Effect of Banning Menthol Flavorant on Cigarette and E-Cigarette Use

NCT03402243

01/16/2020

PROTOCOL TITLE:

Effect of Banning Menthol Flavorant on Cigarette and E-Cigarette Use

PRINCIPAL INVESTIGATOR:

Michael Kotlyar, PharmD
Associate Professor
Department of Experimental and Clinical Pharmacology
612-625-1160
kotly001@umn.edu

Co-Investigators

Dorothy Hatsukami, PhD
Professor
Department of Psychiatry
612-626-2121
hatsu001@umn.edu

VERSION NUMBER/DATE:

Version 5.0
Version Date: 01/16/20

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	1/22/2018	• Daily tobacco diaries to be completed via RedCap with subjects receiving email or text messages daily with survey links. This is instead of the EMA Life Data Application. • Subjects will start completing tobacco diaries after eligibility is confirmed rather than after the baseline visit. • Adding a $15 bonus at the baseline visit if over 85% of daily tobacco diaries are completed prior to the visit. This additional bonus raises the total amount subjects will receive to $190. • The addition of inclusion criteria specifying that subjects must be able to receive daily text and email reminders and respond to the surveys as prompted by the reminders. • Clarifying that the tank-like e-cigarette and liquid use are the Joyetech eGo AIO device rather than the Joyeteich eGo-T • Section 5.2.2 has been clarified to indicate that in determining the number of credits needed for each product, the retail cost will be discounted approximately 66%	Yes
2	8/14/18	• Added additional information to section 18.0 “Provisions to Monitor the	

Revision #	Version Date	Summary of Changes	Consent Change?
		Data to Ensure the Safety of Participants"	
3	10/02/19	• Added information to section 5.2.1 regarding how participants who complete the online screening survey will be notified regarding their eligibility to schedule a screening visit • Updated section 14.1 with additional information about the potential risk of using e-cigarettes / vaping devices	Yes
4	01/16/20	• Changes to inclusion criteria that 1) increases the minimum age for enrollment from 18 to 21; 2) decreases the minimum average number of cigarettes smoked per day from 10 to 5	No

Table of Contents

After completing your protocol, right click on the Table of Contents below and select "Update Field." If prompted, select "Update entire table." This will automatically update the protocol sections and page numbers for you. Do this also each time you modify your protocol after initial approval.

ABBREVIATIONS/DEFINITIONS

- CO – carbon monoxide
- FDA – Food and Drug Administration
- FSPTCA - Family Smoking Prevention and Tobacco Control
- E-Cig – E-Cigarette

STUDY SUMMARY

Study Title	Effect of Banning Menthol Flavorant on Cigarette and E-Cigarette Use
Study Design	Randomized Study
Primary Objective	To obtain preliminary information regarding how a menthol ban that either exempts or includes e-cigarettes is likely to affect overall tobacco use
Research Intervention(s)/Investigational Agents	Smokers of menthol cigarettes will be randomized to one of three experimental marketplace conditions: 1) a simulated ban on menthol cigarettes but not e-cigarettes; 2) a simulated ban on both menthol cigarettes and e-cigarettes and 3) no menthol ban for either product
IND/IDE # (if applicable)	n/a
Investigational Drug Services # (if applicable)	n/a
Study Population	Medically stable smokers
Sample Size (number of participants)	60
Study Duration for Individual Participants	Approximately 8 weeks

1.0 Objectives

1.1 Objective: The objective of this study is to obtain preliminary information regarding how a menthol ban that either exempts or includes e-cigarettes is likely to affect overall tobacco use

1.2 Specific Aims: The following specific aims will be pursued:

Aim 1: Determine the impact of the availability of menthol flavor in e-cigarettes on overall tobacco product use patterns

We hypothesize that menthol cigarette smokers will smoke fewer cigarettes, vape more e-cigarettes, have higher motivation to quit smoking and be more supportive of a ban on menthol cigarettes when given the option of using menthol flavored e-cigarettes than when no such option is present.

Aim 2: Determine if the impact of the availability of menthol flavor in e-cigarettes on tobacco use behavior is moderated by a ban on menthol flavor in cigarettes

We hypothesize that the impact of menthol flavored e-cigarette availability on the above measures will be greater during a simulated ban on menthol cigarettes than if smokers can continue smoking menthol cigarettes.

2.0 Background

2.1 Significance of Research Question/Purpose: With the passage of the Family Smoking Prevention and Tobacco Control Act (FSPTCA), the United States Food and Drug Administration (FDA) acquired broad ability to regulate tobacco products, which included the use of flavorants in cigarettes. In 2009, the FDA banned cigarettes flavored with fruit or candy in response to evidence that such flavoring encourages experimentation by young people and leads to regular use and ultimately addiction.[1] Menthol was specifically excluded from this ban as the FDA examines the role of menthol in initiation, maintenance, and health risks associated with the use of such products.[1] The Tobacco Products Scientific Advisory Committee in a report reviewing the impact of the use of menthol cigarettes to public health, provided the overall recommendation that "Removal of menthol cigarettes from the marketplace would benefit public health in the United States."[2, 3] A report produced by the FDA evaluating the public health effects of menthol in cigarettes similarly concluded that menthol use is likely associated with increased smoking initiation by youth and young adults, that menthol in cigarettes is likely associated with greater addiction, and that menthol smokers are less likely to successfully quit smoking. Overall, this report concluded that it is "likely that menthol cigarettes pose a public health risk above that seen with non-menthol cigarettes."[4] The role of menthol flavoring in other tobacco products was not addressed in either of these reports.

