Menthol Flavored E-cigarette Use During a Simulated Ban of Menthol Cigarettes

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PROTOCOL COVER PAGE

Protocol Title	Menthol Flavored E-Cigarette Use During a Simulated Ban of Menthol Cigarettes
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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
n/a	10-25-18	This site supplement is being completed as requested by IRB during a continuing review submission due to changes in documentation requirements that result in the currently approved protocol not containing enough information necessary for IRB review. The text in this site supplement is copied as much as possible directly from the currently approved protocol and the originally submitted (pre-ETHOS) IRB application.	No.
1	3-29-19	This update includes the requested increase in the number of subjects approved for enrollment in the study from 80 to 110.	No.
2	10-14-19	Updated section 11.1 with additional information about the potential risk of using e-cigarettes / vaping devices	Yes

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ABBREVIATIONS/DEFINITIONS

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

1.1 Description: This study will enroll approximately 40 African American menthol cigarette smokers who will be randomized to a condition simulating a menthol cigarette ban (i.e., required to abstain from menthol cigarettes for two months) or to a condition in which menthol cigarettes continue to be available (i.e., no restrictions on the cigarettes they can smoke). Within each group, subjects will complete a four week period during which they will be assigned menthol flavored e-cigarettes and a four week period during which they will be assigned regular flavored e-cigarettes. The Vuse brand of e-cigarettes is being tested. The order in which the e-cigarettes (i.e., menthol vs. regular flavors) will be assigned will be randomized. During each four week period, subjects will be instructed to use their assigned e-cigarettes ad libitum. After completion of the two study periods, subjects will continue to be followed for an additional 4 week period to determine if any changes in tobacco use patterns persist after e-cigarettes are no longer provided to subjects. Tobacco use (e.g., cigarettes, e-cigarettes), other nicotine containing product use (e.g., medicinal nicotine), product liking, motivation to quit smoking, biomarkers of tobacco and toxicant exposure, and support for banning menthol flavoring in tobacco products will be assessed during the study. This project will provide preliminary data regarding how the continued availability of menthol flavored e-cigarettes affects tobacco use behavior in the context of a ban on menthol flavored cigarettes and in the case that menthol flavored cigarettes are not banned. These data will be used to inform the study design and to power a larger study assessing the regulatory implications of the availability of menthol flavored e-cigarettes.

1.2 Drug/Device Handling: The tobacco product being studiedis a marketed product and is not required to be dispensed by a physician or licensed pharmacy. It will be provided to participants by the study coordinator.

1.3 Biosafety: N/A

1.4 Stem Cells: N/A

2.0 Local Procedures Involved and Local Requirements

2.1 Local Procedures: This site supplement is being completed to provide information not included in the approved protocol due to changes in documentation requirements that have occurred since the protocol has been approved by the IRB. This is a single site study and the procedures implemented are as approved based on the initially approved IRB application and protocol.

2.2 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 collected therefore do not meet the definition of PHI.

2.3 Use of radiation: N/A

2.4 Use of Center for Magnetic Resonance Research: N/A

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

Provision to monitor the data and ensure the safety of participants are as described in the Data and Safety Monitoring Plan section (page 8 – 9) of the approved protocol. As outlined in the original approved IRB application, the PI will monitor study safety, data accuracy and quality assurance, trial management, regulatory issues and any interim analyses (if interim analysis are conducted).

4.0 Data and Specimen Banking

4.1 Storage and Access: Urine samples will be collected from subjects as described in the approved protocol in the Implementation Plan section (pages 6 – 8). 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).

4.2 Data: Urine samples will be labeled with subject number and date of visit. Samples will be assayed for cotinine concentration and NNAL concentrations. Cotinine is a metabolite of nicotine and frequently used to confirm abstinence or quantify nicotine exposure. NNAL is being measured as an indicator of toxicant exposure. Collected urine may in the future be used to assay other measures related to smoking generally or related to smoking menthol cigarettes specifically. Examples of such analyses include assaying nicotine or metabolites of nicotine other than cotinine, assaying menthol concentrations or assaying toxicants associated with smoking.

4.3 Release/Sharing: The current planned analyses will be performed by labs within the University of Minnesota. If however, 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.

5.0 Sharing of Results with Participants

5.1 Sharing of Results: Study results will not be shared with participants.

6.0 Local Study Population

6.1 Inclusion / exclusion criteria are as described in the Research Design and Methods Section, Subjects subsection of the approved protocol (on page 6). Screening procedures are as described in the Implementation Plan section, Screening Visit subsection of the approved protocol (on page 7).

7.0 Vulnerable Populations

7.1 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

7.2 Additional Safeguards: None of the above groups are being recruited; however recruitment will be limited to African American smokers for several reasons. Menthol cigarette use is particularly prevalent in the African American community with 80% of African Americans reporting menthol cigarettes as their usual choice. Additionally, data suggest that greater difficulty in cessation of menthol cigarettes (vs. non-menthol cigarettes) may be limited to African Americans and therefore regulations affecting availability of menthol flavored products, if enacted to improve cessation rates from menthol cigarettes, are particularly relevant to this population.

The risks from participating in this study are small in that subjects will be provided 2 months of commercially available e-cigarettes. Only those who smoke cigarettes regularly will be enrolled and subjects will not be instructed to use more of the product than they would otherwise use were they to obtain the product outside the context of the study.

8.0 Local Number of Participants

8.1 Local Number of Participants to be Consented: We anticipated that approximately 110subjects will go through the consent process in order to recruit 40 subjects who complete this study.

9.0 Local Recruitment Methods

9.1 Recruitment Methods: 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 or after following a web link provided in advertisement, complete an online screening questionnaire (advertisement and questionnaire previously approved by the IRB). For individuals calling the listed phone number, study staff will explain the study to potential study subjects and 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 (phone screening script previously approved by IRB). For individuals completing the online form, study personnel will call subjects to let them know if they are eligible and to schedule a screening visit for those who are.

Additionally subjects that in previous studies agreed to be contacted regarding other research opportunities (by initialing their agreement to be contacted on the consent form) may be called. These 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.

