MRI and Biological Markers of Acute E-Cigarette Exposure in Smokers and Vapers

NCT 03479203

August 11, 2021

UNIVERSITY OF PENNSYLVANIA
RESEARCH SUBJECT
COMBINED INFORMED CONSENT AND HIPPA AUTHORIZATION FORM

Protocol Title:	Acute and Long-Term Effects of E-Cigarette Aerosol Inhalation on Biomarkers of Endothelial Function and Vascular Reactivity
Principal Investigator:	Felix W. Wehrli, Ph.D. Department of Radiology University of Pennsylvania 1 Founders Building 3400 Spruce Street Philadelphia, PA 19104 215-662-7951
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Research Study Summary
You are being invited to participate in a research study. Your participation is voluntary. You should only participate if you completely understand what the study requires and what the risks of participation are. You should ask the study team any questions you have related to participating before agreeing to join the study. If you have any questions about your rights as a human research participant at any time before, during or after participation, please contact the Institutional Review Board (IRB) at 215-898-2614 for assistance.

This research study is being conducted to test whether electronic cigarette aerosol has an effect on the endothelium, a layer of cells that act as a protective barrier and play an important part in controlling the flow of blood around the body. You are eligible for this study because you smoke electronic or conventional cigarettes, and you have no known health problems.

If you agree to join the study, you will be asked to complete two magnetic resonance imaging (MRI) examinations. The second MRI examination will take place 12 months after the first MRI examination. Your involvement in the study will end after both MRI examinations are complete.

There is no direct benefit to you for participating in this study.

The primary risk of participation is from the strong magnetic force emitted by the MRI magnet, which can disrupt or heat-up implanted medical devices or metallic foreign fragments in your body. The magnetic force can also cause metallic objects in the scanner room to become projectiles. There are many safety measures in place to reduce these risks. The alternative to participating in the study is to not participate.

Please note that there are other factors to consider before agreeing to participate such as additional procedures, use of your personal information, possible costs, and other possible risks not discussed here. If you are interested in participating, a member of the study team will review the full information with you. You are free to decline or stop participation at any time during or after the initial consenting process.

Why am I being asked to volunteer?
You are being invited to participate in a research study because you are a conventional cigarette or electronic cigarette user between the ages of 18 and 45 years, with no symptomatic cardiovascular or pulmonary disorders, and a body mass index in the range 18.5 to 30. To participate, you must have smoked only conventional

cigarettes or only electronic cigarettes for at least 6 months. Your participation is voluntary which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in the study, and what you will have to do in the study. The research team is going to talk to you about the research study, and they will give you this consent form to read. You may also decide to discuss it with your family, friends, or family doctor. You may find some of the medical language difficult to understand. Please ask the investigator and/or the research team about this form. If you decide to participate, you will be asked to sign this form. Your doctor may be an investigator in this research study. As an investigator, your doctor is interested both in your clinical welfare and in the conduct of this study. Before entering this study or at any time during the research, you may want to ask for a second opinion about your care from another doctor who is not an investigator in this study. You do not have to participate in any research study offered by your doctor.

What is the purpose of this research study?
The purpose of the study is to test whether electronic cigarette aerosol has an effect on the endothelium by comparing the effect that conventional cigarette smoke has on the endothelium. The endothelium is a layer of cells that acts like a protective barrier and plays an important part in controlling the flow of blood around the body. In this study we will test the effect conventional cigarette smoke or electronic cigarette aerosol has on the function of the endothelium using a blood pressure cuff and magnetic resonance imaging. Magnetic resonance imaging (MRI) is an exam that uses magnetic fields and radio waves to produce pictures of the inside of the body. We will be measuring changes in the endothelium by comparing magnetic resonance images at baseline and after 12 months. We will also take two blood samples to measure blood biomarkers. Biomarkers are biological indicators or molecules that can be measured to detect properties of health. In this study we will be measuring changes in blood biomarkers to detect inflammation by comparing a blood sample taken at baseline and taken again after 12 months. These tests will help us better understand the effects of electronic cigarette aerosol on the endothelium.

