Impact of Very Low Nicotine ContentCigarettes in a Complex Marketplace Telehealth Visits plus Curbside Contact or In-Person Clinic Visits

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Why am I being asked to take part in this research study?

We are asking you to take part in this research study because you are a cigarette smoker who may or may not be interested in quitting smoking, but you are willing to participate in a study that involves study cigarettes and other tobacco or nicotine products.

What should I know about a research study?

- Someone will explain this research study to you.
- Whether or not you take part is up to you.
- You can choose not to take part.
- You can agree to take part and later change your mind.
- Your decision will not be held against you.
- You can ask all the questions you want before you decide.

Why is this research being done?

The purpose of this study is to understand how smoking a very low nicotine content (VLNC) cigarette compared to smoking a cigarette with nicotine levels about the same as your usual brand may affect your tobacco use pattern and measures of health. This study looks at whether you choose to use nicotine products, like nicotine gum or patch, e-cigarettes and other vaping devices or other tobacco products while you are assigned to the study cigarettes. The health measures that we examine include exposure to tobacco toxins and related cancer-causing agents, nicotine levels and risk factors for heart disease. The study will also evaluate how using the study cigarettes and use of these other nicotine and tobacco products affects withdrawal symptoms, mood and responses to the products, such as tobacco satisfaction.

The Food and Drug Administration (FDA) regulates tobacco products. One of the ideas for reducing the use of cigarettes is to reduce nicotine in cigarettes to levels below the point that they lead to addiction. This would mean that smoking a cigarette is truly a choice and not because you are addicted to the nicotine. If the FDA were to reduce these nicotine levels, cigarette smokers may use other less harmful products that contain nicotine. This study looks at whether smokers would choose to use other products and what products they would use.

The cigarettes used in this study are investigational and have been obtained through the National Institute on Drug Abuse. The FDA has not approved these cigarettes for marketing but has given us permission to use these cigarettes after review of our study protocol and the potential effects of the study cigarettes.

How long will the research last?

We expect that you will be in this research study for about 20 weeks after screening. During this time, you will attend 13 telehealth visits that last 1-2½ hours and come in for either an in-person clinic visit or a curbside visit for drop off or pick up of study supplies and drop-off of biological samples at the Delaware Clinic Research Unit. Telehealth visits will require you to have a computer, tablet, iPad or smart phone. You will attend weekly visits for 6 weeks and then every other week for 10 weeks. Finally, you will attend a follow-up visit 4 weeks after you stop the study products.

How many people will be studied?

We expect about 100 or more people will be in this research study at the University of Minnesota. This study will also be done at Duke University, Wake Forest University, University of Pennsylvania, Brown University and the University of California-San Francisco and a total of 500 people will be studied.

What happens if I say "Yes, I want to be in this research"?

Screening Procedures

If you agree to be in this study, we will find out if you are eligible to participate. To see if you are eligible, we will follow these screening steps.

- You will be asked questions about any symptoms of COVID-19 or any exposure to someone who is positive for the virus in the last two weeks.
- You will be interviewed or asked to complete forms through a website link on the computer that asks personal questions about medical and emotional history, tobacco use history and dependence, smoking habits, motivation to quit, use of alcohol and other recreational drugs.
- We will ask your weight.

- If you are a woman, we will ask about your use of birth control.
- You will be enrolled in a daily phone call system where you will track your cigarettes smoked per day (more information below).

If it appears you meet the study criteria thus far:

- You will be asked to attend either a brief in-person visit at our clinic or, if you are not comfortable attending an in-person visit, we can arrange for a curbside pick up, or we will mail you the study materials.
- We will provide a monitor to take your vital signs and another device that you will use to take your carbon monoxide (CO) level at home. CO will tell us whether you have been smoking recently. We will provide instructions and watch you complete the test and you will show us the results. We may also check your urine sample that you drop off at the in-person or curbside visit to see if you are smoking enough to be in this study. If you attend an in-person or curbside visit, we may be able to provide both monitors in the same visit and make assessments in the clinic or in your home, respectively. If the materials are mailed to you, we may send both devices to you or we may need to arrange two separate mailings and telehealth visits.
- If you prefer the devices can be mailed out to you, you will contact us after you have received the monitors to set up another telehealth visit and we will show you how to use the monitors and check if your readings are acceptable.

After you complete all of these measures, our medical staff will review the information to see if you meet study eligibility. If you are eligible, you will be enrolled in the study and begin the study procedures.