The use of electronic nicotine delivery devices (e-cigarettes) has increased dramatically since their introduction in the United States in 2007. Recent surveys

have found that over 12% of adults have tried e-cigarettes and that 5.5% of all adults and 8.9% of young adults use e-cigarettes either every day or on some days.[5, 6] Sales of e-cigarettes for 2016 are estimated at approximately $1.6 billion and some estimates project that e-cigarette sales may overtake cigarette sales within 10 years.[7] [8] Almost every commonly used brand of e-cigarette is currently available in menthol flavor[9] and data from surveys suggest that as many as 30% of e-cigarette users prefer menthol flavored products with over 12% of e-cigarette users stating that they use e-cigarettes "because they come in menthol flavor."[10-13] However, there is little information assessing if the availability of menthol flavorant in e-cigarettes affects smoking behavior in the context of a ban on menthol flavorant in cigarettes.

With the recent extension of FDA authority to additional categories of tobacco products including e-cigarettes,[14] the ability to enact regulations regarding the availability of flavorants (including menthol) will extend to these other categories of tobacco products as well. Although surveys of menthol smokers suggest that a substantial number would attempt to quit smoking if menthol cigarettes were unavailable,[3, 15, 16] our preliminary data found that relatively few in fact made a cessation attempt (only 3 out of 31 subjects). However, it is not known if access to menthol flavored e-cigarettes would increase the likelihood of menthol smokers quitting smoking entirely in the event of a ban since they have an alternate menthol product available or conversely if likelihood of quitting would decrease with smokers opting to use a combination of non-menthol cigarettes and menthol flavored e-cigarettes. The former would support exempting menthol e-cigarettes from a menthol ban whereas the latter would support enacting a menthol ban that would include all tobacco products. Among the numerous research needs regarding e-cigarettes identified in an NIH sponsored workshop are the needs to evaluate the effects of flavorants, biomarkers of exposure, and patterns of use.[14] The purpose of the current study is to obtain initial data regarding how menthol flavoring in e-cigarettes affects tobacco use patterns in menthol cigarette smokers in order to plan future studies that more definitely assess if regulatory policy regarding menthol flavoring should be uniform across products.

2.2 Preliminary Data: Our research team has considerable experience with the methods proposed in this study and with the study population being recruited. The most relevant projects include:

2.2.1 <u>Data demonstrating that in the event of a menthol ban in cigarettes, smokers of menthol cigarettes switch to smoking non-menthol cigarettes:</u> In a pilot study led by Dr. Kotlyar, we asked African American menthol cigarette smokers to not smoke menthol cigarettes for a 4 week period in order to obtain information regarding how they would adjust their smoking behavior were menthol cigarettes not available (as in the event of a ban).[17] No specific instructions were provided regarding how to cope with abstaining from menthol cigarettes. Of the 32 subjects who completed the study, three reported making a quit attempt with all continuing smokers switching to non-menthol cigarettes. Modest decreases occurred in cigarettes smoked per day (11.9 vs. 9.8 cigs/day; $p < .001$) and exhaled CO (13.4 vs. 11.1 ppm; $p = .03$) between the start and the end

of the 4 week period. Motivation to quit smoking was higher at the week 4 visit than at baseline (5.3 vs. 6.3 on a 10 point scale; p = .03). At the end of the study, subjects indicated that quitting menthol cigarettes was difficult (average score = 7.2 on a 10 point scale) but that they were supportive of banning menthol (average score = 7.1). Our finding of substantial support for a ban on menthol cigarettes is consistent with other surveys[16, 18] and is important data since broadening support for a menthol cigarette ban among current users of menthol cigarettes would likely ease passage of such regulations. The current study would expand on these data to determine if these changes in smoking, motivation to quit smoking, and other measures assessed are either enhanced or undermined by the availability of menthol flavored e-cigarettes. This study will also provide information regarding the level of support among menthol flavored cigarette smokers of banning menthol flavoring across tobacco products.

2.2.2 Experience using an experimental marketplace to evaluate smoker product preferences: Dr. Hatsukami conducted a study utilizing an experimental marketplace similar to the one proposed in this project. The goal of the study was to determine the pattern of tobacco use and levels of biomarker exposure when smokers were switched to very low nicotine content (VLNC) cigarettes and had access to alternative nicotine delivery systems.[19] Similar to the proposed study, smokers were randomized to one of three experimental marketplace conditions (i.e., access to combustible and non-combustible products, access to only non-combustible products, and a control normal nicotine content cigarette condition) and were provided a set number of credits which could be used to obtain available products. The study found significant differences in tobacco product use among the three experimental conditions (with greater number of participants in the VLNC condition using alternative products and with higher rate of quit attempts) demonstrating that the experimental marketplace approach was feasible and was acceptable to smokers. The proposed project will evaluate the feasibility of using this approach to study effects of flavorants on tobacco product use.

