that may be associated with the research:**

The daily training sessions require transport to and from the MPRC for most participants. Participants who can drive themselves will be asked to drive daily. Other participants will be provided a cab, or the MPRC driver will transport them. Training will be canceled on days on which driving would be unsafe. No environmental stressors are anticipated for the remaining portions of the study. Research activities take place in quiet rooms behind closed doors.

ID: VIEW4E1B525B87C00

Name: v2_Privacy of Participants

View: v2_Confidentiality of Data

Confidentiality of Data

- 1 * Will stored research data contain identifiers or be able to be linked to and identify individual participants (either directly or through a code/research ID)?

Yes
 - 2 * Where will research data be kept (address electronic and paper data as applicable)? (If this is a VA study please list specific sites that data will be kept.)

All paper records of research data are labeled by subject ID code and are locked in filing cabinets. Access is limited to MPRC study personnel. Records containing the participant's name, such as consent and HIPAA forms, payment forms, inclusion/exclusion checklists etc., are stored in locked cabinets in a locked room, separate from files containing research data. Data from computer tests, identified only by participant number, are backed up onto the MPRC Neuropsychology Branch data drive. Most data recorded on forms will also be entered into secure databases.
 - 3 * How will such data be secured?

Records containing subject names are kept in locked filing cabinets in a locked room. All research data are labeled by MPRC number and study number. Research folders are stored in a locked cabinet. All databases are handled via a local area network (LAN) maintained behind a Netscreen 5XP firewall with multiple layers of protection against unauthorized intrusion. Databases are maintained on the center's server and are additionally protected by a 5-tiered system involving restricted access at the desktop, directory, database, reporting and table levels. All databases are maintained and monitored by a professional data manager. Data downloaded from either database will be identified only by participant number.
 - 4 * Who will have access to research data?

Access to research data is limited to the Principle Investigator, Sub-investigators and team members listed on this protocol. The study nurse will have access to medical screening information. All individuals who will be reviewing or receiving identified study data are on the research team for this protocol. An exception is if a participant requests the release of medical screening data to a third party in writing. Furthermore, regulatory personnel from authorized entities will also have access to research data.
 - 5 * Will study data or test results be recorded in the participant's medical records?

Yes No
 - 6 * Will any data be destroyed? (Please note that data for FDA regulated research and VA research cannot be deleted)

Yes No
- 6.1 If Yes, what data (e.g., all data, some recordings, interview notes), when and how?
- 7 Do you plan to obtain a Certificate of Confidentiality?

Yes No
- 7.1 If Yes, upload your Certificate of Confidentiality. If you have not yet obtained the Certificate, please note that once it is obtained, you will need to submit an amendment to attach the document, make any needed changes to the submission and make needed changes to the Informed Consent Document.

Name

Certificate of Confidentiality

Created

12/11/2013 2:36 PM

Modified Date

6/9/2014 9:05 AM

- 8 * Discuss any other potential confidentiality issues related to this study:

None.

ID: VIEW4E1B5265E0400
Name: v2_Confidentiality of Data

View: v2_Monitoring Plan Selection

Monitoring Plan Selection

- 1 * Type of data safety monitoring plan for the study:

Data Safety Monitoring by a Committee

ID: VIEW4E1B00E30D400
Name: v2_Monitoring Plan Selection

View: v2_Monitoring Plan - Committee

Monitoring Plan - Committee

You indicated that the monitoring will be done by a Committee.

- 1 * Will the Committee be Internal or External?

Internal DSMB
 - 2 * What data will be reviewed?

Adverse Events
Enrollment Numbers
- 2.1 If Other, specify:

- 3 * What will be the frequency of the review?

Annually

- 3.1 If Other, specify:

- 4 * Safety monitoring results will be reported to:

IRB

- 4.1 If Other, specify:

ID: VIEW4E1B025761800
Name: v2_Monitoring Plan - Committee

View: v2_Monitoring Plan - Internal DSMB

Monitoring Plan - Internal DSMB

You indicated that the monitoring committee will be an internal DSMB.

- 1 * List Internal DSMB Members:

Name

View Charles Richardson, M.D.

View Julie Kreyenbuhl, Pharm.D.