9.2 Identification of Potential Participants: Subjects will be recruited via the use of flyers and advertisements in local and neighborhood newspapers or on internet resources such as Craigslist or Facebook. Additionally subjects that in previous studies agreed to be contacted regarding other research opportunities (by initialing their agreement to be contacted on the consent form) may be called.

9.3 Recruitment Materials: Flyers, advertising text and images (for example for Facebook advertising) as previously approved by the IRB will be utilized.

9.4 Payment: Subjects will be paid $20 for the screening visit, the baseline visit and each of the 5 subsequent visits (i.e., visits at week 2, 4, 6, 8, and 12). Subjects who complete all scheduled visits and have complied with study related procedures will receive a $60 bonus. Subject can therefore receive up to $200 for completing the study in addition to payment for points that were not redeemed for e-cigarette cartridges during the final two weeks of each evaluation period. Subjects will additionally be provided bus tokens (for those who take public transportation) or parking (for those who drive) for each visit. Payment is provided via the Greenphire ClinCard.

10.0 Withdrawal of Participants

10.1 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.

10.2 Withdrawal Procedures: We will attempt to contact subjects by telephone who do not show up to scheduled visits 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.

10.3 Termination Procedures: Any data collected prior to a subject withdrawing from a study will be used in the data analysis.

11.0 Risks to Participants

11.1 Foreseeable Risks: Risks of being in the study are described in the Data and Safety Monitoring Plan of the previously approved protocol template (page 8 - 9). Below is the language copied from the protocol template with

additional information added to the third and fourth paragraphs regarding recent reports of respiratory illness.

Risks that subjects are exposed to as a result of enrolling in the study are minimal. Although smoking is clearly detrimental to health, we do not anticipate that their risk will increase as a result of being enrolled in the study since we will only be enrolling those who already smoke at least 5 cigarettes per day. Furthermore, any short term changes in smoking that occur as a result of either being asked to abstain from smoking menthol cigarettes or from using e-cigarettes for an 8 week period are not likely to have long term health effects.

The e-cigarettes used for this study are commercially available and among the most commonly used brands. Although these products do not currently undergo regulatory evaluation, they are easily available and increasingly being used. The risks of using e-cigarettes are not thought to be greater than of smoking (with many advocating that these products are less harmful than smoking). E-cigarettes do contain nicotine and it is possible that overuse can lead to symptoms of nicotine toxicity such as nausea, vomiting, dizziness, weakness and rapid heartbeat. The e-cigarette liquid contains propylene glycol which may be associated with throat irritation. The e-cigarette is a battery powered electronic device so malfunctions are possible.

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 may occur. The risk however of using the product as directed by the manufacturer is no higher than it would be if subjects were to buy the e-cigarettes themselves and use them outside of the study.

11.2 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 products.

11.3 Risks to Others: There are known risks associated with second hand smoke, however we are only recruiting those who are already smoking therefore the risk to others should not increase by participating in this study. The second hand risks of e-cigarette use are unknown but are likely less than the risks of second hand smoke.

12.0 Potential Benefits to Participants

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

13.0 Confidentiality

Measure taken for the protection of the confidentiality of data are described in the Data Safety Monitoring Plan section of the approved protocol (page 8 - 9).

14.0 Provisions to Protect the Privacy Interests of Participants

14.1 Protecting Privacy:

Subjects will be told that participation is voluntary and they may discontinue participation at any time for any reason. Furthermore, subjects will be informed that they are free to not answer any questions that they are uncomfortable with, however by doing so they may be excluded from the study (if eligibility cannot be assessed) or dropped from the study if measures of interest cannot be ascertained.

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 password protected secure computer servers maintained by the University. Access to subject identifiable information will be limited to those that require this information such as study investigators or others who have direct contact with study subjects (e.g., study coordinator).

Data collected via paper forms will be stored in a locked file cabinet or office and data collected electronically will be stored on University maintained servers or on RedCap (a secure web interface).

14.2 Access to Participants: All data will be collected directly from study subjects (i.e., no data will be obtained from medical records).

15.0 Compensation for Research-Related Injury

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

15.2 Contract Language: N/A

16.0 Consent Process

16.1 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.

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

16.3 Waiver of Written/Signed Documentation of Consent (when written/signed consent will not be obtained): N/A

16.4 Non-English Speaking Participants: N/A

16.5 Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age): N/A

16.6 Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent: N/A

16.7 Adults Unable to Consent: N/A

17.0 Setting

17.1 Research Sites: Potential subjects are recruited via the use of flyers and advertisements placed in local publications or on on-line resources (for example, Craigslist and Facebook). 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.

17.2 International Research: N/A

18.0 Multi-Site Research

N/A

19.0 Resources Available

This study is being funded by ClearWay MN. 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.

Menthol Flavored E-Cigarette Use During a Simulated Ban of Menthol Cigarettes

Date: 5/11/2017

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Project Summary:

The rapid increase in the use of electronic nicotine delivery systems (i.e., e-cigarettes) raises questions regarding how their availability will impact tobacco related morbidity and mortality. With the Food and Drug Administration (FDA) considering a ban on menthol cigarettes and recently extending its regulatory authority to e-cigarettes, it will be necessary to determine if regulatory approaches to menthol should be enacted across tobacco products or if cigarettes should be treated differently than other products. The aim of the proposed formative study is to provide preliminary data regarding how the availability of menthol flavored e-cigarettes affects tobacco use behavior in the context of a ban on menthol flavored cigarettes and in the case that menthol flavored cigarettes are not banned. We hypothesize that when smokers are provided menthol (vs. tobacco) flavored e-cigarettes they will 1) smoke fewer cigarettes; 2) use more of their assigned product; 3) have decreased exposure to tobacco toxicants, and 4) be more supportive of a ban on menthol cigarettes than when provided tobacco flavored e-cigarettes. We further hypothesize that the effects of menthol (vs. non-menthol) flavored e-cigarettes on these measures will be greater during a simulated ban on menthol cigarettes than if smokers can continue smoking menthol cigarettes. In order to pursue this aim, we will enroll smokers of menthol cigarettes and randomize them to either a condition in which they are required to abstain from menthol cigarettes (i.e., to simulate a ban on menthol cigarettes) or to a condition in which they can continue to smoke menthol cigarettes. Using a within subject design, smokers in each group would receive one month of menthol flavored e-cigarettes and one month of tobacco flavored e-cigarettes (in random order). Data will be analyzed to determine if there are differences in measures of interest between the four week period when participants are provided menthol e-cigarettes and the period when they are provided tobacco flavored e-cigarettes. We will additionally evaluate if availability of menthol cigarettes moderates the effects of e-cigarette type. Data from this pilot study will be used to plan larger studies examining how menthol flavor in e-cigarettes affects tobacco product use patterns and toxicant exposure among smokers (menthol and non-menthol) using these products.