2.3 *Existing Literature:* Studies have found that when cigarette smokers are provided e-cigarettes to use ad libitum, the number of cigarettes smoked decreases substantially. For example, two studies in which cigarette smokers not interested in quitting were provided e-cigarettes for a 24 week period and asked to use them ad libitum found an overall 80% reduction in median cigarettes per day with 23% - 36% of smokers quitting cigarettes entirely.[20, 21] Similar results were seen in another study in which smokers were given e-cigarettes that they could use ad libitum over a 2 month period while continuing to smoke.[22] All of these studies used tobacco flavored (i.e., non-menthol flavored) products and therefore effects of menthol were not assessed. Studies looking at the effects of e-cigarettes on craving and withdrawal symptoms have found that these products significantly decrease craving and withdrawal symptom severity but most of these studies do not specifically assess menthol flavored products.[22-27]

Studies that have specifically examined menthol flavoring in e-cigarettes include a study in which African American menthol smokers could select using either menthol or tobacco flavored e-cigarettes (or nicotine gum) for a two week quit

attempt. This study found that 74% selected menthol flavored e-cigarettes.[28] A study designed specifically to examine the role of flavor on smoking patterns asked smokers to abstain from cigarettes and only use an assigned flavor of e-cigarettes. This study found that those assigned to menthol flavored e-cigarettes had the largest decrease in number of cigarettes smoked relative to those assigned to tobacco, cherry, or chocolate flavored e-cigarettes.[13] In an additional cross-over study, twenty non-treatment seeking smokers used menthol and tobacco flavored e-cigarettes, each for 7 – 10 days and completed on their last day of e-cigarettes use, a laboratory session at which they used their assigned product for 5 minutes. In female smokers who used their non-preferred flavor (i.e., menthol smokers using non-menthol e-cigarettes and vice versa), nicotine concentrations were lower and the e-cigarette was rated as less likeable than when using their preferred flavor with no such differences found in men.[29] These studies suggest that menthol cigarette smokers prefer menthol flavored e-cigarettes, that menthol flavored e-cigarettes have the potential to decrease smoking to a greater extent than other e-cigarette flavors and that there may be sex differences in response to menthol flavoring in e-cigarettes. The current study will build on this research by providing preliminary data into how availability of e-cigarettes affects cigarette smoking and if these effects are moderated by the availability of menthol flavored cigarettes and / or e-cigarettes.

3.0 Study Endpoints/Events/Outcomes

3.1 Primary Endpoint/Event/Outcome: The primary outcome is the amount of each tobacco product used per week as recorded on their tobacco use surveys.

3.2 Secondary Endpoint(s)/Event(s)/Outcome(s): Secondary outcomes measured at each visit include how much of each product is obtained from the experimental marketplace, motivation and self-efficacy to quit smoking cigarettes and to quit all tobacco product use, number of quit attempts, severity of craving and withdrawal symptoms, and exhaled carbon monoxide concentrations. Support for a menthol ban and urinary cotinine concentrations will be assessed at baseline and at week 6.

4.0 Study Intervention(s)/Investigational Agent(s)

4.1 Description: Subjects will be randomized to one of three experimental marketplaces (20 subjects in each condition): 1) a condition simulating a ban on menthol cigarettes but not menthol e-cigarettes (condition A); 2) a condition simulating a ban on both menthol cigarettes and menthol e-cigarettes (Condition B); and 3) a condition in which menthol is not banned for either product (Condition C – the control condition). All conditions would have medicinal nicotine available if subjects decide to quit tobacco products entirely.

The goal of the experimental marketplace is to provide a context in which product preferences can be evaluated in a systematic way but with a high degree of ecological validity. We have therefore included in the marketplace both a

cigarette-like e-cigarette system and a tank-like e-cigarette system (which has the potential to deliver higher doses of nicotine), as those are the two most commonly used e-cigarette systems currently available.

<table>
<tr><td colspan="3">Products available to subjects in each experimental marketplace</td></tr>
<tr><td>Condition A
(menthol ban for cigs)</td><td>Condition B (menthol ban for cigs and e-cigs)</td><td>Condition C
(no menthol ban)</td></tr>
<tr><td>- Non-menthol cigarettes
- Menthol & tobacco flavored versions of commonly used cigarette-like e-cigarette (e.g., Vuse)
- Menthol & tobacco flavored versions of commonly used tank-like e-cigarette (e.g., Joyetech eGo AIO)
- Nicotine gum and lozenge (various flavors)</td><td>- Non-menthol cigarettes
- Tobacco flavored version of commonly used cigarette-like e-cigarette (e.g., Vuse)
- Tobacco flavored version of commonly used tank-like e-cigarette (e.g., Joyetech eGo AIO)
- Nicotine gum and lozenge (various flavors)</td><td>- Menthol & non-menthol cigarettes
- Menthol & tobacco flavored versions of commonly used cigarette-like e-cigarette (e.g., Vuse)
- Menthol & tobacco flavored versions of commonly used tank-like e-cigarette (e.g., Joyetech eGo AIO)
- Nicotine gum and lozenge (various flavors)</td></tr>
</table>

We will include the subject's usual brand of cigarettes in the marketplace (either the non-menthol version or both the non-menthol and menthol version depending on the randomization). Information about their usual brand will be collected at the screening visit in order to incorporate it into the marketplace.

