The following document is the IRB-approved study protocol. It was downloaded on Dec 28, 2022.

The last Continuing Review approved the study from April 19, 2022 through April 18, 2023.

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

APPROVAL OF RESEARCH NOTIFICATION

OF NOTE: The Principal Investigator should review the University of Maryland Baltimore criteria for performing research during the current COVID-19 pandemic emergency. Understand that IRB approval of this research does not suggest that performance of this research under current guidelines is allowed. Failure to comply with the UMB President's directives would be considered non-compliance. The UMB Research directives can be found at https://www.umaryland.edu/coronavirus/ . If you need clarification or guidance please call the Human Research Protections Office at 410-706-5037.

Date: April 21, 2022

To: Britta Hahn
RE: HCR-HP-00086422-3
Type of Submission: Continuing Review
Type of IRB Review: Full Board

Approval for this project is valid from 4/19/2022 to 4/18/2023

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, "*Cigarette Smoking in Smokers With and Without a Diagnosis of Schizophrenia*".

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 160 local participants.

This study is approved to enroll 160 worldwide participants.

Below is a list of the documents attached to your application that have been approved:
DSMB minutes 2021(0.01)
Consent and HIPAA form
Eligibility Checklist for HP-00086422_2 v7-14-2021-1626273388214
NIDA grant application
Research Match Contact Message
Telephone screening script
Flyer with tear-offs with transportation
Flyer without tear-offs with transportation
Flyer without tear-offs VA

Flyer with tear-offs VA
Flyer with tear-offs
Flyer without tear-offs
Nicoderm CQ
NOT-DA-14-004: NIDA Research Cigarettes
FDA Letter of No Concerns
Evaluation to sign consent
Structured Clinical Interview for DSM
Modified Cigarette Evaluation Questionnaire
Psychiatric Medication Form
Nicotine Use Questionnaire
Nicotine Dependence Questionnaire
Questionnaire for Smoking Urges
Non-Psychiatric Medication Form
Affect-based Withdrawal Scale
Cigarette Discrimination Questionnaire
Side effects checklist
Minnesota Tobacco Withdrawal Scale
Medical History Pre-screen
Wechsler Test of Adult Reading
MCCB Reasoning/Problem solving (Mazes)
WASI Vocabulary subtest
WASI Matrix Reasoning
Debriefing Letter
UMB-COVID-Risk-Statement-09.2020-FINAL.docx

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 participant's 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 4/18**/2023**.** 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 **4/18/2023**. 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.

UNIVERSITY of MARYLAND BALTIMORE

Date: Wednesday, December 28, 2022 1:00:46 PM Print Close

HP-00086422 Introduction Page_V2

Introduction Page

1 * Abbreviated Title:
Cigarette Smoking in Schizophrenia

2 * Full Title:
Cigarette Smoking in Smokers With and Without a Diagnosis of Schizophrenia

3

* Select Type of Submission:

- (●) **IRB Application**
- ( ) Humanitarian Use Device (for FDAapproved Indication & non-research purposes ONLY)
- ( ) Single Patient Expanded Access (pre-use)
- ( ) Single Patient Emergency Use (post-use)
- ( ) Unsure if this proposal requires IRB review (Not Human Subject Research)

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

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

CITI Training: ID00007425

1.1 * Does the Principal Investigator have a potential conflict of interest, financial or otherwise, 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:
Britta Hahn

CITI Training: ID00007425

2.1 Does the Point of Contact have a potential conflict of interest, financial or otherwise, 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?	CITI Training
View	[redacted]	no	no	Research Team Member	no	
View		no	no	Research Team Member	no	
View		no	no	Research Team Member	no	ID00011488
View		no	no	Research Team Member	no	ID00008549
View		no	no	Research Team Member	no	
View		no	no	Research Team Member	no	ID00007003
View		no	no	Research Team Member	no	ID00008357
View		no	no	Research Team Member	no	
View		no	no	Research Team Member	no	ID00007376
View		no	no	Research Team Member	no	
View		no	no	Research Team Member	no	ID00010389
View		no	no	Research Team Member	no	ID00008573
View		no	no	Research Team Member	no	ID00006126
View		no	no	Research Team Member	no	

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

ID: VIEW4DF85C16F2800
Name: v2_Research TeamInformation

HP-00086422 Resources_V2

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:
Clinical:
The proposed study will be conducted at the Maryland Psychiatric Research Center (MPRC, Director: Robert Buchanan) in Baltimore, Maryland. The MPRC is a University of Maryland School of Medicine (UMSOM) Organized Research Center, which resides within the UMSOM Department of Psychiatry. It is an internationally recognized research center and one of the leading institutions in the world dedicated to the treatment of those with severe psychotic disorders. The MPRC is dedicated to conducting research and education of the manifestations, causes, and treatment of schizophrenia and related disorders.
Twenty basic science and clinical PIs work in the same facility and have created a fertile environment for translational research. The MPRC consists of four programs: the Outpatient Research Program (ORP) headed by Dr. Robert Buchanan, the Treatment Research Program (TRP, inpatient) headed by Dr. Deanna Kelly, the Neuroimaging Research Program (NRP) headed by Dr. Elliot Hong, and the Neuroscience Program headed by Dr. Robert Schwarcz.
The current project will be predominantly based in the ORP, but will use TRP facilities for the smoking sessions, and will recruit from all three clinical programs (and from other clinics and providers in the area). Each clinical program has a separate patient pool totaling ~225 patients. The ORP is an outpatient clinic for people with schizophrenia, including 9000 square feet of space, and providing clinical care to ~100 patients. Its research focuses on clinical trials of novel schizophrenia medications and interventions, and on neuropsychological and cognitive neuroscience studies of cognition, motivation and emotion.
The ORP houses all necessary clinical facilities (fully equipped nurses' station, pharmacy, waiting areas, testing rooms), clinical personnel (nurses, physicians, social workers, neuropsychologists, and a pharmacist) experienced with the conduct of such trials, data management resources, and biostatistics support. This facilitates the coordination of medical screenings and clearances, randomization, blinded drug dispensing, clinical support, and data management. Unique to the MPRC is the close physical and interpersonal proximity of all components, which facilitates a smooth interplay of clinical, research and administrative procedures.

Research laboratory setting:
Designated testing rooms are available in the ORP for consenting, paper-pencil testing, and computer testing. A ventilated smoking suite, approved by the fire and safety administration at Spring Grove Hospital, is available in the TRP. The room is private, ~169 square feet, and is designed to house computer equipment. A slot in the door allows passing through materials. The TRP also houses a dayroom equipped with TV, DVDs, books, magazines, and internet access.

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 always be on call. Medical equipment is available in the nurse's station. In the case of any medical emergency, medical services would be called and the participant transferred to a hospital. Should a participant experience any distress, the PI, nurses, psychiatrists, and social workers are on site and could speak with them.

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 any emergency, 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

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

There are no items to display

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:

- ☐ University of Maryland, Baltimore
- ☐ University of Maryland, Upper Chesapeake Kaufman Cancer Center
- ☐ VAMHCS
- ☐ UMB School of Medicine
- ☐ Marlene and Stewart Greenebaum Cancer Center
- ☐ University Physicians Inc.
- ☐ Shock Trauma Center
- ☐ General Clinical Research Center (GCRC)
- ☑ **Maryland Psychiatric Research Center (MPRC)**
- ☐ Johns Hopkins
- ☐ International Sites
- ☐ UMB Dental Clinics
- ☐ Center for Vaccine Development
- ☐ Community Mental Health Centers
- ☐ Private Practice in the State of Maryland
- ☐ Institute of Human Virology (IHV) Clinical Research Unit
- ☐ Joslin Center
- ☐ UMB Student Classrooms
- ☐ National Institute of Drug Abuse (NIDA)

- [ ] National Study Center for Trauma and EMS
- [ ] Univ of MD Cardiology Physicians at Westminster
- [ ] Nursing Homes in Maryland
- [ ] University of Maryland Biotechnology Institute
- [ ] Maryland Department of Health
- [ ] Maryland Proton Treatment Center
- [ ] Mount Washington Pediatric Hospital
- [ ] Institute of Marine and Environmental Technology (IMET)
- [ ] Other Sites
- [ ] University of Maryland Medical System (Select below)

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

HP-00086422

Maryland Department of Health_V2

Maryland Department of Health

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

3.1 * Does this protocol require Maryland Department of Health IRB review?