View Clayton Brown, Ph.D.

View Glenda Housel, M.D.

View Scott Aaronson, M.D.

View Robert McMahon, Ph.D.

- 2 * Confirm that no financial or other conflicts of interest exists for the above individuals.

Yes No

- 3 * Will there be an interim efficacy analysis?

Yes No

- 3.1 If Yes, when?

- 4 * Briefly describe the DSMB review process itself. Will it be an open or closed review to the investigator? Blinded/unblinded data? How will confidentiality of individual participant data be maintained?

The standing MPRC DSMB will oversee this greater than minimal risk protocol. The Principle Investigator is invited to meetings at which the protocol is discussed. Because identifying information is not kept with research data, data can be safely reviewed without disclosure of private information. Data is presented in aggregate and participants' names or identifying information is not used in discussions. The DSMB will: 1) review the proposed protocol and consent forms; 2) evaluate recruitment and rate of enrollment in relation to study targets; 3) monitor the occurrence of reportable events and early withdrawals or terminations; 4) review the study data management system; 5) establish stop rules for the study as a whole. All serious adverse events (SAEs) will be reported to the DSMB, PI, and the University of Maryland School of Medicine IRB. The PI will receive all SAE reports within 24 hours of their occurrence and forward them appropriately. The PI and DSMB will determine whether possible protocol modifications are required to minimize the further occurrence of such events.

- 5 * What are the criteria defined in the protocol to be used for decision making regarding continuation, modification, or termination of study?

Early study termination of the study will be considered in the event of a subject death, seizure, or other unexpected serious adverse event determined to be possibly, probably or definitely related to study drug. Modifications such as changes in recruitment goals or study timeline will be based on enrollment milestones and will be reported to the DSMB and the IRB. Otherwise, the research will continue as projected.

ID: VIEW4E1B0261D9400
Name: v2_Monitoring Plan - Internal DSMB

View: v2_Research Related Costs

Research-Related Costs

- 1 * Is the study's financial supporter (e.g., commercial sponsor, federal or state grant or contract, private foundation, physician-sponsor) covering any research-related costs?

Yes

- 1.1 If Yes, check all that apply:

Research-Related Services (personnel costs, tests, supplies, exams, x-rays, or consultations required in the study)
Investigational or Study Drug

- 1.2 If No, who is responsible for payment?

- 2 * Who is responsible for the uncovered research-related costs?

There will be no uncovered research-related costs

- 2.1 If Other, specify:

- 3 If the participant is responsible for any research-related costs, identify and estimate the dollar amount:

ID: VIEW4E1B5D9641800
Name: v2_Research Related Costs

View: v2_Compensation for Research-Related Injury

Compensation for Research-Related Injury

- 1 * Is this study under a master agreement that includes a provision requiring the sponsor to provide compensation to participants for research-related injury?

Yes No

- 1.1 If Yes, please provide the date and title of the agreement and upload the portion of the contract language relevant to compensation for research-related injury:

Name	Created	Modified Date
------	---------	---------------

There are no items to display

- 1.2 If No (the study is not under a master agreement), is there proposed contract language concerning payment to participants for treatment in the event of a research-related injury?

Yes No

- 1.2.1 If Yes, indicate the status of the contract review/approval with the ORD and upload the proposed language relevant to compensation for research-related injury:

Name	Created	Modified Date
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There are no items to display

ID: VIEW4E1B629EEC000

Name: v2_Compensation for Research-Related Injury

View: v2_Payment to Participants

Payment to Participants

- 1 * Will participants receive payment (money, gift certificates, coupons, etc.) for their participation in this research?

Yes No

ID: VIEW4E1C52A5D7800

Name: v2_Payment to Participants

View: v2_Payment Detail

Payment Detail

You indicated that participants will receive payment (money, gift certificates, coupons, etc.) for their participation in this research.

- 1 * Payment to participants will be for: (check all that apply)

Meals

Time and effort

- 1.1 If Other, specify:

- 2 * What is the total dollar value of the payments over the duration of the study? **Total payment(s) for participation in research of \$600 or more is required to be reported on an IRS Form 1099.**

up to \$810

- 3 * Describe the timing and distribution plan for the payment (schedule, means, etc.)?