Significance and innovation of the proposed research:

Background and Significance: *a) introduction:* 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. One of the areas over which the FDA gained regulatory authority is in the use of flavorants in cigarettes. Effective September 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 use of such products.[1] With the FDA recently extending its authority to additional categories of tobacco products including electronic cigarettes (i.e., e-cigarettes),[2] the ability to enact regulations regarding the availability of flavorants (including menthol) extend to these products as well. As there is little information currently available on how menthol flavoring in e-cigarettes affects overall tobacco use, there is little scientific basis available upon which to formulate menthol regulations in non-cigarette forms of tobacco.

b) Menthol flavoring in cigarettes: In March 2011, the Tobacco Products Scientific Advisory Committee (TPSAC) submitted a report to the FDA reviewing the impact of the use of menthol cigarettes on public health and provided the overall recommendation that "removal of menthol cigarettes from the marketplace would benefit public health in the United States".[3] This recommendation was based on data suggesting that 1) the availability of menthol cigarettes increases experimentation and regular smoking, 2) the availability of menthol cigarettes increases the likelihood and degree of addiction in youth smokers, and 3) in African Americans the availability of menthol cigarettes results in lower likelihood of smoking cessation success. It was therefore concluded that eliminating menthol cigarettes would result in fewer youth initiating smoking and greater success among African Americans in quitting smoking.[3, 4] 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, menthol in cigarettes is likely associated with greater addiction, and menthol smokers are less likely to successfully quit smoking. Overall, this report concluded that the evidence suggests it is "likely that menthol cigarettes pose a public health risk above that seen with non-menthol cigarettes."[5] The role of menthol flavoring in other tobacco products was not addressed in either of these reports.

Although surveys of menthol smokers suggest that a substantial number would attempt to quit if menthol cigarettes were unavailable,[3, 6, 7] our preliminary data found that relatively few in fact made a cessation attempt (only 3 out of 31 subjects). It is not known however if access to menthol flavored e-cigarettes would increase the likelihood of menthol smokers quitting smoking entirely in the event of a menthol cigarette ban since they have an alternate menthol product available or conversely if likelihood of quitting would decrease with smokers switching to 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.

c) Menthol Flavoring in Electronic Nicotine Delivery Devices (i.e., e-cigarettes): The use of e-cigarettes has grown dramatically since their introduction in the United States in 2007. Sales of e-cigarettes in 2014 are estimated at between $800 million and $2 billion with some estimates projecting that as e-cigarette sales continue to increase, they may overtake cigarette sales within 10 years.[8, 9] Almost every commonly used brand of e-cigarette is currently available in menthol flavor[10] and data from surveys suggest that as many as 30% of e-cigarettes users prefer menthol flavored products with over 12% of e-cigarette users stating that they use e-cigarettes "because they come in menthol flavor".[11, 12] Menthol flavored e-cigarettes are therefore widely available and commonly used. However, there is little information assessing if menthol flavoring alters how cigarette smokers are likely to respond to e-cigarettes.

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.[13, 14] 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.[15] 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 again these studies do not specifically assess menthol flavored products.[15-20] A pilot 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 found that among those selecting the menthol e-cigarettes, cigarette consumption was reduced by 61% and among those who selected tobacco flavored e-cigarettes, cigarette consumption was reduced by 57%.[21] This was however not a randomized study since smokers could select the flavor of e-cigarettes they would use.

To date, only one published study (to our knowledge) has specifically evaluated if smoker response to menthol e-cigarettes is different than to non-menthol tobacco flavored e-cigarettes. In this cross-over study, twenty non-treatment seeking smokers used both menthol and tobacco flavored e-cigarettes, each for a 7 – 10 day period. During e-cigarette use, participants were to abstain from smoking cigarettes. On their last day of e-cigarette use, subjects completed a laboratory session at which they used their assigned e-cigarette for 5 minutes. Nicotine concentrations were measured over 30 minutes and questionnaires were administered prior to and after e-cigarette use. This study found that among 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.[22] No such difference was found in men.

This study supports our hypothesis that menthol flavoring in e-cigarettes affects how the product is likely to be used. Our project will expand on these results by providing preliminary data into how ad libitum use of e-cigarettes affects cigarette smoking and biomarker concentrations and if these effects are moderated by flavor of either the e-cigarettes used or cigarettes smoked. Such information is needed in order to determine if regulations are needed to limit the availability of menthol in e-cigarettes.

Preliminary data: We have recently completed a study evaluating how African American menthol smokers would respond to a simulated ban on menthol flavored cigarettes[23] and are currently conducting a follow-up study evaluating if in this population, switching to non-menthol cigarettes is a good first step to cessation.

The former study was an open-label study which was completed by 31 African American menthol cigarettes smokers (smoking $\geq$ 5 cigarettes per day) in which they were asked to abstain from smoking menthol cigarettes for a 4 week period and were given no specific instructions regarding how to cope with the inability to smoke menthol cigarettes. All subjects reported switching to non-menthol cigarettes with three subjects making a smoking cessation attempt during the 4 week period. At the conclusion of the study, subjects were asked to rate on a 10 point scale how difficult it was to quit menthol cigarettes (1=easy; 10=hard) and the extent to which they were supportive of banning menthol cigarettes (1=not supportive; 10=very supportive). Subjects indicated that quitting menthol cigarettes was difficult (average score = 7.2); nonetheless motivation to quit increased slightly during the period (5.3 at baseline vs. 6.3 at week 4, $p=0.03$). Upon switching to non-menthol cigarettes, participants smoked slightly fewer cigarettes over the 4 week period (11.9 cigarettes per day during the week prior to baseline vs. 9.8 during week 4, $p<0.01$) and had lower exhaled carbon monoxide concentrations relative to baseline (13.4 ppm at baseline vs. 11.1 ppm at week 4, $p<0.05$). At the conclusion of the study, subjects were generally supportive of banning menthol (average score = 7.1). These data suggest that a simulated ban on menthol likely did not result in any greater harm than continued menthol cigarette smoking (i.e. smoking did not increase and motivation to quit was not reduced). Furthermore, after experiencing a simulated menthol ban, menthol smokers were supportive of banning menthol cigarettes.