How long will I be in the study?
The study involves two visits to the Hospital of the University of Pennsylvania. The first visit, the baseline visit, will take about two hours. The second visit, the 12-month visit, will also take about two hours. Overall, you will participate in the study for 12 months. There will be a total of 45 conventional cigarette smokers and 45 electronic cigarette smokers participating in this portion of the study. You may be contacted after your completion in the study to collect more, necessary information for analysis. There will be a total of 129 people (smokers and non-smokers) participating in the overall study.

What am I being asked to do?
The study involves two MRI exams and two blood samples. The first MRI exam and the first blood sample will be taken during your first visit. The second MRI exam and the second blood sample will be taken 12 months after your first visit.

It is important that you do not do any vigorous physical activity or smoke any type of cigarette **four hours** before your study visit. You should not eat or drink anything except water for **eight hours** before your visit. You should not take any medications the morning of your visit, but bring your morning medications with you.

You will come to the Hospital of the University of Pennsylvania to meet with the research coordinator. You will read and sign this consent form after all of your questions and concerns have been addressed. You will complete a brief questionnaire about the MRI. Your weight, height, and blood pressure will be measured. A urine pregnancy test will be performed if you are female.

You will go to the outpatient laboratory where a blood sample will be taken. You will then go to the MRI suite where you will change into a gown. You will lie on the MRI table and a standard FDA (Food and Drug Administration) approved device, called a radiofrequency coil, will be placed around your lower leg. A blood pressure cuff will be placed on your upper thigh. Your whole body will go into the machine feet first. During the MRI exam the blood pressure cuff will be inflated to stop the circulation in your leg for **five** minutes. You will feel tightness or pressure around your thigh much like when a blood pressure cuff is inflated on your arm. This portion of the MRI exam will take about 20 minutes. If you are too uncomfortable, you can stop the exam.

You will have a five-minute break while we set up the second part of the MRI exam. The second part of the exam will then take place, which will take about 15 minutes. You will be repositioned on the MRI table. Two radiofrequency coils, a head coil and a surface coil, will be used to examine blood flow in the major artery connected to your heart. Your head will rest inside the head coil and the surface coil will be placed on your chest. The head coil resembles a helmet and the surface coil resembles several flat plastic panels joined together. You will then complete only one of the two procedures below:

1. A mask will be placed over your nose and mouth, which is connected to a piece of equipment called a RespirAct. The RespirAct delivers the air supply and measures the gases that you breathe in and out. You will be given a chance to practice breathing through the mask before you go into the machine. Your entire body, including your head, will go into the machine headfirst. After several short MRI scans lasting 20 to 40 seconds, an exam lasting seven minutes will be performed. You will be breathing air through the mask that has a higher amount of carbon dioxide (hypercapnia). During this exam you will be asked to breathe normally. It will feel like you are inhaling from and exhaling into a large tube about three feet long. During the first minute you will breathe room air only. During the second minute you will breathe air with more carbon dioxide. During the third minute you will breathe room air only. During the fourth, fifth and sixth minute you will breathe air with different amounts of carbon dioxide. You will breathe room air only during the seventh and final minute. The MRI table will then move in further to scan your chest. This last exam will consist of several short scans lasting five to ten seconds. You will be breathing only room-air during this this last scan.

OR

2. After several short MRI scans lasting 20 to 40 seconds, an exam lasting seven minutes will be performed. You will be coached to hold your breath for 30 seconds followed by 90 seconds of normal breathing. This sequence of a 30 second breath-hold and 90 seconds of normal breathing will be repeated three times. You will breathe normally during the seventh and final minute. The MRI table will then move in further to scan your chest. This last exam will consist of several short scans lasting five to ten seconds. You will be breathing normally during this last scan.

This will be the end of your first MRI exam. You will then be asked to return after 12 months to repeat the above process.

You may be contacted after your 12 month visit in order to collect more information for data analysis.

What are the possible risks or discomforts?