◯ Yes ● **No**

3.2 If Yes, will the Maryland Department of Health IRB rely on UM IRB as the IRB of record for review of this protocol?

◯ Yes ◯ No

ID: VIEW4DF86705BB800
Name: v2_Maryland Department of Health

Funding Information

1 * Indicate who is funding the study:

- [x] **Federal**
- [ ] Industry
- [ ] Department / Division / Internal
- [ ] Foundation
- [ ] Private
- [ ] State Agency

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

- [x] **Drug**
- [ ] Device
- [x] **Staff**
- [x] **Participant Compensation**
- [x] **Procedures**
- [x] **Other**

3 Please discuss any additional information regarding funding below:
Afree meal will be provided to participants on test days.

ID: VIEW4DF85DF452400
Name: v2_Funding Information

HP-00086422

DHHS Funded Study_V2

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
NIDA grant application(0.01)	6/5/2019 4:13 PM	6/5/2019 4:13 PM

ID: VIEW4DF87B9560800
Name: v2_DHHS Funded Study

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:
Dr. Mary Kautz

* Phone Number:
301-443-3206

* Federal Agency Email:
kautzm@nida.nih.gov

Grant Number 1 (if applicable):
1 R21 DA048198-01A1- 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:
Nicotine Insensitivity and Cue-Controlled Smoking Behavior in People with Schizophrenia
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

HP-00086422

Research Protocol_V2

Research Protocol

1 * Do you have a research protocol to upload?

- ○ Yes
- ● **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

HP-00086422

Risk Level_V2

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:

- ○ Minimal - The probability & magnitude of harm/discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations/tests.
- ● **Greater Than Minimal - Does not meet the definition of Minimal Risk.**

ID: VIEW4E02805225800
Name: v2_Risk Level

HP-00086422

Type of Research_V2

Type of Research

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

- [x] **Use of unapproved drug(s)/biologic(s) or approved drug(s)/biologic(s) whose use is specified in the protocol.**
- [ ] Evaluation of food(s) or dietary supplement(s) to diagnose, cure, treat, or mitigate a disease or condition.
- [ ] Use of device(s) whose use is specified in the protocol
- [x] **Psychological/Behavioral/Educational Method or Procedure (i.e., survey, questionnaires, interviews, focus groups, educational tests).**
- [x] **Sample (Specimen) Collection and/or Analysis (including genetic analysis).**
- [ ] Data Collection or Record Review (i.e., chart review, datasets, secondary data analysis).
- [ ] None of the above.

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

HP-00086422

Lay Summary_V2

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.

Higher rates and severity of tobacco dependence in people with schizophrenia, as compared with the general population, contribute to the lower life expectancy seen in this population. Dependent tobacco smoking tends to be controlled by stimuli associated with nicotine intake, and is marked by automatized routines. There is evidence suggesting that people with schizophrenia are less sensitive to the subjective effects of nicotine and particularly prone to stimulus-controlled habitual tobacco smoking, which, if confirmed, would have implications for tailoring successful treatment interventions for smoking cessation in schizophrenia. In the present study, we compare nicotine sensitivity between smokers with and without schizophrenia, i.e., in one session, participants discriminate between very low nicotine content cigarettes (VLNCcigs) and conventional cigarettes. Furthermore, we measure the degree to which smoking is maintained by habitual cue-controlled smoking routines, i.e., in another session, we measure ad libitum smoking of VLNCcigs.

ID: VIEW4E02805CF7000
Name: v2_Lay Summary

HP-00086422 Justification Objective Research Design_V2

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:

Rates and severity of tobacco dependence are ~3 times higher than in the general population, contributing significantly to the greater morbidity and lower life expectancy in this population. Mechanisms inherent in the neuropathology of schizophrenia appear to create greater tobacco dependence vulnerability. The present proposal is testing specific hypotheses about parallels between the pathology associated with schizophrenia and factors promoting automatized, cue-locked drug-taking.

The rationale behind these hypotheses is linked to the paradox of nicotine's demonstrably high abuse potential despite relatively weak primary reinforcing effects. Multimodal stimuli and behavioral routines associated with nicotine intake over thousands of pairings are thought to eventually control tobacco smoking more powerfully than nicotine delivery itself.

A factor which may facilitate such stimulus-controlled smoking routines in PSZ is that smokers with schizophrenia (SmoSz) appear remarkably insensitive to subjective effects of nicotine. According to theories of drug dependence, drug effects insensitivity would facilitate a habitual, cue-locked drug taking mode. Furthermore, automatized drug-taking is reportedly associated with frontoexecutive control deficits, a hallmark of the neurocognitive profile of schizophrenia. Thus, nicotine insensitivity and cognitive control deficits may facilitate automatized, stimulus-driven smoking in SmoSz.

The overall aim of this proposal is to determine whether tobacco smoking in PSZ is under dis-proportionately strong cue control, and to test whether insensitivity to the subjective effects of nicotine and/or cognitive control deficits can account for this.

Aim 1 is to test whether tobacco smoking behavior is under greater cue control in SmoSz than in matched healthy control smokers (SmoCon). Approach: Indices of cue-controlled smoking are obtained by quantifying the degree to which virtually nicotine-free cigarettes can maintain smoking behavior over eight hours under standardized laboratory conditions, in the presence of transdermal nicotine replacement. Nicotine-free cigarettes evoke a near-complete set of internal and external stimuli and behavioral routines associated with tobacco smoking, but without ensuant nicotine delivery, thus capturing the essence of stimulus control over smoking behavior.

Aim 2 is to test whether SmoSz are less sensitive to the subjective effects of nicotine than SmoCon. Approach: In a standardized laboratory paradigm, SmoSz and SmoCon discriminate research cigarettes of differing nicotine yields, and report on subjective state measures after each cigarette.

Aim 3 is to determine whether nicotine insensitivity is related to cue-control over smoking behavior, and can account for the group difference therein.

Aim 4 is to determine whether cognitive control deficits are related to cue-control over smoking behavior, and can account for the group difference therein. Approach: A cognitive control index will be derived from tasks selected from the RDoC matrix.

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.:

Smokers with and without a diagnosis of schizophrenia or schizoaffective disorder will undergo the same laboratory research protocol (4 sessions). Nicotine sensitivity and cue-controlled smoking behavior will be compared between these groups and correlated within groups.

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

Nicotine's abuse liability is comparable to other drugs of abuse despite relatively weak primary rein-forcing effects(7-12). Substituting nicotine causes only small reductions in smoking(13, 14), and nicotine replacement is relatively ineffective in quit attempts(15). Conversely, denicotinized cigarettes maintain a level of smoking, satisfaction, relaxation, and craving relief(16-18). Thus, acute pharmacological effects cannot fully explain nicotine's dependent use. Instead, plentiful evidence suggests that tobacco dependence is marked by automatized, cue-locked behavior. Environmental and physiological stimuli associated with nicotine intake exert powerful control over tobacco consumption, elicit craving and autonomic responses, capture attention, and precipitate relapse(19-30). Consistent with behavioral automaticity, cue-induced cigarette smoking becomes resistant to nicotine devaluation by satiety(31, 32). Rat self-administration studies concur that stimuli paired with nicotine infusions promote acquisition of nicotine seeking, slow its extinction, and reinstate it(33-35). In direct comparison, cue delivery had greater influence over nicotine-seeking than nicotine delivery itself(33).

Influential theories of addiction based on clinical and preclinical evidence state that the rise of an automatized, cue-locked drug seeking mode and a concomitant decline in awareness of the drug's specific subjective effects are central to the transition to dependence(36, 37). Interestingly, a study in rats employing cocaine showed that heightening the sensitivity to subjective drug effects by discrimination training slowed the acquisition of its self-administration on a higher-order schedule(38).

There is evidence that smokers with schizophrenia (SmoSz) are less sensitive to subjective effects of nicotine than healthy control smokers (SmoCon): (1) "Rapid smoking", which typically induces unpleasant subjective effects(39, 40), is more than twice as common in SmoSz than Con(41). Anicotinic acetylcholine receptor (nAChR) subunit (α5) gene polymorphism that is associated with tobacco dependence severity(42-45) and reduced aversive effects of large-dose nicotine(46) is more frequent in PSZ(47). Other nAChR subunit polymorphisms associated with schizophrenia(48), may also contribute to reduced nicotine sensitivity. (2) Our own data suggest that subjective effects of nicotine, as measured by self-reported mood variables, ability to concentrate, and craving, are blunted in SmoSz(49). Other studies concur that craving in SmoSz is less responsive to the presence vs. absence of nicotine(50, 51). Abstinence (i.e., absence of nicotine and smoking-associated cues) increases the carbon monoxide (CO) boost by ad libitum smoking more in SmoSz than SmoCon, but nicotine replacement has minimal effects thereon(50). (3) Reduced nicotine sensitivity is consistent with thinning and blunted activation of the insular cortex in PSZ(52), a structure implicated in processing the interoceptive sequelae of tobacco smoking and translating sensations into subjective feelings(53).