The proposed project 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. A recently completed study found that African-American menthol smokers strongly preferred menthol flavored e-cigarettes relative to tobacco flavored e-cigarettes or nicotine lozenge but did not assess if the availability of menthol flavored e-cigarettes is likely to result in a pattern of tobacco use suggesting increased health benefits.[21]

The proposed project would expand on these data to determine if changes in smoking, motivation to quit smoking, and other measures assessed are either enhanced by or undermined by the availability of menthol flavored e-cigarettes. The proposed project would further obtain data on the extent to which use of menthol flavored e-cigarettes are influenced by the availability of menthol flavored cigarettes. As such, these data would begin to form the scientific base for determining if regulatory approaches to menthol should be enacted across tobacco products or if cigarettes should be treated differently than other products.

d) Interest in banning menthol cigarettes: Menthol cigarettes are used at particularly high rates among minority populations, adolescents, and young adults. For example, although menthol smokers account for between 28% and 34% of all US cigarette smokers, over 80% of African American smokers and over 40% of adolescents smokers report menthol cigarettes as their usual choice.[3] Among Hispanics smokers, almost 30% of males and over 40% of females report smoking menthol cigarettes.[3] A ban on menthol would therefore affect many smokers but would have a disproportionate effect on African American smokers.

There is support among smokers for a menthol ban with rates of those favoring the ban higher in African Americans than in Caucasians. A nationally representative cross-sectional sample contacted by telephone found that 53% of whites and 68% of African Americans supported a ban on menthol

cigarettes.[24] Another survey found that 20% support a ban on menthol cigarettes (with an additional 52% not expressing a strong opinion) with the level of support higher among Hispanics (36%) and African Americans (29%).[7] As reported previously, our preliminary study found high levels of support for banning menthol cigarettes even after finding it difficult to abstain from menthol cigarettes over a four week period. The proposed study would determine if the availability of alternate menthol flavored products (i.e., menthol e-cigarettes) would further increase support for a ban on menthol flavoring in cigarettes. This is important data since broadening support for a menthol cigarette ban among current users of menthol cigarettes would likely ease passage of such regulations. This study will also provide initial information regarding the level of support among menthol flavored cigarette smokers of banning menthol flavoring across tobacco products. A recent survey found that if menthol cigarettes were banned, 24% of menthol smokers who would not quit stated that they would switch to menthol e-cigarettes.[11, 25] Another survey found that 15.1% of menthol smokers would switch to menthol e-cigarettes were menthol cigarettes banned.[26] Since a sizable proportion of menthol cigarette smokers see menthol e-cigarettes as a viable alternate product, it may be that support for a ban on menthol flavoring varies by product.

Innovation: Although the number of publications assessing e-cigarettes has grown considerably in recent years,[27] there is currently very little data regarding how flavorants in general and menthol specifically affect the use of these products. Considering that a notable number of e-cigarette users indicate that menthol is their preferred flavor and menthol in cigarette smoking has been associated with negative public health consequences, research into how menthol in e-cigarette affects tobacco use patterns is critical. Generating research in this area is therefore innovative with this line of research being significant to tobacco regulation.

Specific Aims/Study Objectives:

The current study will generate preliminary data assessing how a ban on menthol cigarettes and/or e-cigarettes would affect use of tobacco products. In this study, African American menthol smokers will be randomized to a condition in which they are either required to abstain from menthol cigarettes (i.e., to simulate a ban on menthol cigarettes) or given no instructions to abstain from menthol cigarettes. Using a within subject design, in each group smokers would then receive one month of menthol flavored e-cigarettes and one month of tobacco flavored e-cigarettes (in random order). A one month follow up period would determine any changes in smoking behavior that persist after e-cigarettes are no longer provided. The central hypothesis of the application is that the availability of menthol flavored e-cigarettes will lead to the largest reductions in cigarette smoking and toxicant exposure when paired with a ban on menthol flavored cigarettes with smaller effects seen if menthol flavored cigarettes continue to be available. We propose to study the following specific aims:

Aim 1: Determine the impact of menthol e-cigarettes on tobacco use behavior

We hypothesize that when smokers of menthol cigarettes are provided menthol flavored e-cigarettes they will 1) smoke fewer cigarettes; 2) use more of their assigned product; 3) have decreased exposure to tobacco toxicants (i.e., exhaled CO concentrations, urinary NNAL concentrations); and 4) be more supportive of a ban on menthol cigarettes than when provided tobacco flavored e-cigarettes.

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

We hypothesize that the effects of menthol (vs. tobacco) flavored e-cigarettes on the above measures (i.e., amount smoked, amount of product used, exposure to tobacco toxicants) will be greater during a simulated ban on menthol cigarettes than if smokers can continue smoking menthol cigarettes.

Research Design and Methods:

Sampling Plan

Design Overview: This study will enroll approximately 40 African American menthol cigarette smokers who will be randomized to a condition simulating a menthol cigarette ban (i.e., required to abstain from menthol cigarettes for two months) or to a condition in which menthol cigarettes continue to be available (i.e., no restrictions on the cigarettes they can smoke). Within each group, subjects will complete a four week period during which they will be assigned menthol flavored e-cigarettes and a four week period during which they will be assigned regular flavored e-cigarettes. The order in which the e-cigarettes (i.e., menthol vs. regular flavors) will be assigned will be randomized. During each four week period, subjects will be instructed to use their assigned e-cigarettes ad libitum. After completion of the two study periods, subjects will continue to be followed for an additional 4 week period to determine if any changes in tobacco use patterns persist after e-cigarettes are no longer provided to subjects. Tobacco use (e.g., cigarettes, e-cigarettes), other nicotine containing product use (e.g., medicinal nicotine), product liking, motivation to quit smoking, biomarkers of tobacco and toxicant exposure, and support for banning menthol flavoring in tobacco products will be assessed during the study. This project will provide preliminary data regarding how the continued availability of menthol flavored e-cigarettes affects tobacco use behavior in the context of a ban on menthol flavored cigarettes and in the case that menthol flavored cigarettes are not banned. These data will be used to inform the study design and to power a larger study assessing the regulatory implications of the availability of menthol flavored e-cigarettes.