MRI Exam: The known risks associated with MRI are minimal. Some individuals may feel claustrophobic (uncomfortable in small spaces) during an MRI or be disturbed by the loud and repetitive sounds of the machine. The study staff will provide you with protective earplugs and make every attempt to ensure your comfort with blankets and pillows during your time in the scanner. The magnet is always on. Metal objects on or inside your body could heat up, move and/or not function properly within the MRI scanning room. Implanted medical devices and metallic foreign fragments inside your body could pose a risk if you were to enter the MRI scanning room. Pacemakers, internal cardiac defibrillators, insulin pumps, and other medical devices could also prevent you from safely having an MRI. Therefore, questions about your medical and work history will be asked prior to your exam. The magnet is very strong. Another risk is that from a metallic object flying through the air toward the magnet and hitting you. There are many safety measures in place to reduce this risk, including screening of all persons and materials entering the MRI scanning room. You will be asked to change into a standard hospital gown to further minimize this risk. The door to the room will be closed when the study starts to minimize the risk of someone accidentally walking into or bringing an object into the magnet room. Some of the pulse sequences (a series of radio wave signals) and/or radio frequency coils (device used to receive the radio wave signals) are not FDA approved but are considered to pose no more than minimal risk.

It is possible that during the course of the research study the research staff may notice an unexpected finding. The appropriate personnel will consider the finding if this occurs and the principal investigator will inform you if necessary. Any possible findings may or may not be significant but may lead to anxiety about your condition and to further work-up by your physician.

Reproductive Risks: If you are pregnant, you should not take part in this study. Although there are no known risks of MRI on pregnant women or a fetus, there is a possibility of yet undiscovered pregnancy related risks. Since there is no direct benefit from participating in this protocol for a pregnant woman, we will exclude pregnant women. A negative urine pregnancy test will be required before a woman of childbearing potential can participate in this study.

Blood Draw: There are minor risks that are associated with drawing blood, which include pain, a bruise at the point where the blood is taken, redness, swelling of the vein, infection, and a rare risk of fainting.

Blood Pressure Cuff: There is a risk of discomfort during the blood pressure cuff inflation. You may feel an uncomfortable tingling or prickling similar to when a part of your body "falls asleep".

Hypercapnia: The symptoms of mild hypercapnia are generally mild or undetectable, but can include: flushed skin, faster heart rate, increased blood pressure, muscle twitches, hand flaps, exhaustion, anxiety, headache, and confusion. If this happens at any time, the emergency stop button on the RespirAct will be used. Mild to moderate hypercapnia induced by a gas mixture through a breathing mask is often used in scientific research to study the blood flow in the brain.

Privacy and/or Confidentiality: Every effort will be made to protect your privacy and confidential information. However, this cannot be guaranteed.

Unforeseen Risks: The long-term risks of electronic cigarette use are unknown at this time.

Reproductive Risks: If you are pregnant, you should not take part in this study. Although there are no known risks of MRI on pregnant women or a fetus, there is a possibility of yet undiscovered pregnancy related risks. Since there is no direct benefit from participating in this protocol for a pregnant woman, we will exclude pregnant women. A negative urine pregnancy test will be required before a woman of childbearing potential can participate in this study.

What if new information becomes available about the study?
During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

What are the possible benefits of the study?
While there is no direct benefit to the individual subjects, this study has the potential to affect society as a whole.

What other choices do I have if I do not participate?
The alternative is not to participate in the study.

Will I be paid for being in this study?
You will be compensated for your time and travel after the study with $100 for each MRI test completed. If you complete one MRI scan you will receive $100. If you complete both MRI scans you will receive a total of $200. You will receive this money as a ClinCard, by Greenfield. The ClinCard will have the specified, loaded amount that you are owed at the time of the visit. For the baseline visit, the card will have $100. For the 12-month visit, the card will be re-loaded another $100. This is a total of $200 for both the MRI scans and completion of the study. It is important that you do not lose the University of Pennsylvania debit card (your ClinCard). Costs for replacing lost or stolen University of Pennsylvania debit cards will be your responsibility. The cost to replace the debit card is $3.00 and that amount will be deducted from your study visit payment. To be compensated for your participation in this study, you must provide your social security number. The University of Pennsylvania is required to report to the IRS any cumulative payments for participation in research studies that exceed a total of $600 in a calendar year.