Study Procedures

There will be three phases in this study.

Phase 1: During this Phase you will attend weekly telehealth and curbside or in-person clinic visits for two weeks. Our study research assistants will gather “baseline” information while you are still smoking your regular cigarette at your normal amount.

Phase 2: In this Phase, you will attend weekly telehealth and curbside or in-person clinic visits for two weeks. We will show you our web-based marketplace on your computer, tablet, iPad or smart phone. This marketplace will have your usual brand cigarettes and other tobacco and nicotine products. These other products include snuff, snus, nicotine pouches, electronic cigarettes (e-cigs or vaping devices) and nicotine patch, gum and lozenge. You will be provided vouchers with points that can be exchanged for any of these products in our marketplace during the study. If you don’t use all of your points during the study, they can be traded for cash at the very end of the study. All tobacco or nicotine products that you use during the study should only be from our web-based market. You will come by our clinic for pick-up of the study products you have chosen and drop off your first morning urine sample.

Phase 3: Phase 3 is the experimental phase. During this phase, you will attend 7 telehealth and curbside or in-person clinic visits over 12 weeks. For the first 2 weeks, you attend telehealth visits once every week. For the remaining 10 weeks, you will attend once every other week. You will be randomly assigned (like the flip of a coin) to a reduced nicotine content study cigarette or a study cigarette with levels of nicotine about the same as your usual brand of cigarettes. You will be told which of the study cigarettes you will receive. These cigarettes will be provided in the web-based marketplace along with the other tobacco and nicotine products. You will also be able to get other products (snuff, snus, nicotine pouches, electronic cigarettes (e-cigs or vaping devices) and nicotine patch, gum and lozenge) during Phase 3. You will continue to be provided a voucher with points at each visit that can be exchanged for your assigned study cigarette and/or any of the other products from our marketplace.

If you need more tobacco products, you can contact the clinic at any time during normal clinic hours to arrange to pick up products as long as you have enough saved points to trade. You may need to take your carbon monoxide level, vital signs or other safety measures on a telehealth visit prior to the pick-up of products.

At the end of Phase 3, we will stop providing the study cigarettes and we will talk to you about the benefits of becoming smoke-free and provide you with information about quitting smoking. However, you can quit smoking at any time throughout the study and still remain in the study.

Follow-up: You will attend a telehealth and curbside or in-person clinic follow-up visit 1 month after the end of Phase 3, when you stop using the study cigarettes or our study products. At that final visit, you will return any Marketplace products except for nicotine replacement. We will also ask about your tobacco use and health since your last visit and complete other questionnaires.

Curbside or In-Person Clinic Visits: You will have an option of either picking up study product and dropping off your samples, empty cigarettes packs and used products either curbside or in our clinic for a brief visit. This option depends on your preference and the whether your clinic staff is able to see participants in person in the clinic due to clinic policies.

Study Visit Procedures:

At most of the telehealth visits, the following procedures will be carried out:

- Answer questions about any symptoms of COVID-19 or any exposure to someone who is positive for the virus in the last two weeks. We will also have you take your temperature and provide us with the reading. If you do not show any indications that you might have or at risk for COVID-19, we will conduct a telehealth visit and ask you can come to the clinic for a visit.

- Collect breath carbon monoxide (CO) level to measure your amount of smoking.
- Complete several online forms asking about tobacco use, withdrawal symptoms, urges to smoke, mood, reaction to the products, and current medication use and health symptoms. A website link will be sent to you.
- Collect blood pressure and pulse.
- Provide your weight.
- Provide you with supportive counseling to help you follow the study instructions.
- Review the amount of study cigarettes that you have decided to get with your points.
- Review your study cigarette packs (full, empty or partial packs) and how many you have smoked since last visit. These cigarettes are owned by the government and we are required to keep careful track of them. You will need to keep track of all of the study cigarettes we give to you.
- For Phase 2 and 3, select study products using the Marketplace App (link will be provided to you). Review the amount of other tobacco or nicotine products that you decided to get with your points.

After you have completed these measures, we will set up a time for you to come to the clinic's curbside location or be seen in-person in the clinic. You will be provided a mask that you will be required to wear while interacting with the researcher who will also be wearing personal protection to keep you safe.

