Establishing the Effect of Flavor on the Addictive Potential of Electronic Cigarettes

Principal Investigator: Andrea Hobkirk, PhD, Penn State College of Medicine

NCT03905928

Funded by NIH R03-DA047582

Last approved by IRB on November 20, 2024

Prepared on April 30, 2025

Version Date: 10/19/2022

CONSENT FOR RESEARCH
Penn State College of Medicine
Penn State Health

Title of Project: Establishing the effect of flavor on the addictive potential of electronic cigarettes

Principal Investigator: Andrea Hobkirk, PhD.
Address: 500 University Dr. Hershey, PA 17033
Telephone Numbers: (717) 531-0003 ext. 286415.

Subject's Printed Name: _____

We are asking you to be in a research study.

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, and there will be no penalty or loss of benefits to which you are entitled.

This form gives you information about the research. Please ask questions about anything that is unclear to you and take your time to make your choice.

KEY INFORMATION

The following is a short summary of this study to help you decide whether or not to be a part of this research. More detailed information is provided later in this form. If you have any questions, be sure to ask the study team.

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

We are asking you to take part in this voluntary research study because you are a current inhaled nicotine user.

What is the purpose of this research study?

The purpose of this voluntary research study is to determine if different electronic cigarette (ECIG) flavors and nicotine levels affect inhaled nicotine users' subjective liking and brain reward responses to ECIGS.

How long will the research study last?

You will participate in the study for 5 weeks, attend 2 in-person visits at the Penn State Hershey Medical Center and take part in 4 remote visits via Zoom.

What will I need to do?

You will come to the study center to provide a urine sample, complete an exhaled breath carbon monoxide (eCO) measurement and cue-reactivity tasks in the MRI scanner. For the cue-reactivity task, you will be asked to smell several odors, including the odor of an ECIG flavor that you will be assigned to use for 4 weeks. The scan will last about 45 minutes. You will be randomized to receive one of four ECIG products. You will be asked to use your assigned ECIG product as a replacement for cigarette smoking or e-cigarette use. You will track your ECIG and cigarette use daily. You will then complete some questionnaires remotely via Zoom. Two weeks later, you will take part in a remote visit where you can discuss any issues you are having with with ECIG use. At the last visit, you will again complete questionnaires remotely, provide a urine sample, complete an eCO measurement, and complete cue-reactivity tasks in the MRI scanner. You will be

asked to return all study ECIG cartridges at the end of the 4 weeks. At the end of the visit, you will be provided with information about quitting smoking.

What are the main risks of taking part in the study?
For this study, the main risks to know about are:

- ECIG use: There have been reports of risks related to the use of e-cigarettes, including serious lung illness and seizures. E-cigarettes containing THC and e-cigarettes purchased off the street (not from retailers) have been linked with most of the cases involving lung illnesses.
- MRI (Magnetic resonance imaging): MRI does not involve radiation and there are no known long-term risks of MRI. The major discomforts of MRI scanning include lying still in a supine position for a sustained period of time and hearing loud tapping sound during image acquisition. If at any time you want to stop, you can press a "panic" button and the scan will stop.

What are the possible benefits to me that may reasonably be expected from being in the research?
There are no benefits to you from taking part in this research. Results of the study may benefit other people in the future by helping us learn more about the addictive potential of flavored ECIG use.

What happens if I do not want to be in this research?
Participation in research is completely voluntary. You can decide to participate or not to participate. You may choose not to take part in this research study.

DETAILED INFORMATION
The following is more detailed information about this study in addition to the information listed above.

1. Why is this research study being done?
This research is being done to determine if different electronic cigarette (ECIG) flavors and nicotine levels affect inhaled nicotine users' subjective liking and brain reward responses to ECIGS.

Approximately 75 people will be enrolled in this study at Penn State Health.

2. What will happen in this research study?
You will attend 2 in-person visits over a period of 5 weeks at the Penn State Hershey Center for Nuclear Magnetic Resonance Research (CNMRR). During those 5 weeks, you will also complete 4 remote visits via Zoom.