Will I have to pay for anything?

All of the tests or procedures performed during this study will be free of charge to you and will not be billed to your insurance company. You are responsible for any deductibles or applicable co-pays for routine office visits, scans and blood work that are not related to this research study.

What happens if I am injured from being in the study?
We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

There are no plans for the University of Pennsylvania to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

If you think you have been injured as a result of taking part in this research study, tell the person in charge of the research study as soon as possible. The researcher's name and phone number are listed in the consent form.

When is the study over? Can I leave the study before it ends?
This study is expected to end after all participants have completed all visits, and all information has been collected. This study may also be stopped at any time by your physician, the study Sponsor, or the FDA without your consent because:

- The principal investigator feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- You have not followed study instructions.
- The sponsor, the study principal investigator, or the FDA has decided to stop the study.

If you decide to participate, you are free to leave the study at any time. Withdrawal will not interfere with your future care.

How will my personal information be protected during the study?
We will do our best to make sure that the personal information obtained during the course of this research study will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. The Institutional Review Board (IRB) at the University of Pennsylvania will have access to your records. If this study is being overseen by the Food and Drug Administration (FDA), they may review your research records. Your study results will be filed using a unique subject identification number rather than your name. This identification number will be destroyed after all data from the study has been collected and analyzed. Research records and information from your examinations will be kept on a secure computer available only to the study investigators, and if necessary, for your medical management. You will have access to this information if you desire. Any paper files containing your information will be stored in a locked cabinet in the study coordinator's office during the study. Data from this study will be kept for at least six years per regulations set by the Department of Health and Human Services. Paper files from the study may be archived at the University of Pennsylvania Archives and Records Center following completion of the study.

Will information about this study be available to the public?
Information about the study will not be available to the public.

What may happen to my information and samples collected in this study?
Your information will be de-identified. This means that all identifiers have been removed. The information could be stored and shared for future research in this de-identified fashion. It would not be possible for future researchers to identify you as we would not share any identifiable information about you with future researchers. This can be done without again seeking your consent in the future, as permitted by law. The future use of your information only applies to the information collected on this study.

Collection of Identifiable Specimens

Your samples may be used to create products, 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.

Whole genome sequencing will not be conducted on your samples. Whole genome sequencing involves analyzing your entire personal genetic code.

Future Use of Data and/or Specimens
Specimens will not be stored or distributed for future research studies. Data from your imaging exam and blood serum analysis will be de-identified. De-identified means that all identifiers have been removed. This data could be stored and shared for future research in this de-identified fashion. It would not be possible for future researchers to identify you as we would not share any identifiable information about you with future researchers. This can be done without again seeking your consent in the future, as permitted by law. The future use of your information only applies to the information collected on this study.

Electronic Medical Record and Release of Study Related Information

What is an Electronic Medical Record?
An Electronic Medical Record (EMR) is an electronic version of your medical chart within a health system. An EMR is simply a computerized version of a paper medical record.

If you have never received care within Penn Medicine and are participating in a University of Pennsylvania research study that uses Penn Medicine healthcare related services, an EMR will be created for you for the purpose of maintaining any information produced from your participation. The creation of this EMR is a requirement of your participation in this study. In order to create your EMR, the study team will need to obtain basic information about you that would be similar to the information you would provide the first time you visit a hospital or medical facility. If you have been a patient at Penn Medicine in the past, information from your research participation will be added to your existing medical record.

What may be placed in the EMR?
Information related to your participation in the research (e.g., laboratory tests, imaging studies) will be placed in your EMR maintained by Penn Medicine.

Once placed in your EMR your information may be accessible to appropriate Penn Medicine workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by Penn Medicine to be appropriate to have access to your EMR (e.g. health insurance company, disability provider, etc.).

Penn Medicine also participates in automated information sharing through Health Information Exchanges (HIEs). HIEs securely share parts of your electronic health record, including research information, with other healthcare organizations involved in your care. This information is shared to improve the quality, safety, and efficiency of your healthcare. To request that your health information not be shared through HIEs, please call 215-662-4484.