At the curbside or in-person visit, you will:

- Return your study tobacco or nicotine products containers (full, empty or partially used) and review how much you have used.
- Receive the study products you have chosen using the Marketplace app.
- Provide a saliva sample you had collected on the telehealth call. A few of the samples will be randomly picked to check for accurate reporting of the products that you are using.

At several visits, the following added measures will take 30-45 minutes more to complete:

- A urine sample from the first time you urinate in the morning after waking up will be collected and brought to the curbside or in-person clinic visit. This urine sample will be tested for nicotine, cancer-causing agents and other chemicals that are in tobacco and their breakdown products. This sample will be collected six times.
- Additional questionnaires that you will complete through telehealth that look at things that might affect the results from your urine samples. These questionnaires are related to your diet, contact with smoke at home or work, and alcohol or recreational drug use.
- If you are a woman who could get pregnant, we will also test your urine sample for pregnancy at some visits using your first void urine sample. If your visit is over 8 hours from the time of collection, we will ask you to collect a spot urine right before your visit. If you become pregnant while you are smoking the study cigarettes or using any tobacco products, you will not be eligible to continue in the study.

- You will provide a saliva sample at the Phase 1 visits. The sample may be used for looking at genes related to how your body breaks down nicotine and other toxins related to tobacco and nicotine or your health risks related to tobacco and nicotine use.

Daily Phone Call

Every day throughout the study, you will report the number of cigarettes you smoke and any other tobacco or nicotine products you use to an automated message system. You will make this report using your home phone or a cell phone. We will give you instructions on how to complete the daily calls. You will complete the daily telephone calls every morning for 17 weeks while you are in the study. These phone calls will take less than 3 minutes. To be enrolled in this telephone system, we will be providing the vendor's website with some identifiable information (your telephone number only). This information will be used for website enrollment only; the data analysis group will not have access to identifying information nor will it be shared with anyone outside of this study.

Randomization to Study Cigarettes

The study cigarettes you will receive are chosen by chance, like flipping a coin. Neither you nor the study staff will choose what treatment you get. You will have an equal chance of being given either the Very Low Nicotine Content (VLNC) cigarette or the Normal Nicotine Content (NNC) cigarette. Both you and the researchers will know which type of cigarette you receive. You will be able to choose to receive menthol or non-menthol cigarettes.

What are my responsibilities if I take part in this research?

If you take part in this research, you will be responsible for completing the procedures described above including attending visits, keeping track of tobacco and nicotine use through daily calls, keeping track of the study products you receive and providing the biological samples. In addition, you will be asked to avoid smoking any non-study substances including marijuana use, for 48 hours before each appointment as the exposure to smoke will interfere with our tests.

What happens if I do not want to be in this research?

This is a research study and you can choose whether or not you want to participate.

What happens if I say "Yes", but I change my mind later?

You can leave the research study at any time. Leaving will not be held against you. If you decide to leave the research study, contact the study staff so that we can schedule an exit visit and you can bring back any study cigarettes.

Choosing not to be in this study or to stop being in this study will not result in any penalty to you or loss of benefit to which you are entitled. Meaning, your choice not to be in this study will

not negatively affect your right to any present or future medical treatment, your academic standing as a student, or your present or future employment.

If you stop being in the research, already collected information about you will not be removed from the study database.

What are the risks of being in this study? Is there any way being in this study could be bad for me?

This research may hurt you in the following ways and you should be aware of these before deciding to be part of the study:

Smoking Any Cigarettes

Cigarette smoking is the leading cause of preventable death in the United States and kills half of all long-term users. On average, smokers die 10 years earlier than nonsmokers.

Smoking any cigarette is harmful to a person's health and can lead to the following medical problems:

a) Heart and blood vessel disease: Heart disease, heart attack, stroke, peripheral vascular disease (PVD), reduced blood circulation, abdominal aortic aneurysm;
b) Lung disease: Emphysema, asthma, bronchitis, tuberculosis and chronic airway obstruction (COPD);
c) Cancer: Lung, bladder, liver, colon, cervical, esophageal, kidney, larynx, mouth, pancreatic, throat, stomach cancers and acute myeloid leukemia;
d) Diabetes;
e) Changes in immune function, rheumatoid arthritis;
f) Other health risks:
   - Infertility
   - Tubal pregnancy
   - Miscarriage
   - Sudden infant death syndrome (SIDS)
   - Birth defects
   - Lower bone density in postmenopausal women and increased risk for hip fracture in women
   - Male sexual dysfunction
   - Vision problems
   - Age-related macular degeneration
g) Smoking and nicotine can affect your heart and blood vessels which may result in changes in blood pressure and/or heart rate;
h) Addiction to nicotine.