Randomization/Pre-Conditioning fMRI Visit (Remote/In-Person)

Exhaled breath CO (eCO) will be measured and a urine sample will be collected at the start of the visit to verify nicotine use and to complete a pregnancy test if you are of child-bearing potential (Women who are pregnant or nursing may not participate in this research.). If you did not refrain from cigarette smoking or nicotine use, we will reschedule your visit. Eligible participants will then be assigned by chance to receive an ECIG from one of four conditions; an ECIG with 0mg/ml nicotine concentration in tobacco flavor, an ECIG with 0mg/ml nicotine concentration in strawberry vanilla flavor, an ECIG with 18mg/ml nicotine concentration in tobacco flavor, or an ECIG with 18mg/ml nicotine concentration in strawberry vanilla flavor. You have a 25% (1 in 4) chance of being assigned to any of the ECIG flavors and nicotine conditions. You and most members of the research team will not know which ECIG condition you are receiving, but the research team will be able to get this information quickly if it is needed to ensure your safety.

You will complete the fMRI odor cue-reactivity task in the MRI scanner lasting approximately 45 minutes. During the scan, you will be administered four scents in separate 4 minutes blocks for eight runs. The scents will be delivered to your nostrils via tubing from the olfactometer machine. Then you will be asked to complete questionnaires of cigarette use, cigarette dependence, liking, and withdrawal these will be done at your home remotely via Zoom immediately after your visit.

At the end of this visit, you will be given the ECIG device and 4-week supply of the randomly assigned e-liquid cartridges (approximately 2 cartridges/day) and provided with instructions on how to use the study ECIG. We ask that you take at least 50 puffs a day on your ECIG to replace conventional smoking or e-cigarette use. You will bring back all used and unused cartridges to the study center. You will continue to track any cigarette use and will start tracking ECIG puffs per day.

Conditioning Phase Check-in Visit (Remote)

Two weeks later, you will complete a remote visit via Zoom to report ECIG use and cigarettes smoked. We will discuss any challenges with ECIG use and you will complete questionnaires about cigarette use, ECIG use, dependence, liking, and withdrawal. You should continue to use your ECIG as a replacement for cigarette smoking and to log your ECIG use and report any cigarettes smoked. Prior to your next visit, you should remain abstinent from all tobacco products and nicotine use including your ECIG for at least 14 hours and to eat prior to the next visit.

Post-Conditioning fMRI Visit (Remote/In-Person)

Two weeks later, you will attend a final visit. Exhaled breath CO (eCO) will be measured and a urine sample will be collected at the start of the visit to verify smoking or nicotine use and to complete a pregnancy test if you are of child-bearing potential. If you did not refrain from cigarette smoking or nicotine use, we will reschedule your visit. Eligible participants will be asked to complete computerized questionnaires and to complete the same fMRI cue-reactivity test in the MRI scanner lasting approximately 45 minutes. At the end of the visit, you will be encouraged to quit smoking and will be provided with information from the Surgeon General.

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

If you take part in this research, your major responsibilities will include:

- Use assigned ECIG product as a replacement for cigarette smoking for 4 weeks
- Track ECIG and cigarette use daily
- Refrain from tobacco and nicotine use for at least 14 hours prior to the MRI portion of Visit 2 and Visit 4
- Provide breath and urine samples
- Complete questionnaires
- Complete cue-reactivity tasks in the MRI scanner

3. What are the risks and possible discomforts from being in this research study?

- **ECIG use:**

  There may be some unknown risks related to the use of ECIGs.

  - The most common side effects associated with using an ECIG are changes in taste, dehydration, mucus in throat/sinus, dry mouth, dry cough, throat irritation, mouth irritation, sore throat, mouth ulcers, dizziness, headache, and nausea.
    - There are reports that some people who use e-cigarettes have experienced seizures, with most involving youth or young adult users. If you have a history of seizures or take medications to prevent seizures you should not be in the study.