Participants will be paid \$10 for each completed day, an additional \$20 for each outcome measurement day, \$10 for each completed week without omitted days, and \$50 for completing the entire study including the follow-up session in week 14. Payment will be processed upon completion of the study, or when the participant decides to discontinue the study. If a participant requests more frequent intermittent payment, payment may be processed on an, e.g., weekly basis.

- 4 * Method(s) of payment to be Used:

Check

Other

4.1 If Other, specify:

Lunch vouchers may be provided on outcome measurement days.

ID: VIEW4E1C54A6ACC00
Name: v2_Payment Detail

View: v2_HIPAA

HIPAA (Health Insurance Portability and Accountability Act)

- 1 * HIPAA applies to the University of Maryland School of Medicine, the University of Maryland School of Dentistry and the VA. Are you affiliated with, or will be accessing data from, any of these places? Yes No
- 2 If Yes, will the study view, access, share, collect, use, or analyze health information that is individually identifiable under HIPAA? Yes No

ID: VIEW4E1B0A2114400
Name: v2_HIPAA

View: v2_Protected Health Information

Protected Health Information (PHI)

You indicated that HIPAA applies and the study will view, access, share, collect, use, or analyze health information that is individually identifiable.

- 1 * Which PHI elements will be used or disclosed in this study? (Check all that apply)
- Name
Address (if more specific than Zip Code)
Dates
Telephone numbers
Email addresses
Social Security numbers
- 2 * Why is the PHI necessary for this research?
If SSNs are going to be used, describe the specific use and type of SSN to be used (real, scrambled, last 4 digits).
The name and address are needed to issue and mail the check. Date of birth is needed to verify the age inclusion criterion. Telephone number and e-mail address are for scheduling study appointments.
The Social Security Number (SSN) is requested of an individual the first time they enroll in a study. The SSN is requested so that the University may be compliant with IRS reporting requirements for aggregate payments exceeding \$600. The SSN information is stored for about 5 years following the participant's last study payment. Thereafter this information is destroyed using secure shredding. Forms with SSN information are stored in locked cabinets which are accessible only to approved staff individuals.
- 3 * What is the source(s) of the PHI?
The participant (driver's licence for name and age). In rare cases, the participant's physician may be contacted, with the participant's written permission, to verify or clarify health information relevant to testing the study inclusion/exclusion criteria. The participant may also be asked if they would obtain this information from their physician to share with the study team
- 4 * Provide written assurance that Protected Health Information will not be reused. (Note: this refers to re-use on another study or for a purpose which has not been approved, not to the re-use of screening data during the current study).
Protected Health Information will not be reused for any other study, or for any purpose which has not been approved.
- 5 * How will permission to allow the use/disclosure of the individual's protected health information (PHI) be obtained? (Choose all that apply):
Obtain written authorization (*upload authorization form at the end of the application under "Consent and HIPAA Authorization Forms"*)
Requesting waiver/alteration of authorization (includes waiver of authorization for recruitment only)

5.1 If you are using a limited data set (LDS), please attach the Data Use Agreement (DUA):

Name	Created	Modified Date
------	---------	---------------

There are no items to display

ID: VIEW4E1B0A24AA400
Name: v2_Protected Health Information

View: v2_Waiver/Alteration of Authorization

Waiver/Alteration of Authorization

You indicated that a waiver/alteration of authorization is requested.

- 1 * Provide rationale for how the research presents no more than minimal risk to the privacy of individuals:
PHI for this study will be protected from improper use and disclosure and will not be reused or disclosed to any other person or entity, except as required by law for authorized oversight of the research study, or for other research for which the use or disclosure of the requested information would be permitted by the HIPAA Privacy Rule.
- 2 * Describe the plan to ensure the protection of PHI collected during this study from improper use and disclosure:
PHI for this study will not be reused or disclosed to any person or entity not involved with the study, except as required by law for authorized oversight of the research study, or for other research for which the use or disclosure of the requested information would be permitted by the HIPAA Privacy Rule. All source documentation for

the study will be kept in a locked cabinet in a locked room. Data for the study will be entered onto a secured server. No publication of study results will disclose information that could be linked to a single participant.