Subjects: In order to be eligible for this study, subjects must: 1) be African American (based on self-identification); 2) smoke primarily menthol cigarettes (greater than 80% of products used are menthol); 3) be between the ages of 18 and 64; 4) Smoke on average at least 5 cigarettes per day for a period longer than 1 year; and 5) agree to abstain from menthol cigarettes for an 8 week period. Subjects will be excluded if they have: 1) a current serious, unstable medical or psychiatric condition as determined by self-report; 2) Regularly use any form of nicotine or tobacco other than cigarettes (i.e. greater than 9 times per month); or 3) Are pregnant or breast feeding based on self-report (subjects will be given a urine pregnancy test at the screening visit with pregnancy later in the study and breast feeding based on self-report). Regular users of e-cigarettes will be excluded as they likely have identified a preferred flavor.

As the risks associated with the study procedures are small, all medical assessments are based on self-report (except for a urine pregnancy test at screening).

Recruitment will be limited to African American smokers since menthol cigarette use is particularly prevalent in this community[3] and because data suggest that greater difficulty in cessation of menthol (vs. non-menthol) cigarettes may be limited to African Americans.[3] Regulation of menthol in non-cigarette tobacco products (such as e-cigarettes) may therefore be particularly relevant to this population.

African American menthol smokers will be recruited via the use of flyers and advertisements in local and neighborhood newspapers with a high African American readership or on internet resources such as Craigslist or Facebook. If additional advertisement becomes necessary, radio or television advertisements may be utilized.

Implementation Plan

Overview: Each subject will attend a screening visit to determine eligibility for the study. If subjects are eligible, they will be scheduled to attend a baseline visit until which they will be asked to continue smoking in their normal manner in order to gather information on their baseline smoking patterns. At the baseline visit, subjects will be randomized to either the 'simulated menthol cigarette ban' or 'no menthol cigarette ban' conditions and additionally will be randomized to the order in which they will receive their assigned e-cigarettes (i.e., menthol flavored e-cigarettes followed by non-menthol tobacco flavored e-cigarette or vice versa). Based on their randomization, subjects will be instructed

as to whether they are to abstain from menthol cigarettes and will be provided a supply of e-cigarettes in the flavor they were randomized to for the first 4 week period. Subjects will be seen at visits scheduled approximately two and four weeks after starting use of their assigned e-cigarettes and will receive a phone call one week after starting use of their e-cigarettes to address any questions that arise. At the week four visit, subjects will receive a supply of the alternate e-cigarette products that they will use for the subsequent four week period. We do not believe that a washout period is needed based on a published cross-over study in which differences were found between menthol and tobacco flavored e-cigarettes after each was used for only a 7 to 10 day period (with no wash-out in between).[22] During the second four week period, subjects will again receive a phone call 1 week after starting use of their assigned e-cigarette product and will be seen at visits scheduled two and four week after starting use of their assigned product. In order to ascertain if subjects change their tobacco use behavior once e-cigarettes are no longer provided by the study, subjects will have an additional follow-up visit 12 weeks after the baseline visit (i.e., four weeks after the end of the second assessment period). Subjects who complete the entire study will therefore be seen at a screening visit and 6 additional visits over an approximately 3 month period. The procedures occurring during each of these visits are described below.

Vuse brand of e-cigarette (manufactured by RJ Reynolds) were selected for this study for several reasons. Studies suggest that as e-cigarette technology evolves, newer products become more effective at delivering nicotine than older products and are perceived as more satisfying.[16, 28] Vuse is one of the newest and most commonly used products currently on the marketplace. Vuse was introduced nationally in June 2014 and based on reports from May 2015 has achieved the highest market share of any product at 35.7% of the US market.[29] Vuse is available in regular and menthol flavor and is therefore appropriate for this investigation.

Screening Visit: All subjects will complete a screening visit prior to enrollment at which written informed consent will be obtained and eligibility will be verified. Medical and psychiatric history will be obtained via subject report. Baseline questionnaires assessing smoking history will be administered. Exhaled carbon monoxide (CO) will be measured to confirm that they are smokers (CO $\geq$ 8 ppm) with a NicCheck performed (with a cut-off of $\geq$5) for those who state that they smoke $\geq$ 5 cigarettes per day but for whom CO is less than 8 ppm (e.g., they didn't smoke that morning, they are coming from a smoke free work environment, etc.). Subjects that qualify and are interested in participating will be asked to maintain a paper smoking diary for the duration of the study and will be scheduled for the baseline visit.

Baseline and Evaluation Visits: Subsequent to the screening visit, there will be a baseline visit and four additional evaluation visits scheduled at approximately 2 week intervals (i.e., at 2, 4, 6 and 8 week after the baseline visit). A follow-up visit will occur at week 12 (i.e., 4 weeks after e-cigarettes are no longer provided to subjects).

To the baseline visit, subjects will bring a first morning urine sample from which baseline urinary cotinine and total NNAL 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, self-efficacy to quit smoking, and support for a ban on a variety of menthol containing tobacco products. Subjects will then be told if they have been assigned to the condition in which they are to abstain from menthol cigarettes for the next eight weeks and will be provided (at no cost to them) with a two weeks supply of the product that they have been randomized to receive (i.e., menthol or tobacco flavored e-cigarettes, based on randomization) for the first four week period. Subjects will be instructed in how to properly use the product and will be given all of the packaging that normally accompanies the product. They will be told to use as much or as little of the product as they like. Subjects will also be provided with a tobacco use diary that they are to complete daily in which they are to record the number of cigarettes smoked and how often and how many puffs they used of their provided e-cigarette. Puffs per day has been used in other studies to evaluate e-cigarette use.[22, 30, 31] They will additionally be asked to record use of any other tobacco or nicotine containing products. Subjects will also be asked to bring to all subsequent visits all e-cigarette cartridges as well as samples of the cigarettes or other tobacco or nicotine products that

they have been using in order to verify the accuracy of the smoking diary. Partially used cartridges will be weighed to determine the extent to which they were used. They will be given no specific instructions regarding using medicinal nicotine (i.e., nicotine patch, gum) or other tobacco products but will be asked to record any instances of using such products.