        - There have been some reports of serious lung illnesses among those who used e-cigarettes, and even some cases of death as a result (not all causes of death have been identified). The investigations being conducted by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) have found that the majority of people experiencing these illnesses were using e-cigarette products that contained tetrahydrocannabinol (THC) and/or products that were bought off the street or from other illicit channels and so it is important that participants avoid such products. The e-cigarette products used in this study do not contain THC and were bought from manufacturers where quality testing and control is performed. Nonetheless, please call your doctor immediately if you experience cough, shortness of breath, chest pain, nausea, vomiting, diarrhea, or fever after using your e-cigarette. Please ONLY use the e-cigarette and liquid pods (cartridges) given to you by our researchers. Do not tamper with your e-cigarette and do not use other liquids with your e-cigarette device.
    - If stored improperly (in pocket or where the ECIG device can turn on accidently), overheating of the device may occur, which presents a minor burn risk.
    - Electronic cigarette liquid contains vegetable glycerin, propylene glycol and flavorings. Participants with known allergies to these substances will be excluded in the study. The most common reported allergic reaction to these substances is skin rash.
- **Nicotine addiction:** You may be given an ECIG that contains nicotine, which is an addictive substance. The amount of nicotine they receive from this product depends on what product you are given and how you use it.
- **Nicotine withdrawal symptoms:** Smoking fewer conventional cigarettes may result in nicotine withdrawal symptoms (e.g. irritability, anxiety, restlessness, depressed mood, increased appetite, fatigue, difficulty concentrating). These symptoms will be monitored bi-weekly.
- **New development of pregnant or want to become pregnant:** Nicotine, either from cigarettes or from the study product (ECIG), is known to be harmful to the developing human fetus. If you are pregnant or become pregnant, cigarette and ECIG use may cause problems to your unborn baby. Women who are pregnant or are nursing a child may not participate in this research study. Females capable of becoming pregnant will be administered a pregnancy test prior to beginning the research. You must agree to take reasonable and necessary precautions against becoming pregnant during the period of the investigation.
- **MRI (Magnetic resonance imaging) Risks**: MRI does not involve radiation and there are no known long-term risks of MRI. You will be assessed for MRI safety at the screening visit and again at the scan visit before entering the scanner. We will be assessing for potential MRI hazards like metal fragments in the body or metal implanted devices that could shift during scanning. You will be instructed to remove all metal from their body and clothing before entering the scanning room. The major discomforts of fMRI scanning include lying still in a supine position for a sustained period of time and hearing loud tapping sound during image acquisition. You may be uncomfortable inside the MRI scanner, especially if you do not like to be in closed spaces ("claustrophobia"). In between scanning sequences, you will be able to talk with the MRI staff through a speaker system. At any time, you can choose to stop the scan by squeezing a "panic" button.
- **Loss of confidentiality:** There is a risk of loss of confidentiality if your information or your identity is obtained by someone other than the investigators, but precautions will be taken to prevent this from happening. The confidentiality of your electronic data created by you or by the researchers will be maintained as required by applicable law and to the degree permitted by the technology used. Absolute confidentiality cannot be guaranteed.

- **Randomization in clinical trials:** You will be assigned to a research intervention by chance. The research intervention you receive may prove to have more side effects than the other research intervention(s).
- **Incidental Finding:** None of the tests carried out in this study are intended to provide diagnoses for clinical purposes, but you will be alerted to findings that should be discussed with a healthcare provider. They are intended solely for research purposes. The investigators for this project are not trained to perform medical diagnosis, and the scans to be performed in the study are not optimized to find abnormalities. On occasion, a member of the research team may notice a finding on a scan that seems abnormal. When a finding is noticed, one of the investigators may consult a physician specialist, such as a radiologist or neurologist, as to whether the finding merits further investigation. If the specialist recommends further follow-up, the investigator or another member of the research team will contact you within 48 hours (via phone) of the recommendation and suggest that you contact your private medical provider for follow-up. To facilitate follow-up care, you will be given a copy of your images via a letter if you would like a copy. Being told about a finding may cause anxiety as well as suggest the need for additional tests and financial costs. Medical insurance may be affected whether or not the finding is ultimately proved to be of clinical significance. Costs for clinical follow-up are not covered in the cost of research. The decision as to whether to proceed with further examination or treatment lies with you.
- **Questionnaires:** It is possible that some of the questions in the questionnaires may make participants uncomfortable. You are free to skip any questions that make you uncomfortable.

