HRP-503B – BIOMEDICAL RESEARCH PROTOCOL
(2016-1)

Protocol Title: **Impact of Switching to Non-Menthol Cigarettes Among Smokers**

Principal Investigator: Krysten Bold, Ph.D.

Version Date: 6/11/2018

(*If applicable*) Clinicaltrials.gov Registration #: NCT03075839

INSTRUCTIONS
This template is intended to help investigators prepare a protocol that includes all of the necessary information needed by the IRB to determine whether a study meets approval criteria. Read the following instructions before proceeding: 1. Use this protocol template for a PI initiated study that includes direct interactions with research subjects. Additional templates for other types of research protocols are available in the system Library. 2. If a section or question does not apply to your research study, type "Not Applicable" underneath. 3. Once completed, upload your protocol in the "Basic Information" screen in IRES IRB system.

SECTION I: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

In this pilot study of 30 non-treatment-seeking adult smokers, we will investigate within-person changes in smoking behavior when current menthol smokers are systematically switched to using non-menthol cigarettes. We will recruit adult daily smokers who currently use menthol cigarettes, observe their smoking behavior with their usual brand of menthol cigarettes in vivo for two weeks, and then switch them to a matched-brand non-menthol cigarette for two weeks. We will assess the impact of switching on cigarette satisfaction (e.g., craving, liking, taste, willingness to continue use, intentions to quit) and smoking behavior, including compensatory use of other tobacco products or menthol products (e.g., gum, mints) to estimate the impact of eliminating characterizing menthol flavor in cigarettes on current menthol smokers. The results will provide novel information on how characterizing menthol flavor additives influence smoking satisfaction and behavior. The FDA could use these results to inform product standards and to predict the effects of restricting characterizing menthol flavor in cigarettes among current menthol smokers. Additionally, the results will inform future study designs by evaluating the feasibility of a cigarette switching paradigm and testing innovative methods to objectively monitor smoking behavior and menthol exposure.

Aim 1: Investigate whether switching to non-menthol cigarettes changes cigarette satisfaction and smoking behavior

Hypotheses: We expect that switching to a non-menthol cigarette will be less reinforcing and result in fewer cigarettes smoked per day, lower nicotine dependence, and greater quitting motivation/interest. Pilot data will be used to estimate effect sizes for these outcomes to inform the development of larger follow-up studies.

Aim 2: Evaluate the utility of objective smoking measures to assess behavior and adherence to the switching paradigm

Hypotheses: We expect that we will be able to quantify and verify self-reported smoking behavior with several objective measures of smoking behavior: collecting spent cigarette filters to measure number of cigarettes and quantify smoking intensity with filter weight and length, quantifying urine menthol glucuronide as a marker of menthol exposure.

2. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

Investigating menthol tobacco product use is critical for informing regulatory efforts. Although the Tobacco Control Act banned the sale of tobacco cigarettes with flavor additives, menthol flavor is currently exempt from this ban. While the overall rate of cigarette smoking has declined in recent years, the proportion of smokers using mentholated cigarettes has increased [1]. Specifically, data from the National Survey on Drug Use and Health indicate the rate of past month menthol cigarette use increased from 7.7% in 2004 to 8.2% in 2010, while the rate of non-menthol cigarette use decreased from 17.1% to 14.6% during that time [1]. Menthol additives are found in several nicotine containing products, including cigars, cigarillos, and e-cigarettes, although conventional cigarettes are still the most frequently used product by adult smokers [2]. Menthol additives in tobacco pose a serious public health problem given evidence that smokers who use menthol cigarettes have greater risk of smoking-related morbidities [3], and worse cessation outcomes [4,5]. Additionally, use of menthol cigarettes is associated with higher rates of smoking and dependence [6,7]. Research is

needed to better understand how menthol additives influence smoking behavior and enhance the addictive potential of tobacco products.

3. Research Plan: Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths. Describe the setting in which the research will take place.

Overview: The proposed project will compare within-person effects of switching from menthol cigarettes to non-menthol cigarettes in current adult menthol smokers (n=30). The primary outcome of interest will be smoking behavior measured via daily monitoring and self-report. Self-reported smoking behavior will be verified by objective biomarkers of nicotine and menthol exposure and by asking participants to return all spent cigarette filters. We expect switching to a non-menthol cigarette will reduce smoking satisfaction and smoking behavior (e.g., fewer cigarettes per day, longer time to first cigarette in the morning) compared to a baseline period of smoking menthol cigarettes.