Evaluation visits will occur at approximately 2 week intervals for eight weeks following the baseline visit. Scheduling considerations will determine the exact intervals of the visits with visits scheduled as close as possible to dates corresponding to those that would occur 2 and 4 weeks after the baseline visit and then 2 and 4 weeks after the week 4 visit (i.e., 2 and 4 weeks after they receive the alternate e-cigarette product). At the week 2 and week 6 visits, subjects will be told that they have 24 points that are worth $1.00 per point, which they can exchange for cash or additional e-cigarette cartridges of their assigned flavor (at a cost of 3 points per cartridge, which is approximately 66% of the cost of the cartridges commercially). This approach is being used in order to better characterize how menthol vs. tobacco flavored e-cigarettes are likely to be used after subjects have become familiar with the product over the first two weeks. Providing free product for the entire four week period may result in participants using more of the product then they would otherwise use and smoke fewer cigarettes since the e-cigarettes are free and the cigarettes are not. Differences between menthol and non-menthol e-cigarette conditions may therefore be underestimated in this circumstance. Products are offered at a discount to the price available in the retail marketplace in order to ensure that any cartridges are obtained from us (rather than commercially) but to minimize hoarding of the points.

At each visit, exhaled carbon monoxide concentrations will be measured and subjects will complete questionnaires assessing craving and withdrawal symptoms, motivation to quit smoking, product liking, perceived health risks of using the product, and level of support for a ban on a variety of menthol containing tobacco products. The tobacco use diaries that subjects had been asked to complete will be collected at each visit.

At the week 4 and week 8 visits, subjects will be asked to bring a urine sample with their first morning void which will be used to measure urinary cotinine and urinary total NNAL concentrations.

Follow up visit: Subjects will attend one follow-up visit that will occur at week 12 of the study period (i.e., four weeks after they are no longer provided e-cigarettes). To this visit, subjects will again be asked to bring their first morning urine void and an exhaled CO will be measured. The final set of tobacco use diaries will be collected. Questionnaires assessing level of craving, withdrawal, motivation and self-efficacy to quit smoking, perceived health risk, and support for a ban on a variety of menthol tobacco products will be completed as in the evaluation visits. All subjects will be provided information regarding the smoking quitline as a resource available if they are interested in quitting smoking.

As the purpose of this formative proposed project is to provide pilot data for a subsequent grant submission, subjects will be asked at the end of the study ways in which to improve future studies addressing menthol e-cigarettes (for example, asking what they would change about the study and how honest they think others were in their reporting of menthol cigarette use). Subject responses will be examined for consistent themes so as to help inform study design for future projects.

Subjects will be paid $20 for the screening visit, the baseline visit and each of the 5 subsequent visits (i.e., visits at week 2, 4, 6, 8, and 12). Subjects who complete all scheduled visits and have complied with study related procedures will receive a $60 bonus. Subject can therefore receive up to $200 for completing the study in addition to payment for points that were not redeemed for e-cigarette cartridges during the final two weeks of each evaluation period. Subjects will additionally be provided bus tokens (for those who take public transportation) or parking (for those who drive) for each visit.

Data and Safety Monitoring Plan:

In this study, one-half of smokers will be asked to stop using menthol cigarettes and all smokers will be provided e-cigarettes to use over a 2 month period. Those randomized to abstain from smoking menthol cigarettes will be given no specific instructions regarding modifying their smoking

behavior in order to more closely mimic what would occur if menthol cigarettes were banned. Based on our previous research, it is expected that most will smoke non-menthol cigarettes instead.

Risks that subjects are exposed to as a result of enrolling in the study are minimal. Although smoking is clearly detrimental to health, we do not anticipate that their risk will increase as a result of being enrolled in the study since we will only be enrolling those who already smoke at least 5 cigarettes per day. Furthermore, any short term changes in smoking that occur as a result of either being asked to abstain from smoking menthol cigarettes or from using e-cigarettes for an 8 week period are not likely to have long term health effects. The e-cigarettes used for this study are commercially available and among the most commonly used brands. Although these products do not currently undergo regulatory evaluation, they are easily available and increasingly being used. The risks of using e-cigarettes are not thought to be greater than of smoking (with many advocating that these products are less harmful than smoking). E-cigarettes do contain nicotine and it is possible that overuse can lead to symptoms of nicotine toxicity such as nausea, vomiting, dizziness, weakness and rapid heartbeat. The e-cigarette liquid contains propylene glycol which may be associated with throat irritation. The e-cigarette is a battery powered electronic device so malfunctions are possible. As with any product, there is a risk that unanticipated effects from using the e-cigarette may occur. The risk however of using the product is no higher than it would be if subjects were to buy the e-cigarettes themselves and use them outside of the study.

The study procedures will consist of filling out questionnaires, maintaining a tobacco use diary, and providing breath and urine samples. These activities are not expected to pose any risk to subjects. This study will be submitted for approval by the University of Minnesota Institutional Review Board. The study will be explained to all subjects and all subjects will have an opportunity to ask any questions prior to signing an informed consent form. Informed consent will be obtained by one of the investigators or a study coordinator trained per university guidelines. No study related procedures will take place until an informed consent form has been signed. Subjects with serious, unstable medical or psychiatric conditions at the time of screening will be excluded from the study since their pattern of smoking may be influenced by their concurrent disease states.

To ensure confidentiality, all subjects enrolled in the study will be assigned a study identification code which will be used on all study related data collection forms except for those on which the 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 password protected secure computer servers that meet university guidelines. Access to subject identifiable information will be limited to those that require this information such as investigators or others who have direct contact with study subjects (e.g., study coordinator).

At each visit, subjects will be asked if they are experiencing any adverse effects or difficulties with the study. The Principal Investigator will review reports with study staff to determine if changes are needed to any of the study related procedures or if the subject has symptoms/difficulties that would warrant discontinuation from the study.