Smoking Study Cigarettes

The study cigarettes are made in the same way as your usual cigarettes. But in order for the study cigarettes to be lower in nicotine, they are made from genetically modified tobacco plants (GMO). As with other tobacco products made by tobacco companies, this tobacco has not been tested for safety. Long-term effects of inhaling the study cigarettes are unknown. Smoking the study cigarette is not any less risky than your usual brand of cigarette and could pose increased health risks.

There is a potential for a change in your use of cigarettes due to the lower nicotine levels including how you inhale the smoke or smoking more cigarettes per day. This increased rate of smoking may continue after completing the study. You may experience an increase in exposure to carbon monoxide, a gas from smoke, due to altered smoking habits.

Nicotine Withdrawal or Too Much Nicotine

You may experience symptoms of nicotine withdrawal if you are assigned to the very low nicotine content cigarettes. These symptoms may include: craving tobacco, irritability, frustration or anger, anxiety, nervousness, impatience, restlessness, sleep problems, trouble with concentration, depressed or sad mood, constipation, dizziness, coughing, nausea, sore throat and increased appetite or weight gain. These feelings can be uncomfortable, but are of low risk.

The use of the nicotine replacement products (gum, lozenges or patch) and use of other tobacco or nicotine products in addition to smoking cigarettes may cause some symptoms of too much nicotine. Symptoms of too much nicotine may include headache, dizziness, shakiness, nausea, vomiting or diarrhea, weakness and fast heartbeat. You will be monitored for any of these side effects to make sure you are you safe. If serious side effects occur, we may stop the use of the nicotine replacement or study products. Use of both cigarettes and other tobaccos may result in an increase in your nicotine and tobacco related toxin levels.

Worsening of Mental Health Symptoms

Smoking cigarettes and nicotine can affect a person's mood and emotions and are associated with mental health problems including major depressive disorder, general anxiety disorder, bipolar disorder and eating disorders. Any changes in nicotine or tobacco consumption could have a negative effect on mental health conditions.

Interaction of Study Cigarettes with Medications

Quitting smoking can greatly benefit your health. However, changes in your smoking can lead to changes in the levels of your medications. Please make sure to tell us about all the medications you take. We also recommend you discuss any planned or actual changes in how much you are smoking with your doctor, especially if you are taking medications for mental health, heart or blood vessel problems, or other serious diseases.

Nicotine Replacement (Medicinal Nicotine) or Nicotine Pouches

Side effects of the nicotine replacement (nicotine lozenge, gum, or patch) or nicotine pouches may occur. Side effects from the nicotine gum or lozenge or nicotine pouches include mouth and throat irritation, mouth sores, hiccups or belching, dizzy or lightheaded, upset stomach, vomiting, heartburn, diarrhea and high blood pressure. Using the nicotine gum may aggravate the jaw joint or dental work. You should not use the gum if you have dentures. Side effects of the nicotine patch primarily include redness, itching or swelling at patch site and sleep problems.

Smokeless Tobacco/Snus

If you use smokeless tobacco products, you could experience an increased risk for mouth sores, gum disease and tooth loss, nausea or upset stomach, vomiting, or high blood pressure. These risks also include nicotine addiction. Smokeless tobacco products may increase the risk of cancer, particularly oral and pancreatic cancer. However, these risks are less than the health risks you are exposed to as a cigarette smoker.

E-cigarettes (e-cigs, vaping devices)

Do not let anyone else use your study e-cigarette or vaping device.

Side effects of the electronic cigarette or vaping devices are not known since little research has been done on this product. There is a notice from the FDA regarding the safety of this product that says they do not know whether e-cigarettes or vaping devices are safe for their intended use, how much nicotine or other potentially harmful chemicals are being inhaled during use, or if there are any benefits associated with using these products. Some of the samples tested have low but detectable levels of toxic chemicals. Side effects may be similar to the use of the nicotine inhaler, such as sore throat or burning in the throat, stomachache, nausea, or pain, belching, coughing, or stuffy nose. They may also include changes in taste, mouth sores, dry mouth, headache, dizziness, increased heart rate or palpitations, tremors, vomiting or diarrhea. The FDA has recently acknowledged reports of seizures following the use of an e-cigarette between 2010 and 2019. They are carefully monitoring e-cigarette adverse event reports to determine if e-cigarette use is linked to seizures. If you experience loss of consciousness, memory lapse, change in mental status, confusion, tremor, shaking, or seizure discontinue the use of the device and contact study staff immediately.

