Version Date: October 18, 2023

CONSENT FOR RESEARCH

Penn State College of Medicine
Penn State Health

Title of Project:	Translational Studies on Electronic Cigarette-derived Oxidants and their Long-term Cardiopulmonary Effects
Principal Investigator:	Rebecca Bascom, MD, MPH
Address:	500 University Drive, Hershey, PA 17033
Telephone Numbers:	Weekdays: 8:00 a.m. to 5:00 p.m. (717) 531-6525. After hours call (717) 531-8521. Ask for the pulmonary fellow on 24-hour call.

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 have Chronic Obstructive Pulmonary Disease (COPD) and currently smoke greater than 10 cigarettes a day.

What is the purpose of this research study?

The purpose of this voluntary research study is to evaluate the effects of switching from cigarettes to electronic cigarettes (EC) on disease-related clinical symptoms and biomarkers in smokers with preexisting COPD.

How long will the research study last?

Your participation in the study will be for a total of 3 months.

What will I need to do?

You will be asked to attend 2 clinical visits at the Clinical Research Center (CRC) and participate in 4 telephone visits. During the clinical visits you will be asked to complete questionnaires, have heart rate, blood pressure and pulse oximetry taken, have exhaled carbon monoxide measured, height (Baseline Visit) and weight measured, provide medical history, perform pulmonary function tests , complete a 6-

minute walk,provide urine specimen and have blood drawn. You will also have an electrocardiogram performed at both visits. If you withdraw from the study early, for any reason, you will be asked to come in to the Clinical Research Center for an Early Termination Visit.

You will be asked to reduce your cigarette smoking and use the study-provided e-cigarettes for 3 months. We are not asking you to change your overall smoking as measured by the amount of nicotine you take into your body. We are asking you to change your pattern of smoking as follows:

- We would like you to reduce your usual cigarette use by 75%.
- We would like you to replace the nicotine you normally get from your cigarettes with the e-cigarette which will provide you with an equivalent amount of nicotine.

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

There may be some unknown risk related to the use of ECs. The most common side effects associated with using an EC are changes in taste, dehydration, mucus in throat/sinus, dry mouth, dry cough, throat irritation, mouth irritation, sore throat, mouth ulcers, dizziness, headache, nausea, and hiccups.

Other risks include:

Possible loss of confidentiality, discomfort associated with spirometry test performance, electrocardiogram tests, and drawing of venous blood samples. Testing and procedures are all performed by a qualified clinical technologist.

What are the possible benefits to me that may reasonably be expected from being in the research?

You will receive information regarding smoking reduction strategies and information on cessation at the beginning and end of the study. You may experience decreased toxicant exposure and decreased addiction to cigarettes if you are able to reduce your cigarette use. There are no other expected 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 EC use.

What happens if I do not want to be in this research?
Participation in research is completely voluntary.

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 evaluate the effects of switching from cigarettes to EC on disease-related clinical symptoms and biomarkers in smokers with preexisting COPD.

Approximately 30 people will take part in this research study at Penn State Health.

2. What will happen in this research study?

At the Baseline Visit you will visit the CRC where the consent form will be reviewed with you by the research study coordinator and you will be required to sign the consent form. A copy will be provided to you. Educational materials will be provided to you regarding smoking.

During the in-person visits (Baseline and Month 3),you will come to the CRC and complete questionnaires. These questionnaires will include COPD Exacerbation History (number of COPD exacerbations experienced), COPD Assessment Test (CAT; measures the impact that COPD is having on your wellbeing and daily life), PROMIS questionnaires (ask about nicotine dependence and expectancies), Nicotine Usage Questionnaire (asks about nicotine usage), the St. George's Respiratory Questionnaire (SGRQ; asks about your respiratory problems), and Modified Medical Research Council Dyspnea Scale (mMRC; describes your shortness of breath). Also at these visits height (Visit 1/Baseline only) and weight measurements, heart rate, blood pressure and pulse oximetry measurements will be taken. You will be asked to perform pulmonary function tests, a 6-minute walk (walking at a normal pace while pulse oximetry is measured for 6 minutes), and electrocardiograms (ECG). Additional ECGs may be performed throughout this study if the study doctors feel that they are necessary. You will also be asked to provide a blood sample [approximately 20 milliliters (mls) which is equivalent to 4 teaspoons] and provide a urine specimen. You will also have your exhaled carbon monoxide measured. You will be provided with a patient diary to record your daily cigarette and e-cigarette use throughout the study period. These visits will last approximately 3 hours.

If you withdraw from the study, you will complete an Early Termination Visit. This will be an in-person visit at the CRC. During this visit you will complete a COPD Exacerbation History Questionnaire, have your weight measured, complete an In Person Nicotine Usage questionnaire, return your used and unused NJOY pods, return your patient diary and receive smoking cessation information. Additionally, any of the procedures described above (such as spirometry, ECG,etc.) may be performed at this visit at the discretion of the Study Doctor.