4. What are the possible benefits from being in this research study?

4a. What are the possible benefits to me?

You will not benefit from this research study.

4b. What are the possible benefits to others?

Medical science may gain further understanding of how flavors affect the addictive potential of ECIG use.

5. What other options are available instead of being in this research study?

You may choose not to be in this research study.

6. How long will I take part in this research study?

If you agree to take part, it will take you at least 5 weeks but no more than 8 weeks to complete this research study. You will be asked to visit the research site 2 times (including today's visit). The randomization/pre-conditioning visit, remote check in and post-conditioning visit will happen within a 4 week period.

7. How will you protect my privacy and confidentiality if I decide to take part in this research study?

7a. What happens to the information collected for the research?

Efforts will be made to limit the use and sharing of your personal research information to people who have a need to review this information. Reasonable efforts will be made to keep the personal information in your research record private. However, absolute confidentiality cannot be guaranteed, and there may be situations where disclosure is required by law.

In our research files at Penn State Health (PSH) and Penn State College of Medicine (PSU) we will include these identifiers: your name, address, email address, phone number, date of birth, social security number and a code number.

- A list that matches your name with your code number will be stored electronically in REDCap.
- Your research records will be labeled with your code number and initials and will be kept in a safe area in Dr. Hobkirk's research office.
- Your research samples will be labeled with your code number and will be stored in the Penn State TCORS lab space on the 3rd floor of the Penn State Hershey Cancer Institute.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot disclose information that identifies you to anyone not connected with the research. This protection also prevents this information from being used or disclosed for legal proceedings, such as being accessed through a court order. The Certificate of Confidentiality however does not prevent disclosures required by law, such as information about child abuse or neglect and harm to yourself or others. Also, your information may be disclosed in accordance with any consent you provide, including for your medical treatment or use in other research. Additionally, the Certificate of Confidentiality does not prevent your information from being disclosed to National Institutes of Health in order for it to evaluate or audit the research, or prevent disclosures required to meet FDA requirements. For additional information ask the principal investigator or a member of the study team or contact the Human Subjects Protection Office at (717) 531-5687.

In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

7b. What will happen to my research information and/or samples after the study is completed?
We may use your research information and your biological samples in future studies or may share your information or biological samples with other investigators for future research without your additional informed consent. Before we use or share your information or samples we will remove any information that shows your identity.

Most tests done on samples in research studies are only for research and have no clear meaning for health care. If the research with your identifiable information or samples gives results that do have meaning for your health, the researchers will contact you to let you know what they have found.

7c. How will my identifiable health information be used?
In general, under federal law (including the Health Insurance Portability and Accountability Act – HIPAA or privacy laws) your health information is private. By signing this form, you are authorizing us to collect, use, and disclose your identifiable health information, sometimes referred to as "Protected Health Information" or "PHI" under HIPAA, for the purposes of this research study. We will use and disclose your information only as described in this form, in the PSH Privacy Notice, and as may be required or allowed under the applicable privacy laws.

The research team may use the following health information:

- New health information from tests, procedures, visits, interviews, or forms filled out as part of this research study.