CDC and FDA are investigating recent reports of serious lung disease associated with use of vaping devices. Many of the incidences are related to vaping cannabis (THC) oil. FDA has advised consumers to avoid buying vaping products on the street and refrain from using THC oil or modifying or adding any substance to products purchased at stores. If you experience any symptoms such as cough, shortness of breath or chest pain, nausea, vomiting or diarrhea seek prompt medical attention.

In addition, there have been rare occasions where the batteries in e-cigarettes and vaping devices have exploded and injured users. You should not store a device where the power button can be repeatedly turned on accidently (like in a pocket) as it may overheat and cause burns. Some people may have an allergic reaction to the compounds in the e-liquid such as propylene glycol, glycerin or flavor additives. Defective cartridges, tanks or devices may leak e-liquid. If this should happen, wash the exposed area to remove the e-liquid immediately. The e-liquid does contain nicotine, an addictive chemical that could lead to long-term use. In addition, nicotine may contribute to diseases associated with smoking. While not harmless, e-cigarettes and vaping devices generally contain fewer toxins than smoked tobacco products.

The liquid used in e-cigarettes and vaping devices (often called e-liquid or e-juice) can contain nicotine that can cause harm and possible death if the e-liquid or the refill cartridges containing e-liquid are swallowed.

Keep all e-liquid and cartridges away from pets and children.

If you or someone else drinks the liquid, call the Poison Control Center (1-800-222-1222) immediately and contact study staff. For skin exposure: wash well with soap and water for 10-15 minutes.

Continued use of dual tobacco products

There is a risk you may continue to use other tobacco products along with smoking after the study is completed. We will look at your use at your one-month follow-up visit and will look at your nicotine levels to see whether you are exposed to more nicotine than when you started the study. We will encourage you to quit tobacco use and we will provide referral information for you if you are using any tobacco products. You are encouraged to call us at the number listed at the beginning of this document if you have any questions or concerns.

Survey Questions

You will be asked questions about your medical history, drug and alcohol use and mood. Answering these kinds of questions may make some people feel uncomfortable.

Abnormal Vital Signs or Other Health Findings

You will have your vital signs (heart rate and blood pressure) taken every visit. You may find out that your blood pressure or heart rate is out of the normal range. You may tell us about health problems during the study (things like chest pain, numbness or shortness of breath) that our medical staff feels should be examined more closely. If this should happen, we will ask you to follow up with your primary care doctor and may require you to do so to stay in the study.

Breach of Confidentiality

There is a risk of loss of privacy if other people find out about your participation. This would include the alcohol and drug testing results. All efforts are made to keep your information confidential, but confidentiality cannot be guaranteed.

Other

If you are using public transportation to get to your appointment, you may put yourself at increased risk for exposure to the COVID-19 virus. We advise you to wear a mask and practice social distancing when possible while using public transportation.

In addition to these risks, this research may hurt you in ways that are unknown. These risks may be a minor inconvenience or may be so severe as to cause death. At each visit, we will ask you how you feel, and if we think that being in this study is putting your health at risk, we will stop your participation.

If any of these side effects mentioned above occur, please notify the research staff (612-624-5178 or 763-242-5119 after hours). If these side effects are serious, discontinue the use of the study products.

What do I need to know about reproductive health and/or sexual activity if I am in this study?

Risk of Smoking While Pregnant

Smoking any cigarette is a risk for pre-mature birth, stillbirth, and low birth weight. To avoid these risks, it is important that you are not pregnant during this study or while using any tobacco products. Avoiding sexual activity is the only certain method to prevent pregnancy unless you are at an age where your periods have stopped for more than 2 years or you have had a hysterectomy. However, if you are sexually active and able to become pregnant, you should use an appropriate "double barrier" method of birth control (such as using a diaphragm, intrauterine device (IUD), or contraceptive sponge, in addition to your partner's use of a condom). You should be aware, pregnancy could still result even with the use of these birth control methods. While use of prescribed "birth control" pills, injections, or implants is an acceptable method of birth control to be in this study, you should be aware that use of this type of birth control is not recommended for women who smoke. Smoking greatly increases the chance of serious heart or blood vessel side effects from oral contraceptive (birth control pills) use. The risk increases with age and with heavy smoking (about 15 or more cigarettes per day) especially in women over 35 years of age. It is unclear whether smoking while using birth control injections or implants increases the risks of heart attack and stroke, so it is recommended that women who use injections or implants do not smoke.