Settings: Participants will be recruited from the community. Research study visits will take place at our outpatient research offices (34 Park Street CMHC or 1 Long Wharf SATU, New Haven, CT) or a location that is convenient for participants, such as their home or public place

Procedures:
Interested study candidates will be screened by telephone. Those meeting initial eligibility criteria will attend an in-person screening appointment to learn more about the research study, provide written informed consent, and complete intake measures. Eligible participants will then begin a four week monitoring period. Participants will be provided with free menthol cigarettes of their own usual brand to smoke for one week (Phase I, days 0-7) and then will be switched to non-menthol cigarettes for two weeks (Phase II, days 7-21). Participants will be provided with all cigarettes in both Phase I and II to control for the possibility of increased consumption due to free cigarettes (as seen in other studies, [8]) and to encourage adherence to smoking the specified cigarette. To enhance the naturalistic nature of the study, research staff will provide subjects with their usual brand of menthol cigarettes (Phase I), and then will switch them to a matched-brand non-menthol cigarette (Phase II). At the end of the study, we will provide information on tobacco treatment programs to all participants.

Screening Assessments: To screen for eligibility, participants will complete several assessments: 1) Cigarette preference questions assess current use of menthol cigarettes (i.e., “what brand of cigarettes do you prefer?” “what brand of cigarettes do you normally smoke?”). 2) Smoking history to assess smoking quantity and frequency such as number of cigarettes per day and number of years smoked. 3) Expired breath carbon monoxide (CO) measured in parts per million to confirm smoking status. 4) Drug use: to confirm participants are not currently using other substances (other than caffeine or nicotine) assessments will include i) a time-line follow-back interview to assess self-reported drug use quantity and frequency, ii) urine drug toxicology screens, and iii) current blood alcohol level measured with a breathalyzer.

Visit Assessments: Eligible individuals will complete self-report assessments at baseline and research visits: 1) Nicotine dependence, measured by 1) Time to first cigarette in the morning as an index of smoking reinforcement [9,10], 2) Fagerstrom Test for Nicotine Dependence [9] and Wisconsin Inventory of Smoking Dependence Motives [11,12] to assess multiple dimensions of tobacco dependence such as automaticity, loss of control, and affective enhancement. Additional

assessments include: 3) Questionnaire on Smoking Urges-brief [13] to measure cigarette craving, 4) Wisconsin Smoking Withdrawal Scale [14], to assess 7 constructs of nicotine withdrawal: anger, anxiety, concentration, craving, hunger, sadness, and sleep and 5) Confidence and interest in quitting smoking, rated from 1 (not at all) to 10 (extremely) and 6) measures of smoking behavior and cigarette reinforcement and satisfaction.

Biological Measures: Biomarkers of cigarette and menthol exposure will be collected at baseline and weekly research visits (day 7, 14, 21) to examine changes from baseline and to corroborate self-reported tobacco product use and menthol exposure during the trial. 1) Expired breath carbon monoxide (CO) measured in parts per million, 2) Urine cotinine to quantify nicotine exposure, 3) Menthol glucuronide measured in the same urine sample as a marker of menthol exposure.

Adherence**:** Adherence to use of the specified cigarettes in Phase I and II will be closely monitored via subjective and objective measures. Participants will report the total number of cigarettes consumed each day and will be instructed how to save and return spent cigarette filters so the count can be verified by research staff, a procedure that has been utilized previously to verify adherence [15]. Biological measures will monitor menthol exposure and can be compared between Phase I and Phase II to quantify reductions in menthol exposure. We aim to restrict access to menthol cigarettes during Phase II by recruiting only smokers who do not currently live with menthol smokers, collecting any remaining mentholated cigarettes from participants before switching to non-menthol cigarettes, and providing free cigarettes to discourage substitution. Additionally, we will assess participants' use of other mentholated products (e.g., mint toothpaste or gum) or other extraneous tobacco products that are not a part of the study (e.g., e-cigarettes, other tobacco products) each week during the trial. This will allow us to estimate any compensatory menthol or tobacco product use during the switching phase of the study. Lastly, we will incentivize participant reporting by providing compensation for returning spent cigarette filters.

4. Subject Population: Provide a detailed description of the types of human subjects who will be recruited into this study.

   We will recruit current adult (at least 18 years old) daily smokers who report smoking at least 5 cigarettes per day for at least the past 6 months. See detailed inclusion and exclusion criteria below.