Will I, as a subject, have access to research related information within the EMR?
The 21st Century Cures Act requires healthcare institutions to allow patients increased access to their electronic medical record. As part of your participation in this research, you will have access to research related information within your EMR through Penn Medicine's patient portal – called MyPennMedicine (MPM).

Will I receive the results of research testing that may be relevant to my health?
Many of tests done in research studies are only for research and have no clear impact on your healthcare. Research results for this study will not be returned to you because they would not be relevant to your healthcare

What information about me may be collected, used or shared with others?
The following personal health information will be collected and may be disclosed for this research study:

- Name, address, telephone number, email
- Birthdate, medical record number, medical history, current and past medications or therapies

- MRI images
- Social security number is required for payment only and is stored in a separate file

Why is my information being used?
Your information is used by the research team to contact you during the study. Your information and results of tests and procedures are used to:

- do the research
- oversee the research
- to see if the research was done right
- to evaluate and manage research functions

Where may my information be stored?
Information related to your participation in clinical research will be contained in a clinical trial management system (CTMS). A clinical trial management system (CTMS) is used to register your information as a participant in a study. This allows for your research data to be entered and stored for the purposes of study operational and financial applications and other activities required as part of the conduct of the research. Once placed in the CTMS your information may be accessible to other authorized personnel at Penn Medicine that support research operations. Your information may be held in other research databases.

Who may use and share information about me?
The following individuals may use or share your information for this research study:

- The investigator for the study and the study team
- Other authorized personnel at Penn Medicine and the University of Pennsylvania, including offices that support research operations
- Other research personnel with access to the databases for research and/or study coordination and as otherwise approved by the IRB

Who, outside of Penn Medicine, might receive my information?
The following oversight organizations might receive your information:

- The Food and Drug Administration
- The National Institutes of Health
- The Office of Human Research Protections

Once your personal health information is disclosed to others outside the School of Medicine, it may no longer be covered by federal privacy protection regulations.

The principal investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to University of Pennsylvania procedures developed to protect your privacy.

How long may Penn Medicine use or disclose my personal health information?
Your authorization for use of your personal health information for this specific study does not expire.

However, Penn Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization
- The University of Pennsylvania's Institutional Review Board grants permission
- As permitted by law

IRB Approval From: 08-10-2021 To: 06-13-2022

Can I change my mind about giving permission for use of my information?
Yes. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the investigator for the study. If you withdraw your permission, you will not be able to stay in this study.

What if I decide not to give permission to use and give out my health information?
Then you will not be able to be in this research study.

You will be given a copy of this Research Subject HIPAA Authorization describing your confidentiality and privacy rights for this study.

By signing this document, you are permitting Penn Medicine to use and disclose personal health information collected about you for research purposes as described above.

Who can I call with questions, complaints or if I'm concerned about my rights as a research subject?
If you have questions, concerns, or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, you should speak with the principal investigator listed on page one of this form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the IRB at the number on page one of this form.

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this consent form will be given to you.

_____	_____	
Name of Subject (Print)	Signature	Date
_____	_____	
Name of Person Obtaining Consent (Print)	Signature	Date

UNIVERSITY OF PENNSYLVANIA
RESEARCH SUBJECT
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Protocol Title: Acute and Long-term Effects of E-cigarette Aerosol Inhalation on Biomarkers of Endothelial Function and Vascular Reactivity

Principal Investigator: Felix W. Wehrli, Ph.D.
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215-662-7951

Emergency Contact: Frank T. Leone, M.D., M.S.
Office: (215) 662-8766
Mobile: (215) 243-3265

24-Hour Emergency Contact:
Radiology Fellow on Call:
215-662-6059

Research Study Summary
You are being invited to participate in a research study. Your participation is voluntary. You should only participate if you completely understand what the study requires and what the risks of participation are. You should ask the study team any questions you have related to participating before agreeing to join the study. If you have any questions about your rights as a human research participant at any time before, during or after participation, please contact the Institutional Review Board (IRB) at 215-898-2614 for assistance.

This research study is being conducted to test whether electronic cigarette aerosol has an effect on the endothelium, a layer of cells that act as a protective barrier and play an important part in controlling the flow of blood around the body. You are eligible for this study because you are a non-smoking healthy individual with no known health problems.