For female participants of child-bearing age, a urine sample will be collected at each in-person visit for a urine dipstick pregnancy test.

At the baseline visit you will be provided with a three month's supply of NJOY pods. The pods will come pre-filled in sealed packages.

If at any time the device becomes defective and not working, notify the study team at which time a replacement device will be offered and you will be asked to return the defective item. You will also be asked to notify the study team if your supply of pods will not last for the three months.

You will return all used and unused e-liquid pods to the study team at the last visit. You will also return your diary at the last visit.

During each visit, your medical information will be collected from your medical chart and you will be asked to provide any changes in medications as well as any adverse events.

During the phone assessments [Weeks 1 and 2 (Visits 2 and 3); Months 1, 2, (Visits 4 and 5)] you will be contacted by the study coordinator to complete a phone assessment and to answer a PROMIS questionnaire about nicotine dependence. You will also be reminded of your next scheduled visit. These phone calls will last approximately 15 minutes.

For the Baseline Visit, you will continue to smoke your usual cigarettes. For the next 3 months (intervention period) you will be asked to reduce your cigarette smoking by >75% and increase the use of the EC which will be provided to you. At the final Month 3 visit, the study will no longer supply EC and you will be allowed to choose your tobacco product use.

Smoking cessation information will be provided to you at the first Day 1/Baseline visit and the final Month 3 visit.

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

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

- Attend all CRC visits and participate in all telephone call visits.
- Decrease cigarette smoking and begin using the EC for 3 months.
- Agree to provide lab and urine specimens.
- Agree to perform testing and complete questionnaires.
- For your safety, you must tell the study doctor or nurse about all the prescription drugs, herbal products, over-the-counter drugs (OTC), vitamins and other supplements you are taking. Check with the study doctor before starting any new medicines (including prescription, OTC drugs, vitamins and herbal supplements) or changing doses of medications that you are already taking.

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

Loss of Confidentiality: There is a risk of loss of confidentiality if your information or your identity is obtained by someone other than the study team, but precautions will be taken to prevent this from happening. The confidentiality of your electronic data will be maintained to the degree permitted by the technology used. Absolute confidentiality cannot be guaranteed.

Blood Collection: You will have blood collected from a vein in your arm at specified visits. You may have discomfort or pain when the needle is inserted. You may feel faint or pass out. There is a risk of infection, bleeding, soreness, blood clots, tenderness, or bruising at the puncture site. Approximately 20ml of blood will be taken at the specified visits.

Pulmonary Function Tests: Pulmonary Function Tests will be performed at various time points. You may experience lightheadedness, fainting, shortness of breath, or chest tightness.

6-minute Walk: You may have shortness of breath, tightness of the chest, tiredness, lightheadedness, dizziness or fainting, incoordination, or confusion while walking. In the event that you have symptoms or wish to sit for any reason, you may sit down. You may stop and rest as often as you need or stop the test early. You may use your walking aids and prescribed oxygen as needed.

Electrocardiograms (ECG): Electrocardiograms will be done at various time points. An ECG measures the electrical activity of the heart. You may have mild irritation, slight redness, or itching at the sites on your skin where the recording patches are placed.

NJOY use: There may be some unknown risk related to the use of ECs. The most common side effects associated with using an EC are changes in taste, dehydration, mucus in throat/sinus, dry mouth, dry cough, throat irritation, mouth irritation, sore throat, mouth ulcers, dizziness, headache, nausea, and hiccups. Allergic reaction may include breathing issues including worsening or more frequent asthma attacks in individuals with asthma.

- EC liquid contains vegetable glycerin, propylene glycol, and flavorings. It is possible that you may have an allergy to one or more of these ingredients. If you have an allergy to these substances, you will be excluded from the study. The most common reported allergic reaction to these substances is contact dermatitis (or rash).
- There are reports that some people who use ECs 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 will be excluded from the study.
- There have been some reports of serious lung illnesses among those who used ECs and even some cases of death as a result. The cause of all deaths has not 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 EC products that contained tetrahydrocannabinol (THC) and/or products that were bought off the street and not from retail establishments. The EC products used in this study do not contain THC and were bought from manufacturers where quality testing and control is performed. Nonetheless, you will be advised to call your doctor immediately if you experience cough, shortness of breath, chest pain, nausea, vomiting, diarrhea, or fever after using your EC. You are to only use the EC and liquid pods (cartridges) given to you by the study team and to not tamper with your EC or use other liquids with the EC device.

New Pregnancy or intention to become pregnant: Nicotine from ECs is known to be harmful to the developing human fetus. Women who are pregnant or are nursing a child may not participate in this research study. You must agree to take reasonable and necessary precautions against becoming pregnant during the study period. If you become pregnant during the study you must notify the study team immediately and you will be removed from the study.