5. Subject classification: Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐Children	☐ Healthy	☐Fetal material, placenta, or dead fetus
☐Non-English Speaking	☐ Prisoners	☐Economically disadvantaged persons
☐Decisionally Impaired	☐ Employees	☐Pregnant women and/or fetuses
☐Yale Students	☒ Females of childbearing potential	

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects?
Yes ☐ No ☒

6. Inclusion/Exclusion Criteria: What are the criteria used to determine subject inclusion or exclusion?
   Inclusion Criteria:

(1) 18 or older
(2) English literate
(3) Smoke at least 5 cigarettes per day for the past 6 months
(4) Expired breath carbon monoxide level ≥ 6ppm at baseline or detected urine cotinine level with NicAlert test strip
(5) Report currently smoking menthol cigarettes

Exclusion Criteria:
(1) Seeking smoking cessation
(2) Currently using any stop smoking treatments
(3) History of serious psychiatric condition (i.e., bipolar disorder, schizophrenia)
(4) Current uncontrolled medical condition
(5) Current use of other substances (excluding nicotine and caffeine) or a positive urine toxicology screen
(6) Living with a menthol smoker (to limit access to menthol cigarettes during the non-menthol phase of the trial)
(7) Female participants will be excluded if they are currently pregnant or breastfeeding or report an unwillingness to use effective birth control for the duration of the study

7. How will **eligibility** be determined, and by whom? Write here

Interested participants will call our office and will be provided with verbal information about the project. Interested participants will be initially screened by telephone and will provide their name and contact information and provide answers to short screening questions to assess age, smoking status, menthol preference, and to ensure they are not currently seeking smoking cessation treatment. Participants who meet initial eligibility screening will be invited to complete an intake session. At the intake session, participants will complete an informed consent form. Following this, a research assistant will obtain medical and substance use histories, urine drug and pregnancy tests, and breath CO levels. If study criteria are met, the participant will be scheduled for the subsequent sessions.

8. **Minimizing Risks:** Describe the manner in which the above-mentioned risks will be minimized.

Although we have assessed the proposed study as one of minimal risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we provide a plan for monitoring the data and safety of the proposed study as follows:
Adverse events will be monitored for each subject participating in the study and attributed to the study procedures / design by Dr. Bold according to the following categories:
a.) Definite: Adverse event is clearly related to investigational agent/participation.
b.) Probable: Adverse event is likely related to investigational agent/participation.
c.) Possible: Adverse event may be related to investigational agent/participation.
d.) Unlikely: Adverse event is likely not to be related to the investigational agent/participation.
e.) Unrelated: Adverse event is clearly not related to investigational agent/participation.

The following scale will be used in grading the severity of adverse events noted during the study:

1 Mild adverse event
2 Moderate adverse event
3 Severe unanticipated adverse event resulting in inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect;
4 Life threatening event or
5 Fatal adverse event.

In addition to grading the adverse event, Dr. Bold and the study team will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it:
1. is life-threatening
2. results in in-patient hospitalization or prolongation of existing hospitalization
3. results in persistent or significant disability or incapacity
4. results in a congenital anomaly or birth defect OR
5. results in death
6. based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition, or
7. adversely affects the risk/benefit ratio of the study.

The study team, in consultation with the Yale TCORS Independent Data Safety Monitoring Board (DSMB), will evaluate the adverse event and determine whether the adverse event affects the Risk/Benefit ratio of the study and whether modifications to the protocol or consent form are needed. The DSMB includes experts in the field of tobacco use behaviors. The DSMB will review the study information and the plans for review prior to the initiation of the studies. They will provide an ongoing review every six months or more often if requested by the Board. The summary of the DSMB meeting will be submitted to the Yale HIC and to NIDA following each meeting.

Subjects will be closely monitored for safety throughout the research trial. Although in our experience this is a very rare event, subjects who show significant deterioration (e.g., increased substance use or psychiatric symptoms, including significant suicidal or homicidal ideation), will be withdrawn from the study and referred for appropriate treatment.

At any point if the investigator feels that subjects' health or well-being may be threatened by continuation in the study, subjects will be withdrawn from the study. If participants have a medical emergency, they will be instructed to call 911. Subjects who experience a significant psychiatric or medical problem that requires overnight hospitalization at an acute care facility will be considered to have experienced an SAE.

The Principal Investigator, Dr. Bold, will report the following types of adverse events to the Yale University Human Investigation Committee (HIC):

a) serious AND unanticipated AND possibly, probably or definitely related events;
b) anticipated adverse events occurring with a greater frequency than expected; and
c) other unanticipated problems involving risks to subjects or others.