4.2 Drug/Device Handling: The tobacco and nicotine replacement products that will be provided to subjects are marketed products and are not required to be dispensed by a physician or licensed pharmacy. They will be provided to participants by the study coordinator

4.3 IND/IDE. N/A

4.4 Biosafety: N/A

5.0 Procedures Involved

5.1 Study Design: This is a pilot study in which over a 6 week period, menthol cigarette smokers will receive all of their tobacco products from a simulated experimental marketplace. Smokers will be assigned to one of three marketplace conditions: 1) a condition simulating a ban on menthol cigarettes but not menthol e-cigarettes; 2) a condition simulating a ban on both menthol cigarettes and menthol e-cigarettes; and 3) a condition in which menthol is not banned for either product (i.e., the control condition). All conditions would have medicinal nicotine available if subjects decide to quit tobacco products entirely. Subjects would receive "credits" that they can exchange, at visits occurring every two weeks, for any product available in their randomized marketplace condition. At the end of the experimental period any unused credits can be exchanged for monetary payment.

5.2 Study Procedures: The following procedures will occur during the study.

5.2.1 *Screening Visit:* Initial eligibility will be assessed via a phone interview or online screening form housed on REDCap. All screened participants will be notified by phone or email regarding their eligibility to be scheduled for a screening visit at which written informed consent will be obtained and eligibility

confirmed. At the screening visit, medical and psychiatric history will be obtained via subject report. Women will have a urine pregnancy test to confirm that they are not pregnant. A medical professional (e.g., Nurse Practitioner) will review medical histories to ensure eligibility. Baseline questionnaires assessing smoking history will be administered and an exhaled carbon monoxide (CO) will be measured to confirm smoking (CO $\geq$ 8 ppm). A NicCheck using a urine sample will be performed (with a cut-off = 6 for those who otherwise qualify but for whom CO is < 8 ppm (e.g., they didn't smoke that morning, they came straight from work, etc.). Subjects who qualify and are interested in continuing will be invited to return to the baseline visit.

After eligibility is confirmed, subjects will begin receiving links daily via either text message or email (whichever they prefer) to a tobacco use survey that is to be completed on RedCap. On this survey subjects will report use of all tobacco and nicotine containing products used during the past day. These survey will continue until the end of the subject's participation in the study.

5.2.2 Baseline Visit (i.e., week 0): At the baseline visit, urine will be collected from which baseline urinary cotinine concentrations will be measured. Exhaled CO will be measured from a breath sample. Tobacco use behavior subsequent to the screening visit will be determined as will subjects' level of craving, withdrawal, motivation and self-efficacy to quit smoking and support for a ban on a variety of menthol containing tobacco products. Degree of nicotine dependence will be assessed using the Fagerstrom Test for Nicotine Dependence.[30] Subjects will be informed which products are available in the marketplace that they have been randomized to and will be allowed to handle each of the products and examine the packaging that each normally comes in.

Subject will be given credits at each visit that can be exchanged for products in their marketplace. All products will be discounted to approximately 66% of the retail market value (similar to the study summarized in preliminary data) in order to discourage subjects from purchasing products outside the marketplace and also prevent hoarding credits for payment at the end of the study. The credit amount will be calculated in order to allow on average a 1 pack/day smoker to replace all of their tobacco products based on normal usage patterns (e.g., for example, one cartridge of Vuse lasts about as long as one pack of cigarette). In order to discourage subjects obtaining more products than they need, any credits not used at each visit can be banked and used at later visits or converted to monetary payment at the end of the study. Subjects will be informed that they can obtain any amount or type of product up to the value of current and banked credits and will be provided with the packaging that normally accompanies these products. Instructions for product use will be primarily limited to what is on the packaging so as to more accurately simulate natural marketplace conditions; however subjects can ask questions about the products to which accurate answers will be provided. While subjects will be encouraged to obtain all tobacco products they use from the experimental marketplace, no penalties will be levied for outside purchases in order to encourage truthful reports of noncompliance.

5.2.3 Evaluation Visits (3 visits occurring at 2 week intervals). Subsequent to the baseline visit, subjects will be evaluated at 3 visits occurring at two week intervals (i.e., at approximately 2, 4 and 6 weeks after the baseline visit). To each visit, subjects will be asked to bring back any unused product as well as all used and unused e-cigarette cartridges or e-fluid vials. The cartridges and vials will be weighed prior to distribution and after use to determine the extent to which they were used. Participants will be allowed to keep any of the unused products so as to not discourage them from bringing back unused product.

At each visit, exhaled carbon monoxide concentrations will be measured and subjects will complete questionnaires assessing various aspects of smoking behavior including craving, withdrawal symptoms and motivation to quit smoking. Questionnaires assessing how they rate the effects of the products they are using and their perceived health risks of using these products will also be assessed. A food diary asking primarily about dietary menthol will be completed to determine if dietary intake changes occur if menthol in tobacco products is no longer available. Level of support for a ban on a variety of menthol containing tobacco products will be evaluated at the baseline and week 6 visits. Additionally, at the week 6 visit urine will be collected in order to measure cotinine concentrations. At each visit (except for the week 6 visit), subjects will again have the opportunity to obtain additional products for the subsequent 2 weeks using their available credits. They may choose to obtain any of the available products in their marketplace and are not limited to products that they had previously chosen.

5.3 Individually Identifiable Health Information: All information is collected directly from subjects (i.e., medical records will not be requested) and this is not a treatment study. The data being collected therefore does not meet the definition of PHI.

5.4 Use of radiation*: N/A*

5.5 Use of Center for Magnetic Resonance Research*: N/A*

6.0 Data and Specimen Banking

6.1 Storage and Access: Urine will be collected from subjects at the baseline and week 6. The samples will be stored in freezers located in labs used by faculty in the ECP department (currently these freezers are located on the 5th floor of 717 Delaware Ave).