In contrast to subjective effects of nicotine, SmoSz and SmoCon display similar subjective effects of exogenous smoking-associated stimuli(50, 54-56). This indicates that (a) blunted subjective effects of nicotine do not reflect an inability to experience or report subjective state changes (consistent with the emotion literature(57)), and (b) conditioning processes of smoking-associated stimuli are intact in SmoSz.

Reduced sensitivity to subjective nicotine effects in PSZ would be aligned to promote automatized, stimulus-driven smoking behavior. Furthermore, impairments in frontoexecutive evaluative control and goal-directed behavior, a hallmark of cognitive deficits associated with schizophrenia(58, 59), display significant associations with habitual, cue-locked drug taking(36, 60). Thus, we hypothesize that blunted subjective effects of nicotine and cognitive control deficits make PSZ more prone to automatized, cue-locked tobacco smoking, which could explain greater levels of tobacco dependence and lower quit success.

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

Tobacco smoking is the leading cause of preventable disease and death in the US(1); yet, an estimated 20% of the adult population are current smokers(2). People with schizophrenia (PSZ) display tobacco dependence rates ~3 x higher than the general population, tend to smoke more heavily, and have greater difficulty quitting(3-5). Smoking contributes substantially to the higher morbidity and lower life expectancy in PSZ(6). This study is aimed at identifying mechanisms conferring greater tobacco dependence susceptibility to PSZ.

The above predictions would imply that addressing automatized, cue-locked components of tobacco smoking is of particular importance for smoking cessation in

SmoSz. A lab-based retrieval-extinction intervention(61) and prolonged extinction learning with virtually nicotine-free cigarettes(62-64) both were of benefit in SmoCon and may be of particular efficacy in SmoSz. Nicotine insensitivity predicting cue-control would suggest that nicotine discrimination training to enhance evaluative processing of its effects may be of value, mirroring preclinical findings with cocaine(38). Such procedures are feasible in humans(65-74) but are an unexplored avenue for dependence treatment. Cognitive control deficits predicting cue-control may suggest interventions to strengthen frontoexecutive control. By shaping our understanding of tobacco dependence in PSZ, the present project may inform treatment strategies in the most severely affected by its impact on health and life.

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

HP-00086422 Supporting Literature_V2

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.***

1. Yoon PW, Bastian B, Anderson RN, Collins JL, Jaffe HW, Centers for Disease C, Prevention. Potentially preventable deaths from the five leading causes of death--United States, 2008-2010. MMWR Morb Mortal Wkly Rep May 2 2014;63(17):369-374.
2. Giovino GA, Mirza SA, Samet JM, et al. Tobacco use in 3 billion individuals from 16 countries: an analysis of nationally representative cross-sectional household surveys. Lancet Aug 18 2012;380(9842):668-679.
3. de Leon J, Diaz FJ. A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. Schizophr Res Jul 15 2005;76(2-3):135-157.
4. Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: A population-based prevalence study. JAMA Nov 22-29 2000;284(20):2606-2610.
5. Williams JM, Gandhi KK, Lu SE, Kumar S, Steinberg ML, Cottler B, Benowitz NL. Shorter interpuff interval is associated with higher nicotine intake in smokers with schizophrenia. Drug Alcohol Depend Nov 01 2011;118(2-3):313-319.
6. Wehring HJ, Liu F, McMahon RP, Mackowick KM, Love RC, Dixon L, Kelly DL. Clinical characteristics of heavy and non-heavy smokers with schizophrenia. Schizophr Res Jul 2012;138(2-3):285-289.
7. Anthony JC, Warner LA, Kessler RC. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: basic findings from the national comorbidity survey. Experimental and Clinical Psychopharmacology 1994;2:244-268.
8. Rose JE, Corrigall WA. Nicotine self-administration in animals and humans: similarities and differences. Psychopharmacology (Berl) Mar 1997;130(1):28-40.
9. Manzardo AM, Stein L, Belluzzi JD. Rats prefer cocaine over nicotine in a two-lever self-administration choice test. Brain Res Jan 04 2002;924(1):10-19.
10. Palmatier MI, Evans-Martin FF, Hoffman A, et al. Dissociating the primary reinforcing and reinforcement-enhancing effects of nicotine using a rat self-administration paradigm with concurrently available drug and environmental reinforcers. Psychopharmacology (Berl) Mar 2006;184(3-4):391-400.
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2 If available, upload your applicable literature search:

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HP-00086422 Study Procedures_V2

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:

The study involves 4 visits to the Maryland Psychiatric Research Center (MPRC). Scheduling of these visits is flexible and depends on the participant's schedule. The only limitation is that the third and fourth visits are scheduled with at least one intervening day, and that no more than three months pass between any consecutive visits.

1. Consent and Screening visit:

After Informed Consent has been obtained, participant will undergo the following screening procedures:

- Verification of age.
- The Standard Clinical Interview for DSM (SCID), to determine the presence/absence of current psychiatric conditions. For some participants, a SCID will have already been obtained and does not have 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).
- 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
- Targeted questions about smoking history in the form of the Nicotine Dependence and the Nicotine Use Questionnaire
- Breath CO reading, as an indicator of smoking status and frequency
- Listing of all currently taken medication
- Vision test
- The Wechsler Abbreviated Scale of Intelligence (WASI), as an indicator for possible mental retardation
- If the volunteer has a diagnosis of COPD, they will be asked to walk the length of the MPRC corridor four times (100 m). If they have to stop before completion, it will be determined that their COPD is greater than mild (exclusionary).

2. Characterization and Cognitive Test Session (~2 hrs):

- Participants practice the CO breathalyzer procedure: After 15-s breath-holding, slow and even exhalation into the breathalyzer over 5 s is prescribed by a visual cue: a growing bar on a computer screen (84). The measurement is repeated after 5 min and readings are averaged, to minimize measurement variability,
- Participants complete the following questionnaires:

1. Minnesota Tobacco Withdrawal Scale (77, 99) (MTWS; 4 min): Six DSM-5 symptoms of nicotine withdrawal (excluding the insomnia item) are rated on a 5-point scale (0 = none; 4 = severe).
2. Affect-based withdrawal scale (78) (AWS; 4 min): A list of nine bidirectional 9-point scales sensitive to mood changes induced by tobacco deprivation or by nicotine (e.g., calm - nervous; energetic - tired).
3. Questionnaire of Smoking Urges - Brief (100) (QSU; 4 min): Participants rate 10 statements such as " I have a desire for a cigarette right now" on a scale from 0 (strongly disagree) to 100 (strongly agree).
4. Modified Cigarette Evaluation Questionnaire (mCEQ): Twelve questions such as "Was smoking satisfying" are evaluated on a 7-point scale from 1=not at all to 7=extremely.

- Participants perform the following computerized cognitive control tasks:

1. Expectancy AX-CPT, frequently used in schizophrenia research (101-103): A trial consists of the letters A or B (contextual cue) followed by an X or Y. The default after each letter is a non-target response; only an X that was preceded by an A requires a target response. After the A cue, there is an 80% chance that an X will follow. Out of the three possible non-target trials (AY, BX, BY), we will focus on BX trials. Maintenance of the B contextual cue is critical to overcome the target response bias created by the X. Poor representation of the B cue would result in more false alarms on BX trials (found repeatedly in PSZ (102)).
2. Stroop paradigm: In our simplified version, color-words are presented, and subjects say aloud, as quickly as possible, the color in which the word is written. For congruent trials, the color-word is presented in a matching color (e.g. RED in red), for incongruent trials in a non-matching color (e.g. RED in blue). We focus on differences between congruent and incongruent trials, omitting neutral trials to allow for more trials per condition for greater measurement reliability. This task repeatedly revealed increased Stroop interference in schizophrenia (104). Responses are recorded by a microphone connected to a serial response box with voice key and time stamping hardware.