These adverse events or unanticipated problems involving risks to subjects or others will be reported to the Yale HIC within 5 days of it becoming known to Dr. Bold. The procedures for SAE reporting include written documentation using the clinical notes related to the adverse event and specific forms detailing the event with a sign-off by all appropriate supervisory personnel.

Communication of recommendations and decisions from all parties (Yale Human Investigation Committee) will be made back to Dr. Bold in a timely manner.

i. What provisions are in place for management of interim results?

The principal investigator is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency monthly. During the review process the principal investigator will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. The principal investigator and the Institutional Review Board (IRB) have the authority to stop or suspend the study or require modifications.

ii. What will the multi-site process be for protocol modifications? N/A this is a single-site study

9. Statistical Considerations: Describe the statistical analyses that support the study design.

Data analyses will be conducted with SPSS software. Effect size estimates with 95% confidence intervals will be constructed for each aim to inform future studies. The primary statistical analyses will use within-person repeated measures to test for differences in smoking behavior (e.g., number of cigarettes per day, nicotine dependence) in menthol versus non-menthol phases.

Justification for sample size: Estimation of sample size (n=30) is based on achieving a clinically meaningful precision in effect size estimates for the primary outcome of interest. A power analysis based on α=.05 and β=.80 suggests a sample size of 30 subjects is sufficiently powered to detect medium or large effects (d>.50) within-person. Although we will be unable to detect smaller effects, this sample size is reasonable for a pilot study, and data will be used to test the feasibility of the paradigm and adherence monitoring methodology and to estimate effect sizes to inform the optimal sample size for a larger follow-up study.

Data Monitoring**:** Procedures for data collection, data management, monitoring of data quality and data analysis have been developed and refined in our previous tobacco studies. An experienced data analyst and the PI will supervise these procedures which include use of a computerized database to monitor research activities, screening and enrollment, compliance with protocol, completion of scheduled assessments, and data retrieval. Data quality will be ensured by: 1) extensive training/supervision of research staff in data collection; 2) preliminary review of all assessment instruments prior to data entry and checks for completeness and coding errors; 3) double data entry of written assessment instruments; 4) error-checking statistical programs.

SECTION II: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, check off N/A and delete the rest of the section.

A. RADIOTRACERS ☒N/A

1. Name of the radiotracer: *Write here*

2. Is the radiotracer FDA approved? ☐YES ☐NO

If NO, an FDA issued IND is required for the investigational use unless RDRC assumes oversight.

3. Check one: ☐IND# *Write here* or ☐RDRC oversight (RDRC approval will be required prior to use)

B. DRUGS/BIOLOGICS ☒N/A

B. DEVICES ☒N/A

a)

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. **Targeted Enrollment: Give the number of subjects:**
   a. Targeted for enrollment at Yale for this protocol: 30
   b. If this is a multi-site study, give the total number of subjects targeted across all sites: N/A

2. **Indicate recruitment methods below.** Attach copies of any recruitment materials that will be used.

☒ Flyers	☒ Internet/web postings	☐ Radio
☒ Posters	☐ Mass email solicitation	☐ Telephone
☐ Letter	☐ Departmental/Center website	☐ Television
☐ Medical record review*	☐ Departmental/Center research boards	☐ Newspaper
☐ Departmental/Center newsletters	☐ Web-based clinical trial registries	☒ Clinicaltrials.gov
☐ YCCI Recruitment database	☒ Social Media (Twitter/Facebook):	
☐ Other:		

* **Requests for medical records should be made through JDAT as described at**
http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. **Recruitment Procedures:**

a. Describe how potential subjects will be identified. Potential subjects will be recruited through methods previously used by our team and found to be effective in recruiting smokers. Recruitment methods include flyers, online advertisements (e.g., Facebook, Cragislist), on public boards in New Haven, and by word of mouth. We will provide a $25 referral bonus to any current or previous participants if they refer someone who is eligible for the study. We

will tell subjects only that someone they referred is eligible. We will not release individual names.

b. Describe how potential subjects are contacted. Potential participants can contact the study to determine eligibility through phone call, text message, or a website that will direct them to a Yale Qualitrics website where interested participants can complete a brief screening questionnaire.

c. Who is recruiting potential subjects? The PI and research staff will recruit potential subjects.