If you agree to join the study, you will be asked to complete two magnetic resonance imaging examinations. Your participation will last four hours, including a waiting period of two hours between MRI examinations. Your involvement in the study will end after the magnetic resonance examinations are completed.

There is no direct benefit to you for participating in this study.

The primary risk of participation is from the strong magnetic force emitted by the MRI magnet, which can disrupt or heat-up implanted medical devices or metallic foreign fragments in your body. The magnetic force can also cause metallic objects in the scanner room to become projectiles. There are many safety measures in place to reduce these risks. The alternative to participating in the study is to not participate.

Please note that there are other factors to consider before agreeing to participate such as additional procedures, use of your personal information, possible costs, and other possible risks not discussed here. If you are interested in participating, a member of the study team will review the full information with you. You are free to decline or stop participation at any time during or after the initial consenting process.

Why am I being asked to volunteer?
You are being invited to participate in a research study because you are a non-smoking individual between the ages of 18 and 45 years, with no history of cardiovascular disease and a body mass index in the range of 18.5

to 30. Your participation is voluntary which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in the study, and what you will have to do in the study. The research team is going to talk to you about the research study, and they will give you this consent form to read. You may also decide to discuss it with your family, friends, or family doctor. You may find some of the medical language difficult to understand. Please ask the investigator and/or the research team about this form. If you decide to participate, you will be asked to sign this form. Your doctor may be an investigator in this research study. As an investigator, your doctor is interested both in your clinical welfare and in the conduct of this study. Before entering this study or at any time during the research, you may want to ask for a second opinion about your care from another doctor who is not an investigator in this study. You do not have to participate in any research study offered by your doctor.

What is the purpose of this research study?
The purpose of the study is to test whether electronic cigarette aerosol has an effect on the endothelium. The endothelium is a layer of cells that acts like a protective barrier and plays an important part in controlling the flow of blood around the body. In this study we will test the effect electronic cigarette aerosol has on the function of the endothelium using a blood pressure cuff and magnetic resonance imaging. Magnetic resonance imaging (MRI) is an exam that uses magnetic fields and radio waves to produce pictures of the inside of the body. We will also take two blood samples to measure blood biomarkers. Biomarkers are biological indicators or molecules that can be measured to detect properties of health. In this study we will be measuring changes in blood biomarkers to detect inflammation by comparing blood samples before and after an electronic cigarette challenge. These tests will help us better understand the effects of electronic cigarette aerosol on healthy, non-smoking individuals.

How long will I be in the study?
This study involves one visit to the Hospital of the University of Pennsylvania. You will be in the study for approximately three hours. There will be a total of 39 non-smokers participating in this portion of study. There will be a total of 129 people (smokers and non-smokers) participating in the overall study.

What am I being asked to do?
The study involves two blood samples, smoking a non-nicotine electronic cigarette and two MRI exams. The first blood sample will be taken when you arrive and the second sample will be taken between 1-2 hours after smoking the electronic cigarette. The MRI exams will be taken before and after smoking the electronic cigarette.

It is important that you do not do any vigorous physical activity **four hours** before your study visit. It is also important that you eat a light meal prior to your study visit.

You will come to the Hospital of the University of Pennsylvania to meet with the research coordinator. You will read and sign this consent form after all your questions and concerns have been addressed. You will complete a brief questionnaire about the MRI. Your weight, height, and blood pressure will be measured. A urine pregnancy test will be performed if you are female.

You will go to the outpatient laboratory where a blood sample will be taken. You will then go to the MRI suite where you will change into a gown. You will lie on the MRI table and a standard FDA (Food and Drug Administration) approved device, called a radiofrequency coil, will be placed around your lower leg. A blood pressure cuff will be placed on your upper thigh. Your whole body will go into the machine feet first. During the MRI exam the blood pressure cuff will be inflated to stop the circulation in your leg for **five** minutes. You will feel tightness or pressure around your thigh much like when a blood pressure cuff is inflated on your arm. This portion of the MRI exam will take about 20 minutes. If you are too uncomfortable, you can stop the exam.