- Participants perform the MATRICS Consensus Cognitive Battery (MCCB) mazes, as a measure of reasoning/problem solving ability.
- Participants perform the Wechsler Test of Adult Reading (WTAR) as a measure of premorbid functioning.
- Nicotine patch toleration: At session end, participants are asked to wear a nicotine patch (21 mg/24 hrs) for at least 4 hrs, to ensure that it is tolerated. The patch is applied to the upper arm, to be easily removable at home. A side effects checklist is completed just prior to patch application. The research assistant will follow up with the participant by phone, approximately 4 hrs after patch application, to inquire about any potential side effects using the same checklist. The participant is asked to remove the patch and call the research assistant earlier if they experience any side effects that cause them significant discomfort. If any greater-than-mild adverse effects are reported, the dose will be reduced to 14 mg/24 hrs in the Ad Libitum Smoking Session (see below).

3. Nicotine Discrimination Session (~6 hrs):

Participants are instructed not to smoke or ingest any nicotine from waking up until session start at ~9 am, verified by expired CO ≤7 ppm. If this threshold is exceeded, the session may be rescheduled. Participants first complete the MTWS, AWS, & QSU (see above). The nicotine discrimination procedure is then started. Participants are informed that their task is to compare different types of cigarettes, and that nicotine content is one of the parameters in which these cigarettes may differ. On each trial, participants take four 2-s puffs via the Clinical Research Support System (CReSS) portable device, to standardize smoking topography, with 30 s between puffs (71-74). Puff duration and inter-puff interval is timed by visual cues on an instruction screen. The CReSS time-stamps puff onset and duration. Trials are separated by 20 min no smoking.

The first 2 trials are reference trials, over which participants take 4 puffs on the Very Low Nicotine Content (VLNC) and the 0.8 mg-yield cigarette each, with sequence counterbalanced across participants. The two cigarettes are identified by letter code (A and B, counterbalanced). Four discrimination trials follow, in which the participant is blind with regards to cigarette identity. The sequence in which the two cigarette types are sampled (ABBA, BAAB, ABAB, BABA) is counterbalanced and double-blind, i,e., only the statistician and dispensing pharmacist know the sequence. After each discrimination trial, participants choose whether the sampled cigarette was of type A or B, complete the MTWS, AWS, QSU, and mCEQ, and indicate on a scale from 1 to 5 how much they want to smoke a cigarette like this, and how satisfying and how strong they thought the cigarette was. After the 4th discrimination trial, participants have a break and a light lunch, staying on the premises to ensure continued smoking abstinence. They then receive another reference trial with the VLNC and 0.8-mg cigarette each, and complete another 4 discrimination trials as described above.

After the last discrimination trial, a breath CO reading (x2) is taken, and participants are asked to smoke one research cigarette (A or B) of their choice (not through the CReSS, to create more naturalistic conditions). Choice is recorded. Independent thereof, participants will always be given the VLNC cig. Another CO breathalyzer measurement is taken immediately after smoking to measure the CO-boost from this cigarette, and participants complete the MTWS, AWS, QSU, and mCEQ one last time.

4. Ad Libitum Smoking Session (~8.5 hrs), scheduled ≥2 days after the Discrimination Session:
Participants are instructed not to smoke or ingest any nicotine-containing products from waking up until session start at ~9 am, verified by expired CO ≤ 7 ppm. If the CO threshold is exceeded, the session may be rescheduled. Female participants also provide a urine sample for repeat pregnancy testing, which would end participation.
Anicotine patch is then applied (21 mg/24 hrs; if previously not tolerated: 14 mg/24 hrs). Participants deposit their own cigarettes with the research assistant, and a box of VLNCcigs is provided. More VLNCcigs will be dispensed if needed - smoking is ad libitum. Participants are not told that the research cigarettes are virtually nicotine-free, but the consent form states that research cigarettes and patches may differ in nicotine yield from conventional products. For the next 8 hrs, participants stay at the MPRC, settled in a ventilated fire-proofed smoking room with access to the internet and DVDs. In the first hour, breakfast is offered, at noon, lunch is provided, at 3 pm a light snack. The research assistant's desk is adjacent to the smoking room, separated by a semitransparent window; he is available throughout the day. The research assistant records the time of each smoke, and the number of VLNCcigs smoked each time. After 8 hrs, another breath CO breathalyzer reading (x2) is obtained - the main outcome variable. The secondary outcome, the decline in VLNCcig smoking across the session, is obtained by subtracting the total number of VLNCcigs smoked in the last 2 hrs from that smoked in the first 2 hrs.

2 * Describe all procedures already being performed for diagnostic or treatment purposes (if not applicable to the study, enter "N/A"):
Some participants may already have done a SCID in the context of clinical care or another study. If this SCID was done at the MPRC, it will not be redone. The diagnostic information will have entered clinical records and will be accessed under a partial HIPAA privacy waiver.

3 * Describe the duration of an individual participant's participation in the study:
The shortest time within which the study can be completed by any participant is 1 week. A maximum of 3 months may expire between any of the four sessions described above (although efforts will be made to not exceed 2 weeks). Thus, the maximum completion time is 9 months.

4 * Describe the amount of time it will take to complete the entire study:
The is a two-year study.

5 * Describe any additional participant requirements:
None.

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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:

Power analyses indicate that, at β=0.8, N=45 per diagnostic group would enable detection of medium effect sizes (Cohen's d=0.6, Cohen's f=0.3) with the analyses described below. To prepare for a 20% attrition rate, we will randomize 112 participants for 90 completers. Based on an expected 20% screening failures, we anticipate that screening 140 volunteers will result in 112 enrollments, but to be on the save side, we set the enrollment ceiling at 160.

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:

- Hypothesis 1 (smoking is under greater cue control in SmoSz than SmoCon) is tested by two-sample t-test comparing groups on breath CO after 8 hrs of ad libitum VLNCcig smoking (ANCOVA if group matching is suboptimal for 1 or more variables). Secondary analysis: ANOVA (or ANCOVA) to compare groups on the number of VLNCcigs smoked in the first vs. last 2 hrs of the Ad Lib Smoking Session (group x time point).
- Hypothesis 2 (SmoSz are less sensitive to subjective nicotine effects than SmoCon) is tested by two-sample t-test (or ANCOVA) comparing nicotine discrimination accuracy between groups. Secondary analysis: The composite subjective state score after smoking a VLNC or a 0.8 mg-yield cigarette is compared between SmoSz and SmoCon by ANOVA (group x cigarette type), or ANCOVA if indicated (see above).
- Hypothesis 3 (nicotine sensitivity is related to cue control and can account for the group difference therein): Regression analysis tests the impact of discrimination accuracy on cue control while controlling for the group effect. To evaluate the degree to which nicotine insensitivity can statistically account for the group difference in cue-control, we measure the reduction in the group effect when entering discrimination accuracy, with a >25% reduction in βgroup defined as significant. To determine the percentage of between-group variance in cue control statistically accounted for by nicotine sensitivity, we quantify the reduction in variance explained by the group factor when including discrimination accuracy as a covariate in ANCOVA.
- Hypothesis 4 (cognitive control deficits can account for cue-control and for the group difference therein) is tested in a manner analogous to Hypothesis 3.

ID: VIEW4E02806052800
Name: v2_Sample Size and Data Analysis

HP-00086422 Sharing of Results_V2

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). With written authorization from the participant, test results may also be shared with their care provider.

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

ID: VIEW4E02808CBD800
Name: v2_Sharing of Results

HP-00086422

Research with Drugs or Biologics_V2

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
View	Research cigarettes (0.03 and 0.8 mg nicotine yield)	no	FDA-assigned protocol number P00105	yes
View	Nicotine patch (21 or 14 mg/24 h)	yes		

2 * Attach the drug package insert or investigational drug brochure for the drugs being administered in this study:

FDA Letter of No Concerns(0.01)	11/26/2019 8:10 AM	11/26/2019 8:10 AM
NOT-DA-14-004: NIDA Research Cigarettes(0.01)	6/7/2019 3:02 PM	6/7/2019 3:02 PM
Nicoderm CQ(0.01)	6/7/2019 2:45 PM	6/7/2019 2:45 PM

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

Research cigarettes with 0.03 mg (very low nicotine content) and 0.8 mg (conventional) nicotine yield will be used as part of this study, obtained from the NIDA Drug Supply Program (NOT-DA-14-004, see attachment). Other than the very low nicotine yield of the 0.03 mg-yield cigarette, these cigarettes do not differ from commercially available cigarettes. However, an Investigational Tobacco Product Application was submitted to the FDA for approval of research cigarette use, and a "No Concerns" letter was issued by the FDA Center for Tobacco Products (uploaded above under Question 2).