4. Assessment of Current Health Provider Relationship for HIPAA Consideration:

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐Yes, all subjects

☐Yes, some of the subjects

☒No

If yes, describe the nature of this relationship. *Write here*

5. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

Choose one:

☐ For entire study

☒ For recruitment/screening purposes only

☐ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data:

ii. If requesting a waiver of signed authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data: We request a waiver of signed authorization only for initial participant recruitment/screening purposes to obtain interested participants' phone numbers and/or email for voice and text communication to make initial contact with the research team. At the first phone contact with the research team, participants will provide verbal consent for the screening process. If participants prefer to complete the online screener through the Yale Qualtrics system, participants will provide signed consent in the online screening survey. Participants will be asked to provide brief demographic information and smoking status information to determine initial eligibility prior to setting up an in-person intake appointment where formal written informed consent will be obtained.

The investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

6. Process of Consent/Assent: Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

   After the screening process is complete and the participant is found to be eligible, the RA/PI will schedule them for an in person intake. At this intake, all eligible participants will be asked for written consent using the Yale HIC approved combined consent/HIPAA form. The entire consent form will be reviewed in detail with the participant in a private, one-on-one setting at the first intake appointment. All risks and potential benefits will be described. Any questions the participant may have will be addressed. If the participant wishes, they may take the consent form home and consider it further before signing. They may also request to speak to anyone on the research team about questions they have or to consult others, including their physician and family members. Once the participant has signed the consent, they may withdraw consent at any time. Informed consent must be obtained prior to performance of any protocol specific procedures. All participants will receive a signed copy of the consent form to retain for their records. All eligible participants will also be asked to provide contact information in the following manner. In addition to providing their own personal contact information, participants will be asked to give the names of two friends or relatives whom we can contact to obtain this information. We will contact these individuals only if we are unable to contact the participant directly and then only for the purpose of obtaining a forwarding address and phone number. Participants will be made aware of this information and potential reason for contacting the listed friends/relatives. We will inform the person that the participant has authorized us to contact them and they will be asked if they are willing to give out this information. If they decline, they will not be contacted again.

7. Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent: Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

   We will not be enrolling participants with limited decision-making capacity. We plan to exclude individuals with current serious psychiatric or medical illnesses. During the consenting process, the research assistant will read and review the consent form with the prospective participant. The research assistant will then ask the potential participant various questions about the consent form and study protocol to ensure the prospective participant sufficiently understands the study and the nature of their consent to participate.

8. Non-English Speaking Subjects: Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.

   N/A

As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment? YES ☐ NO ☒

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via modification prior to enrolling the subject. *Please review the guidance and presentation on use of the short form available on the HRPP website.*

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

9. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☐Not Requesting any consent waivers

☒Requesting a waiver of signed consent:

☒ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study (Note that an information sheet may be required.)

For a waiver of signed consent, address the following:

- Would the signed consent form be the only record linking the subject and the research? YES ☐ NO ☐
- Does a breach of confidentiality constitute the principal risk to subjects? YES ☐ NO ☐

OR

- Does the research pose greater than minimal risk? YES ☐ NO☒
- Does the research include any activities that would require signed consent in a non-research context? YES ☐ NO ☒

☒ Requesting a waiver of consent:

☒ Recruitment/Screening only *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☐ Entire Study

For a full waiver of consent, please address all of the following:

- Does the research pose greater than minimal risk to subjects?
  ☐ Yes *If you answered yes, stop. A waiver cannot be granted.*
  ☒ No
- Will the waiver adversely affect subjects' rights and welfare? YES ☐ NO☒
- Why would the research be impracticable to conduct without the waiver? We request a waiver of signed authorization only for initial participant recruitment/screening purposes to obtain interested participants' phone numbers and/or email for voice and text communication to make initial contact with the research team.
- Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date? At the first phone contact with the research team, participants will provide verbal consent for the screening process. Participants who meet initial eligibility during the screening process will be invited for an in-person meeting to learn more about the study, ask any questions, and provide written informed consent before beginning research activities.

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

1. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research? We will collect names and demographic information. Identifiable information will be collected and used to enroll and contact participants. It will only be used for this purpose. This information will be stored in locked cabinet apart from the research records.