- 3 * **Describe the plan to destroy the PHI collected during this study at the earliest opportunity consistent with the conduct of the research. If there is a need to retain PHI, provide a justification:**
PHI collected during a study will be destroyed 7 years following the closure of the study.
- 4 * **Why could the research not practicably be done without access to and use of this PHI?**
This research could not practicably be done without access to and use of PHI because such access allows for efficient screening of individuals. A review of PHI in chart or electronic records will increase the likelihood that only individuals who meet certain readily discernible eligibility criteria are approached as potential study participants.
- 5 * **Why could the research not practicably be done without the waiver or alteration?**
If all volunteers first had to provide Informed Consent before we could check some basic inclusion and exclusion criteria, this procedure would be very costly in terms of investigator and volunteer time and lead to a very large proportion of screening failures.
- 6 * **Will the subjects' PHI be disclosed to (or shared with) any individuals or entities outside of UM?**
 Yes No

- 6.1 If Yes, describe the individuals or entities outside of UM to whom PHI will be disclosed.

ID: VIEW4E1B0A2896400
Name: v2_Waiver/Alteration of Authorization

View: v2_Informed Consent Process

Informed Consent Process

If the study does not involve interaction with participants or a waiver of consent is being requested , answer "N/A" to the questions below.

- 1 * **Indicate the type(s) of consent that will be involved in this study: (check all that apply)**
Written Consent Form
- 2 * **Describe the Informed Consent process in detail:**
Written informed consent will be obtained from each subject at entry into the study by the following process: The subject reviews the study consent form. If desired, they will be given the opportunity to review the consent before the session. When the investigator meets with the volunteer, he/she first reviews the HIPAA "Authorization To Obtain, Use And Disclose Protected Health Information For Research". If this authorization is signed, the investigator then reviews the consent form with the candidate and encourages and answers any questions. This process will include reading through the document with the participant. Volunteers are then required to complete an Evaluation to Sign Consent with the investigator in the presence of a third-party witness, and may not sign the consent form until they have thus demonstrated understanding of study demands, study risks, what they should do if they experience distress or to end participation, and that participation does not require any change in treatment. If necessary, the consent documents will be reviewed several times to ensure comprehension. The consent is then signed by the participant, the PI and a third-party witness to the subject's signature. All participants are given a copy of the consent form for their records, a second copy is attached to their clinical chart, and a third copy is stored with other protocol consents in a master enrollment study binder. Once the signed consent has been obtained, the investigator will note the participant's study enrollment in a secure database.
- 3 * **Confirm that the consent process will explain the following:**
 - The activities involve research.
 - The procedures to be performed.
 - That participation is voluntary.
 - The name and contact information for the investigator.
- Yes No
- 4 * **Describe who will obtain Informed Consent:**
The PI, any physician or Master's level clinical psychologist on the study, or a research assistant administering the cognitive training or study assessments may obtain Informed Consent.
- 5 * **If obtaining consent from a legally authorized representative (LAR), describe how you will confirm that the individual is the LAR and can provide legally effective informed consent. (Answer "N/A" if not obtaining consent from LARs)**
N/A
- 6 * **Describe the setting for consent:**
The setting is sitting at a table in a room with the door shut for participant privacy.
- 7 * **Describe the provisions for assessing participant understanding:**
Volunteers are encouraged to ask questions throughout the consent process and are required to verbally demonstrate comprehension. If necessary, the consent documents will be reviewed several times to ensure comprehension. During the Evaluation to Sign Consent process, performed in the presence of a third-party witness, participants are asked about study demands, study risks, what they should do if they experience distress or to end participation, and whether participation requires any change in treatment. A score of at least 10 out of 12 is needed before the volunteer may sign the consent form.
- 8 * **Describe the consideration for ongoing consent:**
Participants who are actively involved in the study are re-consented if there is a significant change in the consent form, such as if there is a change in study

procedures. Participants will also be re-consented if a period of more than 3 months has elapsed since their last study visit, such as if there are scheduling problems after the consent and screening visit or after the nicotine toleration session.

ID: VIEW4E1C661D0AC00
Name: v2_Informed Consent Process

View: v2_Consent Forms - Draft

Consent and HIPAA Authorization Forms - Draft

- 1 Upload all of your Consent Forms for approval. Use only Microsoft Word.