Participants will not be asked to wear a nicotine patch and smoke conventional-nicotine yield research cigarettes at the same time. However, they will be asked to wear a nicotine patch while smoking the 0.03 mg nicotine yield (virtually nicotine-free) cigarettes. No adverse interactions are expected given that the combination amounts to what would constitute a conventional nicotinized cigarette.

4 * Will you be using Investigational Drug Services?

○ Yes ● **No**

ID: VIEW4E0916E6E1400
Name: v2_Research with Drugs or Biologics

Drug or Biologic Storage and Handling

4.1 * Do you have a plan regarding access controls for essential and approproate research personnel?
● Yes ○ No

4.2 * Will you have procedures for verifying physical access to the drugs(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

HP-00086422

Placebos_V2

Placebos

1

* Is this study placebo controlled?

◯ Yes ● **No**

ID: VIEW4E0514EECCC00
Name: v2_Placebos

HP-00086422

Behavioral Methods and Procedures_V2

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:

- [x] **Surveys/questionnaires**
- [x] **Key informant or semi-structured individual interviews**
- [ ] Focus groups or semi-structured group discussions
- [ ] Audio or video recording/photographing
- [ ] Educational tests or normal educational practices (education instructional strategies, techniques, curricula, or classroom management methods)
- [x] **Individual or group behavioral observations**
- [ ] Psychosocial or behavioral interventions
- [x] **Neuropsychological or psychophysiological testing**
- [x] **Deception**
- [ ] Other psychosocial or behavioral procedures

ID: VIEW4E09416F57800
Name: v2_Psychological/Behavioral/Educational Methods and Procedures

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:
1. Minnesota Tobacco Withdrawal Scale (MTWS)
2. Affect-based withdrawal scale (AWS)
3. Questionnaire of Smoking Urges (QSU)
4. Nicotine Use Questionnaire (NUQ)
5. Nicotine Dependence Questionnaire (NicDepend)
6. Side effects checklist, to test for adverse effects of the nicotine patch
7. Nicotine Discrimination Questionnaire
8. Psychiatric and non-psychiatric medication forms, to record all currently taken medication
9. A medical history pre-screening questionnaire, to be performed by a research assistant prior to the Medical History by the physician
10. Modified Cigarette Evaluation Questionnaire (mCEQ)

2 * Upload a copy of all questionnaires/surveys:

Name	Created	Modified Date
Modified Cigarette Evaluation Questionnaire(0.01)	6/14/2019 3:35 PM	6/14/2019 3:35 PM
Affect-based Withdrawal Scale(0.02)	6/7/2019 4:48 PM	6/7/2019 4:54 PM
Minnesota Tobacco Withdrawal Scale(0.02)	6/7/2019 4:48 PM	6/7/2019 4:54 PM
Questionnaire for Smoking Urges(0.02)	6/7/2019 4:48 PM	6/7/2019 4:54 PM
Cigarette Discrimination Questionnaire(0.02)	6/7/2019 3:29 PM	6/7/2019 4:29 PM
Nicotine Use Questionnaire(0.01)	6/7/2019 3:31 PM	6/7/2019 3:31 PM
Nicotine Dependence Questionnaire(0.01)	6/7/2019 3:31 PM	6/7/2019 3:31 PM
Side effects checklist(0.01)	6/7/2019 3:30 PM	6/7/2019 3:30 PM
Non-Psychiatric Medication Form(0.01)	6/7/2019 3:29 PM	6/7/2019 3:29 PM
Psychiatric Medication Form(0.01)	6/7/2019 3:28 PM	6/7/2019 3:28 PM
Medical History Pre-screen(0.01)	6/7/2019 3:28 PM	6/7/2019 3:28 PM

3 * What is the total length of time that each survey is expected to take?
MTWS: 4 min
AWS: 4 min
NUQ: 5 min
NicDepend: 5 min
Side effects checklist: 4 min
Nicotine Discrimination Questionnaire: 4 min
Medication forms: 2-10 min
Medical pre-screening form: 6 min
mCEQ: 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

HP-00086422 Interviews_V2

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
Structured Clinical Interview for DSM(0.01)	6/14/2019 3:43 PM	6/14/2019 3:43 PM
Evaluation to sign consent(0.01)	6/14/2019 3:42 PM	6/14/2019 3:42 PM

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

Evaluation to Sign Consent: ~3 min
Structured Clinical Interview for DSM: 25-60 min, depending on answers

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

The responses will be recorded by the rater, a clinical research assistant at the MPRC, on assessment forms (attached) labeled by subject ID code, date, study number and rater ID. 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 at the MPRC for an immediate evaluation. These clinicians will then determine appropriate action and follow-up depending on the circumstances.

ID: VIEW4E0947A633C00
Name: v2_Interviews

HP-00086422 Observation_V2

Observation

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

1 * Please describe what is being observed.
Ad libitum smoking of very low nicotine content cigarettes (VLNCcigs) for 8 hours at the MPRC while wearing a nicotine patch. Participants spend their time in a day room and walk to a smoking room whenever they wish to smoke VLNCcigs. The number of smoked cigarettes is recorded, and participants exhale into a CO breathalyzer (see Study Procedures for details).

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

3 * How will individuals identities be protected?
All outcome measures are recorded on forms labeled with only subject ID code, study number, date, and subject and rater initials. No video or audio recordings are taken.

4 * How will observations be recorded?
On paper forms not containing the subject's name or other PII.

ID: VIEW4E0BBF1EF0400
Name: v2_Observation

HP-00086422 Testing_V2

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:
- Two computerized tasks will be performed:
1. Expectancy AX-CPT
2. Stroop paradigm
3. The WASI Vocabulary and Matrix Reasoning subtests to assess intellectual competence
4. The Reasoning/Problem Solving subscale of the MATRICS Consensus Cognitive Battery (MCCB)
5. Wechsler Test for Adult Reading (WTAR)

2 * Describe procedures related to all testing:
- Computerized Expectancy AX-CPT: A trial consists of the letters A or B (contextual cue) followed by an X or Y. The default after each letter is a non-target response; only an X that was preceded by an A requires a target response. After the A cue, there is an 80% chance that an X will follow.
- Computerized Stroop paradigm: Color-words are presented, and subjects say aloud, as quickly as possible, the color in which the word is written. For congruent trials, the color-word is presented in a matching color (e.g. RED in red), for incongruent trials in a non-matching color (e.g. RED in blue).
- 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 outcoume measurement session). The setting is a private room, seated at a table.
- The MCCB reasoning/problem solving domain is tested by a series of mazes, completed as paper & pencil tests, of varying difficulty.
- The WTAR consists of a list of words of varying difficulty which the participant is asked to read out loud.

3 * Upload relevant testing materials:

Name	Created	Modified Date
MCCB Reasoning/Problem solving (Mazes)(0.01)	6/14/2019 4:13 PM	6/14/2019 4:13 PM
Wechsler Test of Adult Reading(0.01)	6/14/2019 4:05 PM	6/14/2019 4:05 PM
WASI Vocabulary subtest(0.01)	6/14/2019 3:58 PM	6/14/2019 3:58 PM
WASI Matrix Reasoning(0.01)	6/14/2019 3:57 PM	6/14/2019 3:57 PM

4 * What is the individual duration of each test and what is the entire duration of all tests?
- Expectancy AX-CPT: ~30 min
- Stroop task: ~ 30 min
- WASI subtests: 15-30 min
- MCCB reasoning/problem solving: ~10 min
- WTAR: 5 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

HP-00086422 Deception_V2

Deception

You indicated that this study involves deception.

1 * Indicate why deception is the only feasible means of conducting the research. Include information about the likely characteristics and cultural values of the participants that contribute to the justification for using deception:
Tobacco smokers tend to have firm beliefs about the role of nicotine for the effects of tobacco smoking and their smoking.

2 * Describe the manner in which the participants are being deceived. Specify the information that will be withheld from the participants or the misinformation that will be provided to them:
Participants will be informed that the research cigarettes they will be smoking as part of this study may differ from each other and from conventional cigarettes in different tobacco constituents including tar, nicotine, and carbon monoxide, when in fact the only difference is in nicotine content. Furthermore, participants will be informed that the skin patch they receive in the Ad Libitum Smoking Session may or may not contain nicotine, when in fact it always contains nicotine.