6.2 Data: Urine samples will be labeled with subject number and date of visit. Samples will be assayed for cotinine concentrations. Cotinine is a metabolite of nicotine and frequently used to confirm abstinence or quantify nicotine exposure. Urine may also in the future be used to assay other measures related to smoking or specifically related to smoking menthol cigarettes or substances related to e-cigarette use. Examples of such measures would include assaying nicotine or metabolites of nicotine other than cotinine, assaying menthol concentrations or

assaying toxicants associated with smoking to determine if exposure to such substances changes when smokers use e-cigarettes or if flavor of e-cigarettes affects these measures.

6.3 The current planned analyses will be performed by labs within the University of Minnesota. However, if by the time the samples are collected these labs are no longer able to provide this service, these samples may be sent elsewhere for analysis. Similarly, if samples are in the future assayed for other measures, they may be sent to external laboratories depending on the capabilities and cost of such analyses. If samples for other measures are sent to external laboratories for additional assays, they will be labeled with a subject code that has no identifiable information on it. Prior to sending samples to an outside source, the IRB will be notified.

7.0 Sharing of Results with Participants

7.1 Study results will not be shared with participants.

8.0 Study Duration

1.2.2 The anticipated duration for an individual participant's participation in the study is approximately 6 to 8 weeks (depending in part on length of time between the screening visit and the baseline visit).

2.2.2 Data collection is expected to be complete within 2 year of starting the study.

9.0 Study Population

9.1 Inclusion Criteria: To be eligible subjects must:

a) Be between the ages of 21 and 64

b) Smoke (on average) at least 5 cigarettes per day over the past year

c) Purchase exclusively menthol cigarettes

d) Not currently motivated to quit smoking

e) Able to receive daily text or email survey reminders and follow the link provided to complete the online RedCap surveys

9.2 Exclusion Criteria: Subjects will be excluded if they:

a) Report a serious, unstable medical or psychiatric condition

b) Have a history of substance abuse (other than nicotine) within 3 months of beginning the study

c) Use any medications that might interfere with measures to be studied (for example, medications known to affect smoking)

d) Have used any smoking cessation therapy during the past month

e) Regularly use any form of tobacco other than cigarettes (> 9 times per month)

f) Are pregnant or breast feeding or planning to become pregnant or breast feed during the study

g) Currently participating in other clinical research studies

9.3 Screening: At the screening visit, subjects will complete a series of questionnaires including those that ask about medical history, smoking history, and motivation to quit smoking. All inclusion / exclusion will be based on self-report except for smoking status which will be confirmed via an exhaled carbon monoxide (CO) concentration of $\geq$ 8 ppm or a urinary nicotine test strip reading of 6. Non-pregnant status will be confirmed via a urine pregnancy test.

10.0 Vulnerable Populations

10.1 Vulnerable Populations:

☐ Children
☐ Pregnant women/Fetuses/Neonates
☐ Prisoners
☐ Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders
☐ Approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.
☐ Disadvantaged in the distribution of social goods and services such as income, housing, or healthcare
☐ Serious health condition for which there are no satisfactory standard treatments
☐ Fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior)
☐ Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research
☐ Undervalued or disenfranchised social group
☐ Members of the military
☐ Non-English speakers
☐ Those unable to read (illiterate)
☐ Employees of the researcher
☐ Students of the researcher
☒ None of the above

11.0 Local Number of Participants

11.1 Local Number of Participants to Be Consented: We plan on recruiting approximately 60 subjects anticipating that approximately 54 will complete the study. We expect that as many as 120 subjects will undergo the consent process. Some of those that attend the screening visit will likely not meet inclusion / exclusion criteria whereas others will not be interested in participating.

12.0 Local Recruitment Methods

12.1 Recruitment Process: Advertisements for the study will be placed in various print and on-line sources and via flyers. Interested participants will call the phone number listed. Study staff will explain the study to potential study subjects. Individuals that indicate an interest in participating in the study will then be screened by telephone to see if they are likely to qualify for the study. Additionally subjects that in previous studies agreed to be contacted regarding other research opportunities may be called – in this case, subjects will be informed why they are being called with the telephone screening process being the same as for subjects who contacted us after seeing the study advertised.

12.2 Recruitment Materials: Flyers and advertisements placed in local publications or on on-line resources (for example, Craigslist) will be used to recruit participants.

12.3 Payment: Subjects will be paid as follows: $20 for completing the screening visit. In addition to receiving credits for tobacco products, they will receive $15 for each of the subsequent 4 visits in this study. They will receive an additional $15 at the baseline visit, and week 2, 4, and 6 visits if they have completed at least 85% of their scheduled electronic diary assessments and have brought in their used e-cigarette cartridges. A $50 bonus will be given to subjects completing the study and all study related assessments. Up to $190 will therefore be paid to subjects for the entire study. Payment will be provided at the end of each visit in the form of a pre-paid debit card.

13.0 Withdrawal of Participants

13.1 Withdrawal Circumstances: Subjects may be withdrawn from the study if they fail to follow study procedures (e.g., show up to scheduled study visits) or if there are changes to their health that are likely to affect smoking behavior. Additionally, subjects will be told that participation is voluntary and that they may discontinue participation at any time for any reasons.

13.2 Withdrawal Procedures: We will attempt to contact subjects by telephone who do not show up to scheduled visit to ascertain if they wish to continue to participate in the study (and if not, why not) and to determine smoking status at the time of their withdrawal.