Name	Created	Modified Date
Consent form	12/13/2013 12:19 PM	2/8/2016 4:35 PM

IMPORTANT NOTE: the above list of consent forms (if any) are DRAFT versions. Under no circumstances should copies of these be distributed to patients/study subjects. If/when this research submission is approved by the IRB, approved consent forms will be available for download and use from the "Documents" tab of the Submission's workspace (click Exit and then look for the Documents tab - approved submissions only)

- 1A Archived Consent Forms:

Name	Created	Modified Date
There are no items to display		

- 2 Upload any HIPAA authorization forms here:

HIPAA form	12/13/2013 12:21 PM	12/13/2013 12:22 PM
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Please refer to HRPO's website for specific instructions for preparing informed consent documents and to access current templates:
<http://hrpo.umaryland.edu/researchers/consents.html>

ID: VIEW4E1C7712D3000
Name: v2_Organization Review Requirements - Draft

View: v2_Organization Review Requirements (other than IRB)

Organization Review Requirements (other than IRB)

Answer the following questions to determine additional organizational review requirements:

- 1 **Department/Division Review** - All research submissions are required to undergo department/division/institutional review prior to IRB review. The following entity is listed as the required department/division/institutional review:

Maryland Psych Research Ctr

If this information is incorrect, please notify the HRPO office.

- 2 **RSC Review Criteria** - select 'Yes' if the answer is 'Yes' for any of the following questions. Review by the Radiation Safety Committee may be required.

* 2.1 Does the research involve the use of ionizing radiation?

Yes No

2.2 Does the research involve the sampling of radioactive human materials for subsequent use or analysis in a laboratory?

- 3 **IBC Review Criteria** - select 'Yes' if the answer is 'Yes' for any of the following questions. Review by the Institutional Biosafety Committee may be required.

* 3.1 Does the research involve human gene transfer?

Yes No

-OR-
Does the research specifically apply to human studies in which induction or enhancement of an immune response to a vector-encoded microbial immunogen is the major goal, and such an immune response has been demonstrated in model systems, and the persistence of the vector-encoded immunogen is not expected? This type of research is often referred to as recombinant vaccine trials.

3.2 Does the research involve the exposure of human subjects to pathogenic microorganisms, or the

exposure of research staff to human subjects or samples known or reasonably expected to carry infectious disease(s)?

3.3 Does the research involve the sampling of materials from persons with no known infectious disease and where the only risk to study staff is occupational exposure to bloodborne pathogens as defined by the OSHA Bloodborne Pathogen Standard?

- 4 **Cancer Center Criteria** - Answer the following to determine if review by the Cancer Center (Hematology-Oncology) may be required.

* Does the protocol involve in any way studies related to the prevention, treatment, diagnosis, or imaging of neoplastic diseases? Yes No

- 5 **General Clinical Research Center Review Criteria** - the GCRC offers free and/or cost shared resources for patient-oriented research. [Click Here for more information.](#)

Answer the following to determine if review by the GCRC may be required.

* Will the General Clinical Research Center (GCRC) facility or resources be used to conduct this activity? Yes No

- 6 **VA Review Criteria** - Answer the following questions to determine if review by the VAMHCS R&D Committee may be required.

* 6.1 - Will the research be conducted by VA Investigators including PIs, Co-PIs, and Site Investigators on VA time (serving on compensated, WOC, or IPA appointments)? Yes No

* 6.2 - Will the research utilize VA resources (e.g., equipment, funds, medical records, databases, tissues, etc.)? Yes No

* 6.3 - Will the research be conducted on VA property, including space leased to and used by VA? Yes No

PLEASE NOTE that the research may be funded by VA, by other sponsors, or may be unfunded.

ID: VIEW4E1AF91AB2400

Name: v2_Organization Review Requirements (other than IRB)

[View: v2_Institutional Biosafety Committee Review Required](#)

Institutional Biosafety Committee Review Required

- 1 **NOTE:** based on your answers to questions on a previous page (see below) review by the Institutional Biosafety Committee (IBC) is required. This will involve extra steps on your (study team) part. Clicking the Continue button will result in the system creating a blank IBC Submission form for you. You will be required to fill out and submit this IBC form before you will be able to submit the Protocol form. The IBC Submission workspace and form can be reached by clicking the appropriate button on the left hand side of the Protocol submission's workspace (web page) after exiting the Protocol form.