3 * Provide the rationale/justification for the deception:
Smokers will be asked to self-report on their subjective state after comparing cigarettes of different nicotine content. For valid research results, they must not focus on expected effects of nicotine but report their subjective state in an unbiased manner. Furthermore, we measure to what degree smoking is maintained by virtually nicotine-free cigarettes in the presence of nicotine replacement, as a measure of cue-controlled smoking. Knowledge that the cigarettes are nicotine-free and that the patch contains nicotine would most likely alter (reduce) smoking behavior based on the conception that smoking is nicotine-seeking.

4 * Will confederates be used?
○ Yes ● **No**

5 * Detail the elements of deception that are incorporated into the informed consent process and document:
The study title is "Cigarette Smoking in Smokers With and Without a Diagnosis of Schizophrenia", not "Nicotine Insensitivity and Cue-Controlled Smoking in People with Schizophrenia", the title of the grant application, which would give away the focus on the presence vs. absence of nicotine effects. Furthermore, the informed consent form states that participants will "sample research cigarettes that may differ in their delivery of tar, nicotine, carbon monoxide, and other tobacco constituents" (p. 1, Summary); that "you will wear a skin patch that may or may not contain nicotine. Whether or not your patch contains nicotine may be determined by chance, like a coin toss." (p. 1, Summary); that "we ask participants to smoke and compare different research cigarettes. These may differ in the amounts of several typical tobacco smoke constituents, such as carbon monoxide, tar, and nicotine." (p. 1, under Purpose); and that "Neither you nor the investigators know if your patch contains nicotine. This is determined by chance. Only the pharmacist handing out the patch will know." (p. 3, second paragraph).

6 * Is the research likely to produce psychological discomfort or negative feelings in the participants?
○ Yes ● **No**

6.1 If Yes, describe the arrangements made to provide professional counseling or support resources to any participants requiring such assistance following their participation in the study:

7 * Will the participants be required to decieve others?
○ Yes ● **No**

8 * Will the participants be debriefed?
● **Yes** ○ No

8.1 If Yes, describe the debriefing process:
Upon completion of the entire study, participants will be sent a letter (see below) explaining that the critical variable in which the research cigarettes differed from each other was nicotine content and none of the other constituents also listed as possibly differing, and furthermore explaining that the nicotine patch contained nicotine for all study participants, not just some. We cannot debrief each individual participant when they complete the study because they may communicate this information to other potential participants.

Upload a copy of the debriefing script:

Name	Created	Modified Date
Debriefing Letter(0.01)	8/26/2019 4:46 PM	8/26/2019 4:46 PM

8.2 If No, justify why the deception will not be disclosed/explained to the participants at the conclusion of the study:

9 * Describe the additional training and qualifications of the research staff who are involved in the deception process and the debriefing:
None of the research staff have any additional training or additional qualifications related to deception.

ID: VIEW4E0BC39027000
Name: v2_Deception

HP-00086422

Sample Collection_Analysis_V2

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)

- [x] **Prospective (will be collected)**
- [ ] Existing (previously collected at the time of initial IRB submission)

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?

Aurine sample will be obtained for drug and pregnancy testing during screening and whenever intoxication is suspected.
Ablood sample (10 ml) will be obtained from a forearm vein, one time, in those individuals who opt in to the procedure. The blood draw can be performed at any time after the consent form was signed - the participant does not have to pass screening for the main study. The blood will be analyzed for heavy metal and aldehyde concentrations. The purpose is to collect pilot data for a new grant application centered around smoking and psychiatric illness. The samples will be frozen until completion of study procedures, upon which they will be analyzed.

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 sample will be analyzed by Drs. Sarah Michel and Maureen Kane at the UM School of Pharmacy. Samples will be labeled with the participant code # and no PII. Drs. Michel and Kane will not be able to link samples to PII and are therefore not listed on this protocol.

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

HP-00086422 Prospective Samples_V2

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)

- [x] **Blood**
- [ ] Bone Marrow Aspirate/Biopsy
- [ ] Cerebrospinal Fluid
- [ ] Saliva
- [ ] Skin
- [ ] Sputum
- [ ] Stool
- [ ] Tissue
- [ ] Tumor
- [x] **Urine**
- [ ] Other

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:
2 teaspoons (10 ml) of venous blood one time, at any one of the study visits.

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

- [x] **Samples obtained specifically for research purposes-obtained via a separate collection procedure done solely for the purposes of the study**
- [ ] Samples obtained specifically for research purposes-additional taken during a clinical procedure
- [ ] Leftover samples that were obtained for clinical purposes (no additional research procedures required)
- [ ] Commercial (for profit) samples
- [ ] Other

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?
Urine samples are not labeled. Drug and pregnancy testing is performed immediately after the sample is obtained. The sample is then discarded.
Blood sample are labeled with the participant's ID code, the date, study number, type of matrix (plasma), and the initials of the person obtaining 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.):
The urine sample will already have been discarded.
The blood sample will be retained unless the participant asks for it to be destroyed.

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

HP-00086422

Clinical Trial Registration_V2

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

HP-00086422

Clinical Trial Registration Info_V2

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
NCT04001114

ID: VIEW4E093BF1D0800
Name: v2_Clinical Trial Registration Information

HP-00086422 Participant Selection_V2

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.***
160

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:
160

Worldwide - the number being enrolled total at all sites (including local enrollment):
160

3 * Gender:

- [x] **Male**
- [x] **Female**

4 * Age(s):

- [ ] 0 to 27 days (newborn infants)
- [ ] 28 days to 12 months (Infant)
- [ ] 13 months to 23 months (Toddler)
- [ ] 2 to 5 years (Preschool)
- [ ] 6 to 11 years (Child)
- [ ] 12 to 17 (Adolescents)
- [x] **18 to 88 years (Adult)**
- [ ] 89 years and older

5 * Race/Ethnicity:

- [x] **All Races Included**
- [ ] American Indian or Alaskan Native
- [ ] Asian/Other Asian
- [ ] Asian/Vietnamese
- [ ] Black or African American
- [ ] Hispanic or Latino
- [ ] Mixed Race or Ethnicity
- [ ] Native Hawaiian or Pacific Islander
- [ ] White or Caucasian

6

* Language(s):

- [x] **English**
- [ ] Chinese
- [ ] French
- [ ] Italian
- [ ] Japanese
- [ ] Korean
- [ ] Local Dialect

- [ ] Spanish
- [ ] Vietnamese
- [ ] Other

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.:

ID: VIEW4E0E519C1D000
Name: v2_Participant Selection

HP-00086422

Vulnerable Populations_V2

Vulnerable Populations

1 * Will you be targeting ANY of the following Vulnerable Populations for enrollment? (Select all that apply)

- [x] **Employees or Lab Personnel**
- [ ] Children (Minors)
- [ ] Cognitively Impaired/ Impaired Decision Making Capacity
- [ ] Pregnant Women/Fetuses
- [ ] Wards of the State
- [x] **Students**
- [ ] Prisoners
- [ ] Nonviable Neonates or Neonates of Uncertain Viability
- [ ] Economically/Educationally Disadvantaged
- [ ] None of the above

Only select populations which you will be targeting for enrollment. Do not include populations that may be enrolled incidentally. Enrollment of a vulnerable population is considered to be "targeted" if the study team will be aware that a subject is from a vulnerable group as a result of interaction with the subject or collection of specific information about the subject, and the research team does not wish to exclude them. "Incidental" enrollment is limited to situations where a study team is unaware that a subject is from a vulnerable group.

ID: VIEW4E0E519917800
Name: v2_Vulnerable Populations

Vulnerable Populations - Employees or Lab Personnel

You indicated that employees or lab personnel are included in this study.

1 * Describe how you will ensure particiption in this research will not affect employment and prevent undue influence:

No special effort is made to recruit UMB employees, 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, ID 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. Medical 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. No information about the employee's study participation will be provided to the employee's immediate supervisor. Participation in research at the MPRC will not in any way affect the employee's relationship with UMB or the University of Maryland Medical System. The $18/hr incentive is not coercive. The Informed Consent process will be as outlined above and will not differ from that of other volunteers.

ID: VIEW4E0E5192BA800
Name: v2_Vulnerable Populations - Employees or Lab Personnel

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. Medical 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 $18/hr incentive is not coercive. The Informed Consent process will be as outlined above and will not differ from that of other volunteers.