Data Analysis

The primary aim of the proposed study is to compare changes in each outcome measure (e.g., number of cigarettes smoked, amount of e-cigarette used, motivation to quit smoking, biomarker concentrations, support for a menthol ban) between the four week period when subjects are provided menthol e-cigarettes compared with the four week period when subjects are provided tobacco flavored e-cigarettes. An additional aim is to determine if cigarette type (i.e., randomization to menthol vs non-menthol) moderates the effects of e-cigarette type.

Outcomes will be described using means and standard deviations, separately for each combination of visit and experimental condition (menthol cigarettes available or not, menthol or non-menthol tobacco flavored e-cigarette). Skewed variables will be log transformed and their geometric means and 95% confidence intervals will be reported. Hypothesis testing will be performed using linear mixed models, with fixed effects for randomization group and time, and a random subject effect. The study is designed to provide pilot data to estimate broad trends and parameters that can be used

to plan larger studies. Enrolling a total of 40 subjects with 15-20% attrition would leave at least 16 subjects per group to compare menthol vs. no menthol cigarettes allowed, and those 16 can be compared within each group to test the effects of e-cigarette flavor since all subjects will receive both flavor options in a crossover design. This would result in approximately 80% power to conclude significance at the two sided 0.05 level if the true effect size is 1.0.

The results of this study will be used to plan future projects that would more definitively address the question of how menthol flavoring in e-cigarettes should be regulated. This formative study would inform future research by 1) demonstrating the acceptability of menthol and non-menthol flavored e-cigarette use in this population; 2) providing pilot data regarding how menthol flavoring in e-cigarettes affects (in the presence and absence of a simulated ban on menthol cigarettes) smoking changes, thereby enabling more informed hypotheses to be developed and more accurate sample size calculations to be performed and 3) providing information for study design refinement via the descriptive data collected from participants regarding their recommendations for future study designs.

Data and Record Keeping:

Data will be managed by the study coordinator(s). 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 password protected secure computer servers. Access to subject identifiable information will be limited to those that require this information such as study investigators or others who have direct contact with study subjects (e.g., study coordinator).

Many of the questionnaires for this study will be entered by subjects directly into a REDCap database. This database is housed on secure servers which are operated by the University of Minnesota Academic Health Center's Information Systems group (AHC-IS). Access to the database will be restricted to members of the study team by username and password. Specific information regarding the database design and features can be found on the Clinical and Translational Science Institutes website, http://www.ctsi.umn.edu/research/tools-software/REDCap/. In circumstances where data cannot be entered into REDCap (e.g., the system is off-line at the time of the visit, subject has difficulty using a laptop computer, etc.), paper forms will be used instead.

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CONSENT FORM
Menthol Flavored E-Cigarette Use During a Simulated Ban of Menthol Cigarettes

You are invited to be in a research study to determine how menthol flavoring in cigarettes and in e-cigarettes affects smoking patterns. You were selected as a possible participant because you are an African American smoker of menthol cigarettes. We ask that you read this form and ask any questions you may have before agreeing to be in the study.

This study is being conducted by Michael Kotlyar, PharmD in the University of Minnesota College of Pharmacy. It is being funded by ClearWay Minnesota.

For questions about research appointments, the research study, research results, or other concerns, call the study team at:

Researcher	Study Staff
Michael Kotlyar, PharmD Phone Number: 612-625-1160 Email Address: kotly001@umn.edu	Sheena Dufresne 612-626-5981 gahmx008@umn.edu

Study Purpose:
The purpose of this study is to determine how menthol flavoring in cigarettes and e-cigarettes affects how smokers use these products. Menthol cigarettes are smoked by a lot of people, and now that e-cigarettes are becoming more popular a lot of people are using menthol flavored e-cigarettes. Several years ago, the Food and Drug Administration (FDA) banned the addition of fruit or candy flavors to cigarettes but did not ban menthol. E-cigarettes are currently available in many flavors including menthol. In the future it is possible that the FDA may want to ban menthol in either cigarettes, e-cigarettes or both, but research is needed to determine what effect banning menthol might have. The aim of this study is to collect information regarding how smokers of menthol cigarettes are likely to adjust their use of tobacco products if menthol flavoring was available only for e-cigarette, only for cigarettes, for both, or if menthol was not available for either product. This includes finding out information such as how much of each product smokers would use and how levels of substances found in the urine of smokers are affected.

Study Procedures:
If you agree to be in this study we ask that you do the following things:

Screening Visit: During the first visit the study will be explained to you and any questions that you have will be answered. If you are interested in enrolling in this study, we will then assess whether you are eligible. This assessment will involve us asking questions regarding your smoking, medical and psychiatric history. We will measure the amount of carbon monoxide you exhale and you will also be given a number of forms to complete. If female, you will have a urine pregnancy test. If you are eligible for the study, you will be scheduled for the next visit. We expect the screening visit to last between 1 and 2 hours.

Evaluation Visits: A total of five visits will be scheduled about 2 weeks apart. Each visit is expected to last about ½ hour. At the first of these visits (which we will call the baseline visit) you will be assigned to a group that either simulates a ban on menthol cigarettes, or does not simulate a ban. The assignment will be random, like by the flip of a coin. If you are assigned to the non-menthol cigarette group, you will be asked to not smoke menthol flavored cigarettes until the last evaluation visit which will be about 8 weeks later. If you are assigned to the menthol cigarette group, you can continue to smoke menthol cigarettes. At the baseline visit you will receive an e-cigarette and a supply of either menthol flavored or tobacco flavored cartridges to be used with the e-cigarette. The flavor you get (either menthol or tobacco flavor) will be randomly assigned. At the week 4 visit, you will receive a supply of the other flavor (for example, if you receive menthol flavored cartridges at the baseline visit then you will receive tobacco flavored cartridges or vice versa). At the week 2 and week 6 visits, you will have an option of receiving additional e-cigarette cartridges, receiving cash or receiving a combination of both e-cigarettes and cash (in which case you would receive less of each).