- 2 **Question** - answered on IBC RSC review requirements page:

Yes

3.1 Does the research involve human gene transfer? - OR - Does the research specifically apply to human studies in which induction or enhancement of an immune response to a vector-encoded microbial immunogen is the major goal, and such an immune response has been demonstrated in model systems, and the persistence of the vector-encoded immunogen is not expected? This type of research is often referred to as recombinant vaccine trials.

3.2 Does the research involve: a) the exposure of human subjects to pathogenic microorganisms, or b) the potential exposure of UMB research staff to infectious materials through the sampling or processing of materials from patients with known infectious disease or from environmental surfaces?

3.3 Does the research involve the sampling of materials from persons with no known infectious disease and where the only risk to study staff is occupational exposure to bloodborne pathogens as defined by the OSHA Bloodborne Pathogen Standard?

If the answer to this question is wrong, an IBC submission is not required, use the Jump To menu or your browser's <

- 3 * **Confirm** - you have read the above information and understand that in addition to the IRB Protocol form, you will fill out and submit the IBC Submission form :

Yes No

ID: VIEW4E1AF91ED4C00

Name: v2_Institutional Biosafety Committee Review Required

[View: v2_Summary of Required Reviews \(other than IRB\)](#)

Summary of Required Reviews (other than IRB)

- 1 **Additional Committee Reviews** - Based on your responses to the previous questions, you have identified the following additional reviews. To complete or view these additional committees' forms, click on the links below or exit this application and click on the appropriate button on left side of this submission's webpage.

Name of Related Submission

IBC: Nicotinic Enhancement of Cognitive Training (HP-00058233_3)

Workspace

SmartForm

- 2 Required Department and Specialty Reviews** - Based on the PI's organization (department, division, etc.) affiliation and answers to previous questions (use of Cancer Center, etc.), the organizations listed below are required to review this application. These reviews are conducted online and no additional forms or steps by the study team are required.

Name of Organization
Maryland Psych Research Ctr

Review Status
Complete

ID: VIEW4E1C8D9AE4000
Name: v2_Summary of Required Reviews (other than IRB)

[View: v2_Additional Documents](#)

Additional Documents

- 1 Upload all additional documents here:**

Name	Created	Modified Date
Cogstate Terms of Use	6/9/2014 10:11 AM	6/9/2014 10:11 AM
DSMB Minutes 2014	6/9/2014 9:03 AM	6/9/2014 9:03 AM

ID: VIEW4E0962513A000
Name: v2_Additional Documents

[View: v2_Final Page of Application](#)

Final Page of Application

You have reached the final page of this application. It is recommended that you click on the "Hide/Show Errors" link on the upper or lower breadcrumb row of this page. The "Hide/Show Errors" will do a search of your application, and highlight areas that are required or need to be completed prior to submitting.

By submitting this application, you are electronically routing the protocol for departmental scientific review and all other necessary reviews. According to information you have provided, this application will be routed to the following Departments for review prior to being forwarded to the IRB for review. These reviews are conducted online and no additional forms or steps by the study team are required.

Name of Organization
Maryland Psych Research Ctr

Review Status
Complete

Required Safety Committee Reviews - In addition to the IRB, the following committees must review this submission. Each additional committee has a separate online form that the study team will be required to fill out. All committee applications (IRB plus those listed here) must be completed properly before the 'package' of applications can be submitted. The team may complete these additional forms in any order or at any time prior to submission of the IRB Application. To complete or view these additional committees' forms, click on the links below or exit this application and click on the appropriate button on left side of this submission's Workspace.

Name of Related Submission

IBC: Nicotinic Enhancement of Cognitive Training (HP-00058233_3)

[Workspace](#) [SmartForm](#)

You may check the progress of your application at any time by returning to the Workspace of this submission. A detailed history, including notes, dates, and times of events, is provided to you for this purpose.