The following people/groups may see, use, and share your identifiable health information:

- PSH/PSU research staff involved in this study
- The PSH/PSU Institutional Review Board (IRB), a group of people who review the research study to protect subjects' rights and welfare
- The PSH/PSU Human Subjects Protection Office

- The PSH/PSU Research Quality Assurance Office
- Non-research staff within PSH/PSU who need this information to do their jobs (such as for treatment, payment (billing), or health care operations)
- Federal and state agencies (such as the U.S. Food and Drug Administration, the Office for Human Research Protections, the Department of Health and Human Services, the National Institutes of Health, and other U.S. or foreign government bodies that oversee or review research)
- People or groups that we hire to do work for us, such as data storage companies, insurers, and lawyers
- Organizations that provide independent accreditation and oversight of hospitals and research
- Public health and safety authorities (for example, if we learn information that could mean harm to you or others, we may need to report this, as required by law)
- The sponsor(s) of this study, monitors and auditors, and other people or groups it hires to help perform this research
- A group that oversees the data (study information) and safety of this research

These groups may also review and/or copy your original PSH/PSU records while looking at the results of the research study. It is possible that some of the other people/groups who receive your health information may not be required by Federal privacy laws to protect your information. We share your information only when we must, and we ask anyone who receives it from us to protect your privacy.

Sometimes a Principal Investigator or other researcher moves to a different institution. If this happens, your identifiable health information and samples may be shared with that new institution and their oversight offices. PHI will be shared securely and under a legal agreement to ensure it continues to be used under the terms of this consent and HIPAA authorization.

We may remove identifying information from your protected health information. Once we do this, the remaining information will not be subject to the privacy laws. Information without identifiers may be used or disclosed with other people or organizations for purposes besides this study.

Because research is an ongoing process, your permission for the use, storage and sharing of your health information will continue indefinitely.

Your privacy rights:

- You have the right to refuse to sign this form that allows us to use and share your health information for research; however, if you don't sign it, you will not be able to take part in this research study.
- You have the right to withdraw your permission for us to use or share your health information for this research study. If you want to withdraw your permission, you must notify the person in charge of this research study in writing using the address on the front of this form. Once permission is withdrawn, you cannot continue to take part in the study.
- If you withdraw your permission, we will stop collecting health information about you for this study; we may continue to use and share your health information that we already have if it is necessary for safety and scientific soundness of the research study; and we will not be able to take back information that has already been used or shared with others.
- You have the right to see and get a copy of your health information that is used or shared for treatment or for payment. However, you may not be allowed to see or copy certain health information that is a part of this research study. This is only for the period of the study. You will be allowed to see that information when the entire research study is complete.

8. What are the costs of taking part in this research study?

8a. What will I have to pay for if I take part in this research study?

For costs of tests and procedures that are only being done for the research study:

- The ECIG device and cartridges will be provided by the study at no cost to you while you take part in this study.
- You and/or your insurance company will not be charged for the cost of any tests or procedures that are required as part of the research and are outside the standard of care (what is normally done) for your condition.
- The research-related tests and procedures that will be provided at no cost to you include: Pregnancy test (if female), Exhaled CO monitoring, Vitals, and MRI scans.

8b. What happens if I am injured as a result of taking part in this research study?

It is possible that you could develop complications or injuries as a result of being in this research study. If you experience a side effect or injury and emergency medical treatment is required, seek treatment immediately at any medical facility. If you experience a side effect or injury and you believe that emergency treatment is not necessary, you should contact the principal investigator listed on the first page of this consent form as soon as possible and the principal investigator will arrange for medical treatment. You should also let any health care provider who treats you know that you are in a research study.

PSH/PSU compensation for injury

- There are no plans for PSH/PSU to provide financial compensation or free medical treatment for research-related injury.
- If an injury occurs, medical treatment is available at the usual charge.
- Costs will be charged to your insurance carrier or to you.
- Some insurance companies may not cover costs associated with research injuries.
- If these costs are not covered by your insurance, they will be your responsibility.

When you sign this form you are not giving up any legal right to seek compensation for injury.

9. Will I be paid to take part in this research study?

You will receive $40 for each visit completed and $20 for each MRI scan that you undergo. In addition, you will receive $20 for returning all your cartridges at your final in-person visit. If you do not complete the study for any reason, you will be paid for the visits and procedures that you have completed.