14.0 Risks to Participants

14.1 Foreseeable Risks: The tobacco products and medicinal nicotine products that are used for this study are those that are commercially available. Although there are numerous risks associated with smoking cigarettes, we are only enrolling those who are already smoking and are at the time of enrollment not motivated to quit. The risks of continuing to smoke cigarettes within the context of the study are no greater than if they were to continue smoking cigarettes outside of the study.

E-cigarettes do not currently undergo regulatory evaluation, however they are easily available and increasingly being used. The risks of using e-cigarettes are generally thought to be lower to an individual than the risks of smoking. Nicotine gum and lozenge are available without a prescription, commonly used and generally well tolerated. Side effects that can occur include hiccups, mouth or throat irritation and upset stomach.

All of the products being provided to subjects contain nicotine and it is possible that overuse can lead to symptoms of nicotine toxicity which could include nausea, vomiting, dizziness, weakness, and rapid heartbeat. Considering that we only enrolling experienced smokers, nicotine toxicity is not likely.

The e-cigarette liquid contains propylene glycol which may be associated with throat irritation. There have been occasional reports of e-cigarette devices malfunctioning and causing injury to users.

There have been recent reports of seizures and breathing problems occurring in people who use e-cigarettes. These cases are being investigated and at this time it is not known how common these problems are or what is causing them. Since many of the cases of breathing problems occurred in individuals using e-cigarettes products with liquids that contain cannabinoid products such as THC, it is likely that the risk is due to people adding substances to e-liquids that were not intended by the manufacturer. The e-cigarette products available in the study are widely available and widely used. The devices and liquids provided to participants are not modified in any way after purchase.

As with any product, there is a risk that unanticipated effects from using the e-cigarette or lozenges may occur, however the risk of using the product as directed by the manufacturer is no higher than it would be if subjects were to buy and use these products outside of the study.

14.2 Reproduction Risks: Smoking cigarettes during pregnancy is known to be harmful to reproductive health. We will therefore exclude women who are pregnant or are planning to become pregnant during the study. Women who inform us that they have become pregnant during the study will not be provided any additional tobacco / nicotine products.

14.3 Risks to Others: There are no anticipated risks to others.

15.0 Potential Benefits to Participants

15.1 Potential Benefits: As this is not a treatment study, there is no direct benefit to individual participants.

16.0 Data Management

16.1 Data Analysis Plan: Means (arithmetic or geometric for log-transformed variables) and their corresponding confidence intervals will be calculated for each study condition. Results will also be tabulated separately for men and women. A linear mixed model will be fit for each outcome variable, with fixed categorical effects of group, time, and their interaction, and random subject effects to account for correlation among repeated measurements on the same subject. We expect randomization to balance groups with respect to important baseline covariates such as cigarettes smoked per day and degree of nicotine dependence; however, we will check this assumption using ANOVA and consider adjustment for imbalanced factors. Exploratory modeling of gender and race / ethnicity effects will also be performed. Model contrasts will be used to evaluate the hypotheses of the two aims, primarily that cigarettes smoked will be lower and e-cigarette use higher when menthol e-cigarettes are available (Aim 1: conditions A and C compared to B), and that these effects will be larger when menthol cigarettes are unavailable (Aim 2: condition A compared to C)

16.2 Power Analysis: The main purpose of this project is to provide initial information regarding how banning menthol in either only cigarettes or in both cigarette and e-cigarettes will influence tobacco use patterns so as to better design a subsequent study that more definitively addresses this issue. This study will also provide feasibility information regarding using an experimental marketplace for assessing this question. For this pilot study, we plan on recruiting 60 subjects and anticipate (assuming 10% dropout), that there would be 18 evaluable subjects per group. If there is a large effect, we should be able to detect it as this sample size will provide 80% power for a between-groups time-averaged effect size of 0.8, assuming two-sided alpha=0.05 and within-subject autocorrelation of 0.6.

16.3 Data Integrity: In order to ensure that data entry is correct, data collected on paper questionnaires will be entered twice with the two entries compared and any discrepancies resolved.

17.0 Confidentiality

17.1 Data Security: To ensure confidentiality, all subjects will be assigned a study identification code to be used on all data collection forms except those for which use of personal identifiers is mandatory (e.g., informed consent form). Forms that link the name of the participant and the subject identification code will be kept in a locked cabinet or office or in an electronic file stored on servers maintained by the University of Minnesota Academic Health Center. Visits will be conducted at the CTSI, therefore there will be a record of the subject's

participation in the CTSI records although a copy of the consent form will not be placed in the participants' medical records.

18.0 Provisions to Monitor the Data to Ensure the Safety of Participants

If the IRB determines this subject to involve Minimal Risk then no independent monitoring will be needed (per IRB guidelines). In this study we will be providing commercially available tobacco products and commercially available over the counter nicotine gum and lozenges to smokers who are not interested in quitting smoking. All products will be provided with the labelling that normally accompanies it. The risks are therefore no greater than if subjects were to purchase these products outside of the study.

If the IRB determines this study to involve more than Minimal Risk, the CTSI monitoring group will be asked to monitor this study using their standard procedures.

The PI will meet regularly with research staff (at least bi-weekly) throughout the project. During these meetings, the study team will evaluate the progress of the trial, review data quality, recruitment, retention, and examine other factors that may affect study outcomes. They will also review adverse events to determine if there are any changes in participant risk. Additional meetings will occur if concerns regarding a particular participant or another problem should arise.