ID: VIEW4E0E519F32000
Name: v2_Vulnerable Populations - Students

HP-00086422 Eligibility_V2

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	18-60 years of age
View	2	Regular smoker of at least 10 cigarettes or cigarillos/day for at least 2 years
View	4	For participants with schizophrenia: DSM-5 diagnosis of schizophrenia or schizoaffective disorder
View	5	For participants with schizophrenia: Able to give informed consent as determined by an Evaluation to Sign Consent.
View	6	For smokers with schizophrenia: No change in psychiatric medication or dosage in the last 4 weeks

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

	Number	Criteria
View	1	Uncontrolled hypertension (resting systolic BP above 150 or diastolic above 95 mm Hg)
View	2	Cardiovascular disease, such as history of myocardial infarction and ischemia, heart failure, angina, severe arrhythmias, or EKG abnormalities (Wolf-Parkinson-White syndrome, complete left bundle branch block, PR interval less than 120 ms or greater than 200 ms, prolonged QT interval of greater than 500 ms corrected, cardiac arrhythmias as defined by PACs greater than 3/min or PVCs greater than 1/min).
View	3	Severe asthma
View	4	Chronic obstructive pulmonary disease (COPD) other than mild COPD
View	5	Neurological illness, such as stroke, seizure disorder, neurodegenerative disease, or organic brain syndrome
View	6	Mental retardation
View	7	Alcohol or substance use disorder except nicotine within the last year
View	8	Use of benztropine (Cogentin), varenicline (Chantix), bupropion (Wellbutrin, Zyban), or any type of nicotine replacement
View	9	Pregnant or lactating
View	10	For healthy control smokers: DSM-5 diagnosis of depression, bipolar disorder, ADHD, autism spectrum disorder, anorexia, bulimia nervosa, or any schizophrenia-spectrum disorder
View	11	For healthy control smokers: immediate family history of psychosis

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-00086422_13 v9-23-2022-1663946434165(0.01)

ID: VIEW4E0E5185F9000
Name: v2_Eligibility

HP-00086422 Recruitment_V2

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.):

Smokers with schizophrenia or schizoaffective disorder will be recruited from:
• The MPRC Outpatient Research Program (ORP), which provides comprehensive case management and treatment for ~100 patients with schizophrenia or schizoaffective disorder, about half of who smoke. There are one to two new referrals per month
• The MPRC Neuroimaging Research Program (NRP), with a separate pool of ~100 outpatients.
• The MPRC Treatment Research Program (TRP), an inpatient unit with 24 beds, headed by Co-investigator Dr. Kelly. This will be the only inpatient program we will recruit from, and always after consulting with therapists familiar with the patient. The TRP admits voluntary patients who wish to participate in ongoing research; the current census is 24. It is located within the same building as the study rooms used for the smoking sessions.
• A network of regional outpatient clinics and day programs, such as Key Point Health Services and Mosaic Community Services (Sheppard Pratt Health System), which the MPRC is tied into.
• Private community mental health treatment providers, which we will approach for referrals, providing flyers and pamphlets.
• A standing recruitment database comprised of individuals who have previously participated in MPRC research studies and have agreed to be re-contacted.
• Online postings including the MPRC website, Craigslist, and ClinicalTrials.gov.
• By registering the study with Smartphone apps such as studyscavenger.com or trialsapp.com.

Healthy control smokers will be recruited:
• Through community advertisement (newspaper, flyers, coasters). Flyers may be posted in clinics, and at strategically chosen locations within UMMS, such as designated smoking areas. This includes flyers posted at the Baltimore VA (contingent upon approval by the VA Research & Development Office). Flyers may also be posted in university settings, in student rooms or on student bulletin boards (permission from universities outside UMB would first be obtained). Coasters will be offered to local bars.
• From pools of participants in past studies who provided consent to be re-contacted.
• Through word-of-mouth.
• Via online postings including the MPRC website, Craigslist, and ClinicalTrials.gov.
• By registering the study with Smartphone apps such as studyscavenger.com or trialsapp.com.
• By registering the study with ResearchMatch.org. ResearchMatch.org is a national electronic, web-based recruitment tool that was created through the NIH Clinical & Translational Science Awards Consortium in 2009 and is maintained at Vanderbilt University as an IRB-approved data repository. UMB is a participating institution.
• By posting our contact information on the NIDA Clinical Trial Locator (https://www.drugabuse.gov/research/clinical-research/search). This tool is designed to assist NIDA-funded investigators in finding subjects for clinical trials related to drugs of abuse. Our contact information will be posted under the Nicotine category. The tool is intended to help volunteers find studies. The posting will read "University of Maryland Baltimore, Maryland Psychiatric Research Center; Britta Hahn, 410-402-6112". Study information is provided if and when a volunteer calls in.

Volunteers responding to ads will undergo an initial phone screen covered by a partial HIPAA waiver for recruitment, and are only invited for a consent and screening session if their answers meet several easily-checked eligibility criteria, such as age and smoking history.
For patients, a chart review will be performed prior to approaching them (covered by a partial HIPAA waiver) to check several easily-collected eligibility criteria, such as age and smoking history.
Recruitment flyers will bear a QR code, which will direct the individual to a website associated with our Qualtrics study account. Qualtrics is a HITRUST-certified system designed to securely store PII and PHI to serve HIPAA entities. Participants answer a few screening questions online (screenshots of all questions uploaded below, under "Online Screen"). Participants who pass the online screen will be called and will complete the phone screen before being scheduled for an in-person screening session.
Patients who are approached in person at their clinical care facility will be asked in a non-suggestive manner if they are interested in learning about a research study. A brief overview is provided in a private setting, and if participants are interested, they are given an consent form to read at home, and a date for consent and screening is scheduled right then, or later over the phone.

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.
All participants are given ample time to study the consent form, ask questions, and consider whether to participate.
Wherever possible, volunteers with schizophrenia will be given the consent form ahead to time to read at home and discuss with a family member if desired.
Volunteers with schizophrenia 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)

- [x] **PI**
- [x] **Study Staff**
- [ ] Third Party

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
Telephone screening script(0.10)	6/19/2019 3:04 PM	9/23/2022 11:24 AM

Name	Created	Modified Date
Online Screen(0.01)	6/16/2022 3:56 PM	6/16/2022 3:56 PM
Research Match Contact Message(0.01)	8/29/2019 11:10 AM	8/29/2019 11:10 AM

ID: VIEW4E0BCAA0A6C00
Name: v2_Recruitment

HP-00086422

Advertising_V2

Advertising

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

● **Yes** ○ No

ID: VIEW4E0BCCF811000
Name: v2_Advertising

HP-00086422 Advertising Detail_V2

Advertising Detail

You indicated that you will be using advertisements to recruit potential participants.

1.1 * Select the mode(s) of advertising (check all that apply):

- [ ] Radio
- [x] **Internet**
- [x] **Print**
- [ ] Television
- [x] **Other**

1.1.1 If Other, specify:

- Flyers to be put up on public bulletin boards in cafes, grocery stores, clinics, etc.
- Smartphone recruitment apps
- Newsletters and online bulletin boards, such as the Elm weekly
- Facebook and other social media platform ads
- MPRC website
- Coasters bearing the printed flyer, to be offered to local bars (uploaded below)

1.2 * Provide exact text of all proposed advertisement(s):

Craig's List ad; newsletter posting:
The University of Maryland Baltimore, Maryland Psychiatric Research Center (Catonsville, MD 21228) is recruiting smokers, 18-60 years of age, for a research study. Dr. Britta Hahn is the principal investigator. The study investigates how different research cigarettes are perceived, and how this differs between smokers with and without a diagnosis of schizophrenia. The study involves 4 visits, only on weekdays (Mon-Fri). Two visits last about 2 hours each, one 6 hours, and one 8 hours. Volunteers will be paid $20/hour. Call 410-402-6888, or e-mail eholzel@som.umaryland.edu.

Smart phone recruitment apps:
"Cigarette Smoking in Smokers With and Without Schizophrenia"
We study how different research cigarettes are perceived, and how this differs between smokers with and without a diagnosis of schizophrenia. The study involves a screening visit (2 h), a cognitive testing visit (2 h), and two visits on which you would be comparing different research cigarettes (6 h), or smoking one type of research cigarette as much as you like (8 h). You would be paid $20/hour. To be in the study, you need to be a smokers, 18-60 years of age, either have no psychiatric diagnosis, or have a diagnosis of schizophrenia."
The text in the app may vary slightly depending on whether the app has separate fields and pre-defined categories for, e.g., age, compensation etc.