2. How will the research data be collected, recorded and stored? Research data will be collected using in-person interviews, survey assessments, objective measures of smoking behavior, and self-reports. All identifiable information (names and demographic information) will be stored in a locked file cabinet. All participants will be assigned a study participant ID made up of numbers and letters. Subsequently, participants will be identified in the Case Report Forms (CRFs) only by that number (e.g., CM24). A list of IDs and the corresponding names will be maintained by the Principal Investigator and stored in a locked research cabinet. All other research data (interviews, survey assessments, objective measures of smoking behavior, and self-reports) will not contain identifiable information and will be labeled only with the subjects' unique numerical indicator.

3. How will the digital data be stored? ☐CD ☐DVD ☐Flash Drive ☐Portable Hard Drive ☒Secured Server ☐Laptop Computer ☒Desktop Computer ☐Other

   Digital data with PHI will be stored on a secured server. Digital data without PHI may be stored and analyzed on a laptop or desktop computer.

4. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?

   Several steps will be taken to safeguard the confidentiality of subjects and their data. Right to privacy for participation in this research will be protected through coding of data and proper storage of

research records. All research data that is collected will be assigned a study participant number and that number will be the only link between participant names/identifying information and the digital databases. The names of participants will not be associated with this data and assessments will be maintained according to participant study number. A master list connecting participant study numbers to participant names will be kept in a locked file cabinet where it can only be accessed by senior level project staff. Any information published as a result of the study will be in aggregate and such that it will not permit identification of any participant.

We are not directly assessing incidents of child abuse or elderly abuse. However, if this information is disclosed by a participant or volunteer in the context of this research, a report will be made to the Department of Child and Families Services or other agency as required by law. Subjects will be informed of this limit to confidentiality as it is stated in the informed consent document.

All investigators and key personnel have taken the required Yale University HIPAA training. Right to privacy for participation in this research will be protected through coding of data and proper storage of research records. A list of numbers and the corresponding names will be maintained by the Principal Investigator in a locked research cabinet.

Individually identifiable health information will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 and by additional protections of substance abuse treatment records afforded under Code of Federal Regulations (CFR) Part 2, Subpart E. All research personnel will be trained on human subjects protection and HIPAA procedures.

All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url http://its.yale.edu/egrc or email it.compliance@yale.edu

5. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured. The data will be stored in a locked room for 7 years after the final data is collected. After this point, the Data Manager and Principal Investigator will oversee the process in which data is destroyed or de-identified.

6. If appropriate, has a Certificate of Confidentiality been obtained?

   A certificate will not be requested.

SECTION V: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

There is a need to understand menthol cigarette use, given the high rates of use among cigarette smokers and negative impact on morbidity and mortality. The purpose of this study is to evaluate whether switching menthol smokers to non-menthol cigarettes reduces the subjective reward of smoking and reduces smoking behavior and nicotine dependence. This study may help to inform federal policy regulations by the FDA to restrict menthol additives in tobacco products and reduce the appeal and addictive potential of these products.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. Alternatives: What other alternatives are available to the study subjects outside of the research?

   This is not a treatment study. Anyone interested in quitting smoking will be provided with a treatment referral and will not be eligible to participate in this study. All participants will receive information about available smoking cessation services at the end of the study.

2. Payments for Participation (Economic Considerations): Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.

   Participants will be compensated $40 for the baseline intake appointment and will receive $25 for each subsequent study visit (days 0-21) reach a maximum of $140 for study visits. Participants will be incentivized to provide adherence measures and will earn additional weekly compensation (e.g., completing self-report assessments ($10/week), and returning spent cigarette filters ($10/week)). Total maximum compensation for completing study tasks including bonuses: $300.

3. Costs for Participation (Economic Considerations): Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

   There are no costs for participation.

4. In Case of Injury: This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).

   a. Will medical treatment be available if research-related injury occurs? *Write here*
   b. Where and from whom may treatment be obtained? *Write here*
   c. Are there any limits to the treatment being provided? *Write here*
   d. Who will pay for this treatment? *Write here*
   e. How will the medical treatment be accessed by subjects? *Write here*

   (a-e) If a participant is injured as a direct result of participation in this study, treatment will be provided. The participant and/or his or her insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available. Participants will not waive their legal rights by participating in this study.

IMPORTANT REMINDERS

Will this study have a billable service? Yes ☐ No☒

A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding

mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes ☐ No ☒

If Yes, please answer questions a through c and note instructions below.

a. Does your YNHH privilege delineation currently include the specific procedure that you will perform? Yes ☐ No ☐

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? Yes ☐ No ☐

c. Will a novel approach using existing equipment be applied? Yes ☐ No ☐

If you answered "no" to question 4a, or "yes" to question 4b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. By submitting this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH.

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