To the baseline, week 4 and week 8 visits, you will bring your first morning urine collected on the day of the visit from which we will measure substances associated with the use of menthol and non-menthol cigarettes and e-cigarettes. We will provide supplies for you to use to collect your urine. To each visit you will bring in a tobacco use diary where you will keep track of all the cigarettes you smoke, each time you use e-cigarettes, and each time you use any other tobacco or nicotine containing products. Additionally, you will need to bring in your e-cigarette and any remaining cartridges you have left to each visit. At each visit we will collect a breath sample to measure the amount of carbon monoxide in your breath and you will complete a number of questionnaires

Follow up Visit: The final visit will occur approximately 12 weeks after your baseline visit. Between the week 8 and week 12 visit, we will not provide e-cigarettes and you are free to smoke either menthol or non-menthol cigarettes. To this visit, we will ask you to bring in your first morning urine and your tobacco use diary. As at previous visits, we will collect a breath sample to measure the amount of carbon monoxide in your breath and you will complete a number of questionnaires.

In total there are 7 visits (a screening visit, 5 evaluation visits and 1 follow-up visit) and several scheduled calls in between visits during the study.

Risks of Study Participation:
Use of tobacco products, including e-cigarettes, is bad for your health. If you are interested in quitting smoking at any time during the study, you are free to do so and we can provide information to you about the QuitPlan services which can help you quit smoking.

Since e-cigarettes contain nicotine, it is possible that if you use too much you can have symptoms such as nausea, vomiting, dizziness, weakness and rapid heartbeat. Additionally, it is possible that use of the e-cigarette can cause throat irritation. Since the e-cigarette is a battery powered electronic device, malfunctions are possible. It is important to keep the e-cigarette product and cartridges away from pets and children. As with any product, there is a risk that unanticipated effects from using the e-cigarette may occur.

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. **It is therefore very important that you not add anything to the e-liquids provided or alter the product in any way.**

Not smoking menthol cigarettes, providing urine and providing a breath sample are not expected to be associated with any risks. During the visits, you will be asked some personal questions about your medical and psychiatric history. You are free to not answer any questions that you are not comfortable with, although we may need certain information in order to determine that you qualify for this study and you may be excluded if we do not have enough information to determine your eligibility.

Benefits of Study Participation:
There are no direct benefits to participating in this study.

Alternatives to Study Participation:
The alternative to participating in this study is to not participate.

Study Costs/Compensation:
You will receive $20.00 for the screening visit, the baseline visit, and the following 5 visits. If you attend all of your visits and follow all study procedures you will receive a $60 bonus. In total this means that you can earn up to $200 for the entire study. You can additionally be paid up to $48 if you choose cash when given the option to choose e-cigarette cartridges or cash. Payment for visits will occur via pre-paid gift cards provided at the end of each visit. The bonus payment will be provided at the last visit. If you take public transportation you will be provided with two tokens per visit starting at the baseline visit and if you drive you will be provided parking (you must however park in the designated spots). If total payment from the University in a calendar year exceeds $600, this will trigger the need for a 1099 tax form. We will therefore ask you to complete a W-9 form at the baseline visit.

Payment will be made using a pre-paid debit card called Greenphire ClinCard. It works like a bank debit card. We will give you a debit card and each time you receive a payment for participation in this study, the money will be added to the card after each completed visit.

You may use this card at any store that accepts MasterCard or you can use a bank machine to remove cash. However, there may be fees drawn against the balance of the card for cash withdrawals (ATM use) and inactivity (no use for 3 months). We will give you the ClinCard Frequently Asked Questions information sheet that answers common questions about the debit card. You will also receive letters with additional information on how you can use this card and who to call if you have any questions. Be sure to read these letters, including the cardholder agreement, for details about fees.

The debit card system is administered by an outside company. The company, Greenphire, will be given your name. They will use this information only as part of the payment system. Your information will not be used for any other purposes and will not be given or sold to any other company. Greenphire will not receive any information about your health status or the study in which you are participating.

Research Related Injury:
In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner, to you or your insurance company. If you think that you have suffered a research related injury let the study physicians know right away.

Confidentiality:
The records of this study will be kept private. In any publications or presentations, we will not include any information that will make it possible to identify you as a subject. Your record for the study, however, may be reviewed by departments at the University, the funders of this study or others who have appropriate regulatory oversight. Since this study is being conducted in the Clinical and Translational Science Institute, your participation will be recorded in their records. To these extents, confidentiality is not absolute.

Voluntary Nature of the Study:
Participation in this study is voluntary. Your decision of whether or not to participate will not affect your current or future relations with the University. If you decide to participate, you are free to withdraw at any time without affecting those relationships.

The investigators also have the right to stop your participation at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped.

Contacts and Questions:
The researcher conducting this study is Michael Kotlyar, PharmD. You may ask any questions you have now. If you have questions later, please contact Dr. Kotlyar at (612) 625-1160 or the study coordinators: Sheena Dufresne at (612) 626-5981.

Who do I contact if I have question, concerns or feedback about my experience?
This research has been reviewed and approved by an Institutional Review Board (IRB) within the Human Research Protections Program (HRPP). To share feedback privately with the HRPP about your research experience, call the Research Participants' Advocate Line at 612-625-1650, (toll free: 1-888-224-8636) or go to z.umn.edu/participants. You are encouraged to contact the HRPP if:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research participant.

● You want to get information or provide input about this research.

Will I have a chance to provide feedback after the study is over?

The Human Research Protection Program may ask you to complete a survey that asks about your experience as a research participant. You do not have to complete the survey if you do not want to. If you do choose to complete the survey, your responses will be anonymous.

If you are not asked to complete a survey, but you would like to share feedback, please contact the study team or the Human Research Protection Program (HRPP). See the "Researcher Contact Information" of this form for study team contact information and "Who do I contact?" of this form for HRPP contact information.

You will be given a copy of this signed form to keep for your records.

Future Studies:

_____ If you initial here, you give permission for the Investigators of this study (or their study staff) to contact you in the future to invite you to participate in future research studies. You may choose to participate or not when contacted. You do not have to agree to be contacted in the future to participate in this study. If you do not wish to be contacted about any future studies, please leave the box blank.

Statement of Consent:

I have read the above information. I have asked questions and have received answers. I consent to participate in the study.

Signature _____ Date _____

Printed Name _____

Signature of Person Obtaining Consent _____ Date _____

Printed Name _____