19.0 Provisions to Protect the Privacy Interests of Participants

19.1 Protecting Privacy: During the consent process, subjects will be told that they can discontinue participation at any time for any reason. Furthermore, they are free to not answer any questions asked on the questionnaires. However since certain information is needed to assess eligibility or to assess measures of interest, declining to answer certain questions may lead to a subject not being eligible to participate or to continue with the study.

20.0 Compensation for Research-Related Injury

20.1 Compensation for Research-Related Injury: No compensation is available in the event of research related injury.

21.0 Consent Process

21.1 Consent Process (when consent will be obtained): Informed consent will be obtained at the screening visit. Subjects will have the opportunity to read the consent document and ask any questions that they have. A member of the study staff will then ask the subject questions to make sure that they understand the

study procedures. No study procedures will be administered until the subject has signed the consent form.

21.2 Waiver or Alteration of Consent Process (when consent will not be obtained): N/A

21.3 Non-English Speaking Participants: N/A

21.4 Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age): Individuals under the age of 18 will be excluded from the study. Subjects will be asked to present ID at the screening visit to confirm that they are at least 18 years of age.

21.5 Cognitively Impaired Adults or Adults with Fluctuating or Diminished Capacity to Consent: We are not planning on enrolling subjects with fluctuating or diminished capacity to consent. Subjects that appear to have impaired capacity to consent during the consent process will be excluded from the study.

21.6 Adults Unable to Consent: N/A

22.0 Setting

22.1 Research Sites: Potential subjects will be recruited via the use of flyers and advertisements placed in local publications or on on-line resources (for example, Craigslist). Additionally subjects that in previous studies agreed to be contacted regarding other research opportunities may be called. Study visits will occur in the Clinical and Translational Research Institutes (CTSI) facilities.

23.0 Multi-Site Research: N/A

24.0 Resources Available

This study has been submitted for funding to the National Institutes of Health with a funding decision pending. The personnel assisting with this study (e.g., study coordinators) work with the research groups of the investigators. Based on previous studies, we believe that that there are adequate smokers in the community interested in participating in research studies in order to meet recruitment goals.

25.0 References

1. Deyton L, Sharfstein J, Hamburg M. Tobacco product regulation--a public health approach. The New England journal of medicine. 2010;362(19):1753-6. PubMed PMID: 20410498.

2. Levy DT, Pearson JL, Villanti AC, Blackman K, Vallone DM, Niaura RS, et al. Modeling the future effects of a menthol ban on smoking prevalence and smoking-attributable deaths in the United States. American journal of public health. 2011;101(7):1236-40. PubMed PMID: 21566034.
3. TPSAC. Tobacco Products Scientific Advisory Tobacco. Menthol Cigarette and Public Health: Review of the Scientific Evidence and Recommendations. 2012. Available from: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/ucm247605.htm.
4. Food and Drug Administration. Preliminary Scientific Evaluation of the Possible Public Health Effects of Menthol Versus Nonmenthol Cigarettes. 2013.
5. Kasza KA, Ambrose BK, Conway KP, Borek N, Taylor K, Goniewicz ML, et al. Tobacco-Product Use by Adults and Youths in the United States in 2013 and 2014. The New England journal of medicine. 2017;376(4):342-53. doi: 10.1056/NEJMsa1607538. PubMed PMID: 28121512.
6. Schoenborn CA, Gindi RM. Electronic Cigarette Use Among Adults: United States, 2014. NCHS data brief. 2015(217):1-8. PubMed PMID: 26555932.
7. Craver R. E-cig sales continue to rebound with FDA regulations looming. Richond Times-Dispatch 2016. Available from: http://www.richmond.com/business/local/article_fdc0da1c-d1d5-5816-84f5-77d2bdc96f40.html.
8. Herzog B. US tobacco trends: Disruptive innovation should drive outsized growth. [July 30, 2015]. Available from: http://www.ecigarette-politics.com/files/WF-DallasMarch2014.ppt.
9. Zhu SH, Sun JY, Bonnevie E, Cummins SE, Gamst A, Yin L, et al. Four hundred and sixty brands of e-cigarettes and counting: implications for product regulation. Tobacco control. 2014;23 Suppl 3:iii3-9. doi: 10.1136/tobaccocontrol-2014-051670. PubMed PMID: 24935895; PubMed Central PMCID: PMC4078673.
10. ClearWay Minnesota and Minnesota Department of Health. Tobacco Use in Minnesota: 2014 Update. Minneapolis, MN2015.
11. Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Spyrou A, Voudris V. Impact of flavour variability on electronic cigarette use experience: an internet survey. International journal of environmental research and public health. 2013;10(12):7272-82. doi: 10.3390/ijerph10127272. PubMed PMID: 24351746; PubMed Central PMCID: PMC3881166.
12. Bonhomme MG, Holder-Hayes E, Ambrose BK, Tworek C, Feirman SP, King BA, et al. Flavoured non-cigarette tobacco product use among US adults: 2013-2014. Tobacco control. 2016;25(Suppl 2):ii4-ii13. doi: 10.1136/tobaccocontrol-2016-053373. PubMed PMID: 27794065.
13. Litt MD, Duffy V, Oncken C. Cigarette smoking and electronic cigarette vaping patterns as a function of e-cigarette flavourings. Tobacco control. 2016;25(Suppl 2):ii67-ii72. doi: 10.1136/tobaccocontrol-2016-053223. PubMed PMID: 27633766.
14. Walton KM, Abrams DB, Bailey WC, Clark D, Connolly GN, Djordjevic MV, et al. NIH electronic cigarette workshop: developing a research agenda.