You should not be or become pregnant or breastfeed while participating in this research study. Pregnancy tests will be done at the beginning (baseline) and every month while you are smoking study cigarettes. If you become pregnant while participating in this research study, it is important that you tell the study doctor or other research team member immediately. You may be required to stop participation in this study. We will ask to follow up with you after you have had your baby to follow pregnancy outcomes in the event of a pregnancy.

Will it cost me anything to participate in this research study?

Taking part in this research study will not lead to any costs to you.

Will being in this study help me in any way?

There is no direct benefit for you from taking part in this study. However, this information will help inform the FDA about what happens when nicotine levels in cigarettes are reduced.

This is not a quit smoking treatment program. If you decide to quit smoking during the study, you may continue in the study. **You will not be required to smoke the study cigarettes if you choose to quit smoking.**

What happens to the information collected for the research?

Efforts will be made to limit the use and disclosure of your personal information to people who have a need to review this information. We cannot promise complete privacy. Organizations that may inspect and copy your information include the Institutional Review Board (IRB - oversees subject safety for all studies) and other representatives of this institution, including those that have responsibilities for monitoring or ensuring compliance.

Certificate of Confidentiality

In this study, you will be asked about illegal activities or highly personal behavior. We have obtained a Certificate of Confidentiality from the federal government. This means in most cases the information you share is protected and will not be released to authorities upon request. However, we may still be required under certain circumstances to release your information. The Certificate cannot be used to resist a demand for information from personnel of the United States federal or state government agency sponsoring the project and that will be used for auditing or program evaluation of agency funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If you provide your written consent to receive research information, then the researchers will not use the Certificate to withhold that information. The Certificate of Confidentiality will not be used to prevent disclosure of certain information to state or local authorities. If we learn about current or ongoing child or elder abuse or neglect, we may be required by law or policy to report this information to authorities. In addition, if we learn that you intend to harm yourself or others, we may be required to report this information.

Some of the urine and saliva collected will be kept for future research along with information on age, race, health and tobacco use history and your response to study products. Although the exact tests that will be done are not known at this time, researchers may study: 1) how diet, lifestyle, environment, race/ethnicity, age and other factors are related to the development of cancer or other diseases or affect use of products; 2) how differences in genes affects one's ability to process substances that cause diseases; 3) how damage to one's chromosomes is related to risk of cancer and other diseases. Any studies using these stored samples for other purposes will be done in accordance with the guidelines of the Committee on Human Studies and with federal regulations for the protection of human subjects. The specimens will be kept at the Masonic Cancer Center Biobank and they will be kept until they are used up or no longer

needed. These samples may be shared with other investigators associated with this Center. These samples will only be identified by your study number.

Information on your participation in this study will be shared, as needed, with the other researchers in the Tobacco Research Programs. This includes information about the type and duration of study, your health information and tobacco use status. The information is shared to make sure you are only in one study at a time, meet the eligibility criteria to participate and to maintain your safety.

A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

The sponsor, monitors, auditors, the IRB, the University of Minnesota Research Compliance Office and other University compliance units, the US Office of Research Integrity (ORI), the US Office for the Protection of Human Research Protections (OHRP), National Institute on Drug Abuse, and the US Food and Drug Administration (FDA) may be granted direct access to your study records to oversee the research. By signing this document, you are authorizing this access.

We may publish the results of this research. However, we will keep your name and other identifying information confidential.

A description of this clinical trial will be available at http://www.ClinicalTrials.gov, as required by U.S. Law. This Website will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Website at any time.

Who do I contact if I have questions, 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?

After the study, you might be asked to complete a survey 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 HRPP. See the "Investigator Contact Information" of this form for study team contact information" and "Whom do I contact if I have questions, concerns or feedback about my experience?" of this form for HRPP contact information.

Can I be removed from the research without my OK?

The study doctor or Principal Investigator may stop your participation without your approval. Some examples of why this could happen is if you develop medical problems, experience serious side effects to the study cigarette, or do not comply with the study requirements or your appointment schedule.

We will tell you about any new information that may affect your health, welfare, or choice to stay in the research.

What else do I need to know?

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.