If a reviewer returns the application to you, you must address their concerns and resubmit the protocol for review to all designated departments. After all departments have reviewed the application, it will automatically be sent to the IRB for review. Changes made to the submission after its approval must be submitted as modifications.

Investigator Attestation

By submitting this application, I, the Principal Investigator (PI), certify that the information provided in this application is complete and correct. Research will be conducted according to the submission as described, only by the approved principal investigator and study team members.

In addition, I agree to the responsibilities of a PI, including:

- Obtaining informed consent (if applicable) from all subjects as outlined in the submission.
- Reporting new information to the IRB per the requirements of the Investigator Manual.
- If Required, obtaining renewal of the protocol prior to the expiration of the approval period or halt all study activities upon study expiration.
- Accepting ultimate responsibility for the protection of the rights and welfare of human subjects, conduct of the study and the ethical performance of the project.
- Ensuring performance of all research activities by qualified personnel according to the IRB approved submission.
- Ensuring that research personnel have or will receive appropriate training.
- Ensuring no changes will be made in the research until approved by the IRB (except when necessary to eliminate apparent immediate hazards to subjects).

[Click the "Finish" button and then click "Submit Application" in the submission Workspace.](#)

ID: VIEW4E1B10C500000
Name: v2_Final Page of Application

[View: IRB - Add a Team Member](#)

Add a Team Member

- 1 * Select Team Member:
Franklin Blatt
- 2 Research Role:
Research Team Member
- 3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
 Yes No
- 4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
 Yes No
- 5 * Does this study team member have a financial interest related to this research?
 Yes No
- 6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Franklin Blatt, PharmD, is the research pharmacist at the Maryland Psychiatric Research Center. He is responsible for storage, blinding, and dispensing of drugs.

[View: IRB - Add a Team Member](#)

Add a Team Member

- 1 * Select Team Member:
Ann Kearns
- 2 Research Role:
Other
- 3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
 Yes No
- 4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
 Yes No
- 5 * Does this study team member have a financial interest related to this research?
 Yes No
- 6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Ann Kearns- Has worked in a variety of psychiatric settings over the past 18years. She has 12 years of experience at the Maryland Psychiatric Research Center, performing a variety of research activities, and regulatory compliance work

[View: IRB - Add a Team Member](#)

Add a Team Member

- 1 * Select Team Member:
James Gold
- 2 Research Role:
Sub-Investigator
- 3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
 Yes No

- 4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:

Yes No

- 5 * Does this study team member have a financial interest related to this research?

Yes No

- 6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:

James M. Gold, PhD; Clinical Psychologist over 25 years of experience as a clinical investigator with a focus on the application of cognitive neuroscience approaches to understanding the cognitive and motivational impairments of schizophrenia. Serves as PI on multiple UMB research protocols; supervises conduct of cognitive and neurophysiological measures under those protocols in his laboratory, as well as in collaboration with other investigators using cognitive endpoints in their studies.

[View: IRB - Add a Team Member](#)

Add a Team Member

- 1 * Select Team Member:

Marie Yuille

- 2 Research Role:

Research Team Member

- 3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.

Yes No

- 4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:

Yes No

- 5 * Does this study team member have a financial interest related to this research?

Yes No

- 6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:

Marie Yuille is an undergraduate student of psychology in her senior year. She has been involved in research projects as part of her course work. She will work under close supervision of other study staff.

[View: IRB - Add a Team Member](#)

Add a Team Member

- 1 * Select Team Member:

Robert Buchanan

- 2 Research Role:

Sub-Investigator

- 3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.

Yes No

- 4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:

Yes No

- 5 * Does this study team member have a financial interest related to this research?

Yes No

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:

Robert W. Buchanan, M.D. is a Psychiatrist with over 25 years of experience as a clinical investigator with a focus on descriptive studies of the phenomenology of schizophrenia; the conduct of structural and biochemical neuroimaging studies; and the conduct of clinical trials, which range from proof of concept Phase 1B and 2a studies to Phase 4 post-marketing studies. I have served as P.I. on multiple UMB research protocols, as well as worked in collaboration with other investigators in the conduct of descriptive, neuroimaging, and clinical trials. I am very familiar and knowledgeable about the study sites, culture and society related to working on this protocol.