Nicotine Tob Res. 2015;17(2):259-69. doi: 10.1093/ntr/ntu214. PubMed PMID: 25335949; PubMed Central PMCID: PMC4311173.
15. O'Connor RJ, Bansal-Travers M, Carter LP, Cummings KM. What would menthol smokers do if menthol in cigarettes were banned? Behavioral intentions and simulated demand. Addiction (Abingdon, England). 2012;107(7):1330-8. PubMed PMID: 22471735.
16. Pearson JL, Abrams DB, Niaura RS, Richardson A, Vallone DM. A ban on menthol cigarettes: impact on public opinion and smokers' intention to quit. American journal of public health. 2012;102(11):e107-14. PubMed PMID: 22994173.
17. Kotlyar M, Mills AM, Shanley R, Okuyemi KS, Robel K, Hatsukami DK. Smoker Response to a Simulated Ban of Menthol Cigarettes: A Pilot Study. Tobacco Regulatory Science. 2015;1(3):236-42. doi: 10.18001/TRS.1.3.5.
18. Winickoff JP, McMillen RC, Vallone DM, Pearson JL, Tanski SE, Dempsey JH, et al. US attitudes about banning menthol in cigarettes: results from a nationally representative survey. American journal of public health. 2011;101(7):1234-6. PubMed PMID: 21566038.
19. Hatsukami DK, Luo X, Dick L, Kangkum M, Allen SS, Murphy SE, et al. Reduced nicotine content cigarettes and use of alternative nicotine products: exploratory trial. Addiction (Abingdon, England). 2017;112(1):156-67. doi: 10.1111/add.13603. PubMed PMID: 27614097; PubMed Central PMCID: PMC5249662.
20. Polosa R, Caponnetto P, Maglia M, Morjaria JB, Russo C. Success rates with nicotine personal vaporizers: a prospective 6-month pilot study of smokers not intending to quit. BMC public health. 2014;14:1159. doi: 10.1186/1471-2458-14-1159. PubMed PMID: 25380748; PubMed Central PMCID: PMC4247211.
21. Polosa R, Caponnetto P, Morjaria JB, Papale G, Campagna D, Russo C. Effect of an electronic nicotine delivery device (e-Cigarette) on smoking reduction and cessation: a prospective 6-month pilot study. BMC public health. 2011;11:786. doi: 10.1186/1471-2458-11-786. PubMed PMID: 21989407; PubMed Central PMCID: PMC3203079.
22. Adriaens K, Van Gucht D, Declerck P, Baeyens F. Effectiveness of the electronic cigarette: An eight-week Flemish study with six-month follow-up on smoking reduction, craving and experienced benefits and complaints. International journal of environmental research and public health. 2014;11(11):11220-48. doi: 10.3390/ijerph111111220. PubMed PMID: 25358095; PubMed Central PMCID: PMC4245610.
23. Dawkins L, Kimber C, Puwanesarasa Y, Soar K. First- versus second-generation electronic cigarettes: predictors of choice and effects on urge to smoke and withdrawal symptoms. Addiction (Abingdon, England). 2015;110(4):669-77. doi: 10.1111/add.12807. PubMed PMID: 25407505.
24. Spindle TR, Breland AB, Karaoghlanian NV, Shihadeh AL, Eissenberg T. Preliminary results of an examination of electronic cigarette user puff topography: the effect of a mouthpiece-based topography measurement device on plasma nicotine and subjective effects. Nicotine Tob Res. 2015;17(2):142-9. doi: 10.1093/ntr/ntu186. PubMed PMID: 25239957.

25. Bullen C, McRobbie H, Thornley S, Glover M, Lin R, Laugesen M. Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial. Tobacco control. 2010;19(2):98-103. doi: 10.1136/tc.2009.031567. PubMed PMID: 20378585.
26. Dawkins L, Corcoran O. Acute electronic cigarette use: nicotine delivery and subjective effects in regular users. Psychopharmacology. 2014;231(2):401-7. doi: 10.1007/s00213-013-3249-8. PubMed PMID: 23978909.
27. Dawkins L, Turner J, Crowe E. Nicotine derived from the electronic cigarette improves time-based prospective memory in abstinent smokers. Psychopharmacology. 2013;227(3):377-84. doi: 10.1007/s00213-013-2983-2. PubMed PMID: 23344557.
28. Richards C, Eischen S, Joseph A, D'Silva J, Gaillard P, Okuyemi K. A Pilot Product Preference Study of Electronic Cigarettes and Nicotine Gum as Potentia l Smoking Cessation Aids for African-American Menthol Smokers. Tobacco Regulatory Science. 2015;1(3):245-53. doi: 10.18001/TRS.1.3.6.
29. Oncken CA, Litt MD, McLaughlin LD, Burki NA. Nicotine concentrations with electronic cigarette use: effects of sex and flavor. Nicotine Tob Res. 2015;17(4):473-8. doi: 10.1093/ntr/ntu232. PubMed PMID: 25762758.
30. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. Br J Addict. 1991;86(9):1119-27. PubMed PMID: 1932883.