The compensation possible for each visit is outlined below:

- **Screening (which you have already completed):** $40 Visit completion
- **Pre-Conditioning Visit:** $40 Visit completion, $20 MRI scan
- **Condition Check-In 3:** $40 Visit completion
- **Post-Conditioning Visit 4:** $40 Visit completion, $20 MRI scan, $20 return bonus payment

You will be compensated via gift cards. The total possible compensation for completing all study procedures and returning all study cartridges is $220.

It is possible that your research information and/or specimens (both identified and de-identified) may be used to create products or to deliver services, including some that may be sold and/or make money for others. If this happens, there are no plans to tell you, or to pay you, or to give any compensation to you or your family.

10. Who is paying for this research study?
The institution and investigators are receiving a grant from the National Institutes of Health to support this research.

11. What are my rights if I take part in this research study?
Taking part in this research study is voluntary.

- You do not have to be in this research.
- If you choose to be in this research, you have the right to stop at any time.
- If you decide not to be in this research or if you decide to stop at a later date, there will be no penalty or loss of benefits to which you are entitled.

If you stop being in the research, already collected data may not be removed from the study database. You will be asked whether the investigator can collect medical information from your routine medical care. If you agree, this data will be handled the same as research data. If you withdraw completely from the research study, no further information will be collected and your participation will end. You may discontinue taking part at any time without penalty or loss of benefits to which you are otherwise entitled.

Your research team may take you out of the research study without your permission.

- Some possible reasons for this are: you become pregnant (if female), you suffer an adverse event related to ECIG use, a serious medical event, inpatient hospitalization, or worsening substance abuse.
- Also, the sponsor of the research may end the research study early.
- If your participation ends early, you may be asked to visit the research team for a final visit.

During the course of the research you will be provided with any new information that may affect your health, welfare or your decision to continue participating in this research.

12. If I have questions or concerns about this research study, whom should I call?
Please call the head of the research study (principal investigator), Dr. Hobkirk at (717) 531-0003 ext. 286415 if you:

- Have questions, complaints or concerns about the research.
- Believe you may have been harmed by being in the research study.

If you are experiencing a medical emergency, please call **911** for immediate medical attention.

You may also contact the research protection advocate in the PSH Human Subjects Protection Office (HSPO) at (717) 531-5687 if you:

- Have questions regarding your rights as a person in a research study.
- Have concerns, complaints or general questions about the research.
- Have questions about your privacy and the use of your personal health information.
- You may also call this number if you cannot reach the research team or wish to offer input or to talk to someone else about any concerns related to the research.

You may visit the Penn State College of Medicine's Clinical Research web site at http://med.psu.edu/clinical-research/faqs for:

- Information about your rights when you are in a research study;
- Information about the Institutional Review Board (IRB), a group of people who review the research to protect your rights; and

- Links to the federal regulations and information about the protection of people who are in research studies. If you do not have access to the internet, copies of these federal regulations are available by calling the HSPO at (717) 531-5687.

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

INFORMED CONSENT AND AUTHORIZATION TO TAKE PART IN RESEARCH

Signature of Person Obtaining Informed Consent

Your signature below means that you have explained the research to the subject or subject representative, provided the subject or subject representative an opportunity to discuss and consider whether or not to participate in the research, and have answered any questions about the research.

_____	_____	_____	_____
Signature of person who explained this research	Date	Time	Printed Name

(Only approved investigators for this research may explain the research and obtain informed consent.)

Signature of Person Giving Informed Consent and Authorization

Before making the decision about being in this research you should have:

- Discussed this research study with an investigator,
- Read the information in this form, and
- Had the opportunity to ask any questions you may have.

Your signature below means that you have received this information, have asked the questions you currently have about the research and those questions have been answered. You will receive a copy of the signed and dated form to keep for future reference.

Signature of Subject

By signing this consent form, you indicate that you voluntarily choose to be in this research and authorize your information to be used and shared as described above.

_____	_____	_____	_____
Signature of Subject	Date	Time	Printed Name