Will I be compensated for my participation?

If you agree to take part in this research study, we will give you up to $770 for your time and effort. You will receive $10 for transportation for curbside or in-person clinic visits and $40 for your time at each visit in the form of a Greenphire Clincard described below. You will receive an additional $15 for the longer visits where we collect samples and you complete additional forms.

In addition, at the end of the study you will receive $10 for each week that you completed all of the daily calls. If you have completed all other study procedures, you will receive a $300 bonus. To be eligible for the bonus you must attend the study visits, provide the urine and saliva samples, keep track of study products, complete your daily phone calls and avoid the use of non-study products you have obtained from outside our Marketplace. If you have a slip and use a non-study product and accurately report this information to us, you will receive $100 for the bonus. In addition, at follow-up you can trade in your unspent points. If you choose not to use the points and have not bought products outside of the study marketplace, the remaining points can be traded for dollars that will be added to your final payment at the end of the study (1 point = $1). **Both the bonus and the exchange of voucher points for money will be provided only if you complete the study, and your biological sample results show you have avoided non-study products or accurately reported a slip.** If you are withdrawn from the study by the Principal Investigator for safety reasons, you will receive the amount you have earned prior to exiting the study.

The bonus and point exchange amount will be available to you when we have received the results of the lab tests form your spot urine samples (at or after the follow up visit). If the lab tests show that you have avoided non-study products, you will receive the bonus and the point exchange amount. You will be paid for all aspects of the study that you do complete and not paid for study tasks that you missed.

The schedule below shows the amount you receive if you complete all study activities.

Visit	Transportation Compensation (Cash or gift card)	Study visits Compensation (Gift card)	Biological Samples (Gift card)
Screening visit	$10 (in-person only)	$40	-
Phase 1 visit 1	$10	$40	$15
Phase 1, visit 2	$10	$40	$15
Phase 2, visit 3	$10	$40	-
Phase 2, visit 4	$10	$40	$15
Phase 3, visit 5	$10	$40	-
Phase 3, visit 7	$10	$40	-
Phase 3, visit 8	$10	$40	$15
Phase 3, visit 9	$10	$40	-
Phase 3, visit 10	$10	$40	$15
Phase 3, visit 11	$10	$40	$15
Phase 3, visit 12	$10	$40	$15
Follow-up, visit 13	$10	$40	$15
Total for visits: $770	$130	$520	$120

After completing the follow-up visit, you would receive the additional amount you have earned for bonus, telephone calls and voucher points:

Diary Calls ($10 per week when all calls are completed)	Maximum $170
Bonus for completing all study requirements	Up to $300

Tobacco/nicotine product points (amount of voucher points that you have left)	Amount will vary but the maximum is $200

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, address, phone number, and social security number. 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.

You should be aware that the income you receive from being in the study may be considered taxable income and need to be reported to the IRS on your income tax return. You will be required to complete a W-9 Request for Taxpayer Identification Number (TIN) to provide the University of Minnesota with the information needed to give you the study payments and report income paid to you. If you receive more than $600 in a calendar year from the University of Minnesota, the income will be reported to the IRS, as required by law, and an IRS Form 1099 (Miscellaneous Income) will be sent to you. It is up to you to understand how this payment may affect your tax or public benefit status.

Study Results

After the study is fully completed, the data has been analyzed and the results written up, you will receive a letter informing you of the results.

Optional Elements:

The following research activities are optional, meaning that you do not have to agree to them in order to participate in the research study. Please indicate your willingness to participate in these optional activities by placing your initials next to each activity.

I agree	I disagree	
_____	_____	I agree to provide a saliva sample that will be stored for possible future gene analysis
_____	_____	The researcher may contact me in the future to see whether I am interested in participating in other research studies by the Principal Investigator of this study or other investigators working with Tobacco Research Programs at the University of Minnesota.
_____	_____	The researcher may keep any leftover urine or saliva samples taken during the study. These samples may be used for other research not related to this study. These samples will be retained in non-identifiable form, meaning that there will be no information associated with the urine or saliva samples that will allow anyone to readily know my identity. The samples may be shared with other investigators in the study Center or working with the Tobacco Research Programs.

Your signature below documents your permission to take part in this research. You will be provided a copy of this signed document.

_____ _____

Signature of Participant Date

_____

Printed Name of Participant

_____ _____

Signature of Staff Obtaining Consent Date

_____

Printed Name of Staff Obtaining Consent