Print ad and Flyer (including online postings in newsletters, online bulletin boards, social media, MPRC website etc.):
"Smokers needed for research study
We are looking for research participants to study how different cigarettes are perceived, and how this may differ between smokers with and without a diagnosis of schizophrenia.
You may qualify for our study if you are:
*A smoker
*18-60 years of age
The study involves 4 visits to the Maryland Psychiatric Research Center (MPRC) in Catonsville. In total, the study takes ~20 hours to complete. [Transportation can be provided if needed.]
*Compensation: $20/hour
For a confidential screening or more information:
Call 410-402-6888 or email eholzel@som.umaryland.edu with your contact information
or scan the QR code and complete a brief online screening to see if you may be eligible.
Maryland Psychiatric Research Center
www.mprc.umaryland.edu"

Text added to VA flyers only:
"This research is not VA research, will not be conducted by VA, has not been reviewed by VA's Institutional Review Board, and is not endorsed by VA. VA is not responsible for any costs incurred by a Veteran if the Veteran enters the study as a research subject. The announcement is being provided for information only."

1.3 * Upload advertisement(s) here:

Name	Created	Modified Date
Flyer with tear-offs with transportation(0.05)	3/10/2022 11:39 AM	9/23/2022 11:19 AM
Flyer with tear-offs(0.05)	6/20/2019 9:47 AM	9/23/2022 11:11 AM
Flyer without tear-offs with transportation(0.03)	3/10/2022 11:40 AM	9/23/2022 11:04 AM
Flyer without tear-offs(0.04)	7/14/2021 10:14 AM	9/23/2022 11:04 AM
Coaster(0.02)	6/16/2022 4:39 PM	9/23/2022 11:03 AM
Flyer without tear-off facebook(0.04)	9/6/2022 9:44 AM	9/23/2022 11:03 AM
Flyer with tear-offs VA(0.01)	1/12/2022 11:46 AM	1/12/2022 11:46 AM
Flyer without tear-offs VA(0.01)	1/12/2022 11:46 AM	1/12/2022 11:46 AM

HP-00086422

Research Related Risk_V2

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:

Risks associated with this study include those related to: a) nicotine patch administration, b) smoking research cigarettes, c) nicotine withdrawal, d) completing questionnaires, and e) loss of confidentiality. All expected adverse events are non-serious.

a) Risks related to nicotine patch administration:
1. Skin irritation is one of the most common side effect of nicotine patches but is expected to be of minor severity and to dissipate spontaneously after patch removal.
2. Nausea can occur in smokers if more nicotine is ingested from the patch than is usually ingested via smoking, which may be the case for some participants. Nausea is expected to dissipate spontaneously within 2 h after patch removal.
3. Vomiting is expected to be rare; the patch will be removed if nausea occurs, which is likely to prevent most occurrences of vomiting.
4. Palpitations and diaphoresis may occur but are not expected to cause severe discomfort.
5. Headache: This is a minor risk.
6. Abdominal pain and dry mouth are expected to be rare, but may cause significant discomfort.
7. Restlessness, sleepiness, dizziness or temporary mood changes may occur but are expected to be mild.

Risk Minimization for all of the above risks: Participants are informed of this risk in the consent form and are aware that they can end participation and remove or ask for the patch to be removed if any side effect becomes too unpleasant. Participants will wear the 21 mg/24 h patch prior to the Ad Libitum Smoking session, and if any side effects occur, they will receive a 14 mg/24 h patch in the Ad Libitum Smoking session.

b) Possible adverse events related to smoking research cigarettes:
The nicotine yield of either the research cigarettes (0.03 and 0.8 mg) is no higher than that of most commercially available cigarettes. Tar yield is comparable. Risks associated with smoking the research cigarettes are comparable to smoking own-brand cigarettes. However, because the research cigarettes to be used in the Ad Libitum Smoking Session are free and of low nicotine yield, participants may smoke more in the Ad Libitum Smoking Session than they would usually have done. As a result, they may be exposed to more of the harmful components of tobacco smoke (other than nicotine) on this day.

c) Signs and symptoms of nicotine withdrawal may include irritability, difficulty concentrating, anxiety, increased appetite, depressed mood, restlessness, craving, and insomnia (the latter is not expected in this study due to the short duration of withdrawal). Given that participants are only nicotine deprived from waking up in the morning until approximately 11 am (at which time they will have obtained nicotine from the sampled research cigarettes in the Cigarette Discrimination Session or absorbed nicotine from the patch in the Ad Libitum Smoking Session), all of these symptoms are expected to be mild, if present.
Risk Minimization: Anicotine patch is administered in the Ad Libitum Smoking Session in which only very low nicotine content cigarettes are smoked. Both the Cigarette Discrimination Session and the Ad Libitum Smoking Session are scheduled to begin at 9 am, to minimize the period between waking up and nicotine ingestion.

d) Participants may be bored by being asked to answer the same questions repeatedly, find the procedure tiring, or perceive the questions as intrusive.

e) It is possible that some participants may find the computer and paper & pencil tasks boring, mildly stressful or frustrating. Risk Minimization: Participants can take breaks.

f) Loss of confidentiality: Study-related health information, in particular schizophrenia diagnosis and smoking status, may lead to stigma and problems with employment or insurability if confidentiality was breached.
Risk Minimization: Strict confidentiality will be maintained for all information, including demographic, health, and experimental data, and the fact that the participant was in the study. Access to research data is limited to the PI, Co-investigator, and study team members (however, regulatory personnel from authorized entities will also have access to data and PII). All study procedures and exams will be performed in private rooms. Data from initial telephone pre-screenings will be recorded on forms and destroyed as soon as volunteers are either consented into the study or disqualified from the study. Enrolled participants are assigned a code number, which will be the only identifier on all research data, including data in electronic and hard copy form. The secure electronic database linking ID codes with the participant's identity is separated from any study data. All study forms and electronic records with identifiers are maintained separately from research data. Hardcopies of all records with identifiers are stored under double-locked conditions. Demographic and medical data are stored in the ORP Clinical Database. All databases are handled via a local area network (LAN) maintained behind a firewall with multiple layers of protection against unauthorized intrusion. Databases are maintained on a university server and protected by a 5-tiered system involving restricted access at the desktop, directory, database, reporting, and table levels. Data downloaded for analysis will be identified only by subject ID code. Research data forms identified by subject ID code will be stored in locked filing cabinets. All electronic research data will be accessible by password-protected computers and networks only. All computers and networks are behind a firewall with up-to-date virus and spyware protection software.

g) Risks related to blood draws:
Skin irritation is expected to be rare and of minor severity. Pain/discomfort is expected to be common but of minor severity. Weakness or light-headedness is expected to be rare and to dissipate quickly. Syncope is expected to be very rare but is of significant severity if it occurs. Bleeding is expected to be common but of minor severity. 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. Participants will be asked to lie down if experiencing weakness or light-headedness.

General Risk Minimization Procedures: Participants are informed of all risks in the consent form, and it is emphasized that participation is entirely voluntary. Each volunteer will undergo rigorous screening prior to study enrollment. Aurine pregnancy test for female participants will be repeated prior to the Laboratory Smoking Session. Aphysician will be on call at all times. Participants will be provided with the contact information of the Principal Investigator and research assistant, and will be encouraged to call with any question, concern, or adverse effect.

ID: VIEW4E1B52509F000
Name: v2_Research Related Risks

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 are no direct health benefits to participants. The study risks are justified by the importance of the knowledge to be gained.

2 * Describe the importance of the knowledge expected to result from the study:
Smoking is the leading preventable cause of death in the US. In people with schizophrenia, rates and severity of tobacco dependence are approximately three times higher than in the general population, contributing significant¬ly to greater morbidity and lower life expectancy in this population. The present study will test a model of tobacco dependence in schizophrenia with implications for successful treatment, and may redirect treatment development for this population toward novel strategies.

3 * Describe how the potential risks to participants are reasonable in relationship to the potential benefits:
The risks related to administration of nicotine replacement, research cigarettes, short periods of nicotine withdrawal, questionnaires, and handling of private information will be minimized as outlined above. We consider these risks to be low in comparison with the potential knowledge and ensuant clinical benefits to be gained.

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.

ID: VIEW4E1B5251B0400
Name: v2_Potential Benefits and Alternatives

HP-00086422

Withdrawal of Participants_V2

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 will be withdrawn if they display adverse effects of the lower-dose (14 mg/24 hrs) nicotine patch, if they cannot or will not follow instructions, or if scheduling cannot be achieved within the prescribed time frame.

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 will end any procedures associated with the study, and the participant will be paid for their time. Already collected data will be retained unless removal is requested by the participant.

ID: VIEW4E1B52531F800
Name: v2_Withdrawal of Participants