Questionnaires: It is possible that some of the questions in the questionnaires may make you 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?

There is no guarantee that you will benefit from this research. The possible benefits you may experience from this research study may be from the information you will receive regarding smoking reduction (Consumer Surgeon General Report Booklet and Cessation Surgeon General Consumer Guide). There are no other expected benefits to the participant by participating in the study.

4b. What are the possible benefits to others?

The knowledge gained from these studies will be used to help better understand the mechanisms involved in tobacco smoking and health and the benefits of switching to potentially lower risk products.

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

You do not have to take part in this study. Instead of participating in this research, you could:

- Purchase commercially available products, including other ECs or commercially available products for smoking cessation.
- Be part of a different research study, if one is available.

Before you decide if you want to be in this research, we will discuss the other choices that are available to you. We will tell you about the possible benefits and risks of these choices.

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

If you agree to take part, it will take you 3 months to complete this research study. You will be asked to visit the research site 2 times and participate in 4 telephone calls.

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, phone number, date of birth, medical record number, and code number.

- A list that matches your name with your code number will be kept in a password protected electronic file and in a paper version locked file in Dr. Bascom's office.
- Your research records will be labeled with the last four digits of the study number followed by your code number, visit number and date of collection and will be kept in a safe area in Dr. Bascom's research office.
- Your research samples will be labeled with a code number until the tests are completed. For the period of the study, the left-over blood will continue to be frozen and used for additional markers if these are developed. They will be stored in a study investigator's laboratory.

- A copy of this signed consent form will be included in your PSH medical record. This means that other PSH healthcare providers will know you are in this study.
- Results of some of the research-related clinical tests (including but not limited to pulmonary function tests) will be kept in your PSH medical record.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health (NIH). 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 the NIH 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.
We will do our best to keep your participation in this research study confidential to the extent permitted by law. However, the following people/groups may check and copy records about this research:

- The Office for Human Research Protections in the U. S. Department of Health and Human Services.
- The PSH/PSU Institutional Review Board (a committee that reviews and approves research studies).
- The PSH/PSU Human Subjects Protection Office.
- The PSH/PSU Research Quality Assurance Office.

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 researcher will not 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:

- Past, present, and future medical records, including identifiable 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).
- 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 NJOY device and supplies 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: PFTs, ECGs, and labs.

For costs of medical services for care you would receive even if you were not in this research study:

- You and/or your insurance company will be responsible for the cost of routine medications, tests and procedures that you would receive even if you were not in this research.
- You and/or your insurance company will be billed for the costs of these routine tests and procedures in the usual manner.
- You will be responsible for any co-payments, co-insurance and deductibles that are standard for your insurance coverage.
- You will be responsible for any charges not reimbursed by your insurance company.
- Some insurance companies may not pay for routine costs for people taking part in research studies. Before deciding to be in this research you should check with your insurance company to find out what they will pay for.

If you have any questions about costs and insurance, ask the research study doctor or a member of the research team.

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 $40.00 for completing the Baseline and Month 3 in-person clinic visits. You will be paid an additional $30.00 at the Month 3 visit for completing this research study. If you withdraw from the study and complete the Early Termination Visit, you will be paid $40.00 at that visit. The maximum total you can be paid for participation in this study is $110.00. If you do not complete the study for any reason, you will be paid for the visits you have completed. The payment will be provided by Greenphire Clincard.

This reimbursement will be issued by an external company called Greenphire, which will issue your reimbursement. You will be issued a ClinCard, which is a debit card that your funds are loaded onto and can be used at your discretion. The research team will give Greenphire some personal information about you, as described below. Greenphire will only use your personal information to process this reimbursement and will not share it with anyone for any other purpose. Details of the debit card system are explained on an additional sheet. If you lose the card, you may be responsible for the $5 replacement fee.

When a visit is completed, funds will be approved and loaded onto your card. The funds will be available within 2-3 business days. In order to assign a ClinCard to you and load funds onto the ClinCard, Greenphire will need your Study/Subject ID, Name, Address, and Social Security Number.

You will have the option to receive updates related to payment alerts via text message and/or email message. Standard text messaging rates will apply. In order to send you messages Greenphire will need your Mobile Phone Number and/or E-mail Address.

Payment received as compensation for participation in research is considered taxable income. If payments from Greenphire exceed $600 in any one calendar year, Greenphire will file a 1099 (Miscellaneous Income) form on behalf of Penn State.

It is possible that your research information and/or specimens (both identifiable 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.

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

- Some possible reasons for this are: continuing the research would be harmful, your condition has become worse, you did not follow the instructions of the study doctor, you experience serious side effects, you become pregnant, or you experience serious cardiovascular events.

If your participation ends early, you may be asked to visit the research doctor for a final Early Termination 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. Bascom at (717) 531-6525 or the pulmonary fellow doctor on 24-hour call at (717) 531-8521 if you:

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

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.

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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 https://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