You will have a five-minute break while we set up the second part of the MRI exam. The second part of the exam will then take place, which will take about 15 minutes. You will be repositioned on the MRI table. Two radiofrequency coils, a head coil and a surface coil, will be used to examine blood flow in the major artery connected to your heart. Your head will rest inside the head coil and the surface coil will be placed on your chest. The head coil resembles a helmet and the surface coil resembles several flat plastic panels joined together. You will then complete only one of the two procedures below:

1. A mask will be placed over your nose and mouth, which is connected to a piece of equipment called a RespirAct. The RespirAct delivers the air supply and measures the gases that you breathe in and out. You will be given a chance to practice breathing through the mask before you go into the machine. Your entire body, including your head, will go into the machine headfirst. After several short MRI scans lasting 20 to 40 seconds, an exam lasting seven minutes will be performed. You will be breathing air through the mask that has a higher amount of carbon dioxide (hypercapnia). During this exam you will be asked to breathe normally. It will feel like you are inhaling from and exhaling into a large tube about three feet long. During the first minute you will breathe room air only. During the second minute you will breathe air with more carbon dioxide. During the third minute you will breathe room air only. During the fourth, fifth and sixth minute you will breathe air with different amounts of carbon dioxide. You will breathe room air only during the seventh and final minute. The MRI table will then move in further to scan your chest. This last exam will consist of several short scans lasting five to ten seconds. You will be breathing only room air during this this last scan.

OR

2. After several short MRI scans lasting 20 to 40 seconds, an exam lasting seven minutes will be performed. You will be coached to hold your breath for 30 seconds followed by 90 seconds of normal breathing. This sequence of a 30 second breath-hold and 90 seconds of normal breathing will be repeated three times. You will breathe normally during the seventh and final minute. The MRI table will then move in further to scan your chest. This last exam will consist of several short scans lasting five to ten seconds. You will be breathing normally during this last scan.

You will then be taken out of the scanner to do the electronic cigarette challenge. Prior to the electronic cigarette challenge you will be shown a brief instructional video. You will be asked to take 16 puffs of an electronic cigarette that does not contain nicotine. Each puff will consist of a drag lasting two seconds, inhalation and exhalation of the electronic cigarette aerosol. After the electronic cigarette challenge you will have a second MRI exam. The second exam will be exactly the same as the first exam. That means there will be a coil placed around your lower leg and a blood pressure cuff placed around your upper thigh (where circulation will be cut off for five minutes and then released). You will have another five minute break and then be repositioned on the MRI table to perform the gas-breathing sequence OR the breath-hold sequence just as before. The MRI table will then move you inside the scanner again so we may scan your chest.

About two hours after you have completed the electronic cigarette challenge, a second blood sample will then be taken in the outpatient laboratory. This will complete the study.

You may have some free time after the second MRI test and your second visit to the outpatient laboratory for a blood sample. During this time please do not engage in any vigorous activity. Please also try to eat another light meal.

It is possible that you may be asked to return for a repeat exam if the results from the MRI scans are not adequate.

What are the possible risks or discomforts?
Taking part in a research study involves risks or side effects. There may be side effects we do not know about yet. You should talk about these risks with the study staff.

MRI Exam: The known risks associated with MRI are minimal. Some individuals may feel claustrophobic (uncomfortable in small spaces) during an MRI or be disturbed by the loud and repetitive sounds of the machine. The study staff will provide you with protective earplugs and make every attempt to ensure your comfort with blankets and pillows during your time in the scanner. The magnet is always on. Metal objects on or inside your body could heat up, move and/or not function properly within the MRI scanning room. Implanted medical devices and metallic foreign fragments inside your body could pose a risk if you were to enter the MRI scanning room. Pacemakers, internal cardiac defibrillators, insulin pumps, and other medical devices could also prevent you from safely having an MRI. Therefore, questions about your medical and work

history will be asked prior to your exam. The magnet is very strong. Another risk is that from a metallic object flying through the air toward the magnet and hitting you. There are many safety measures in place to reduce this risk, including screening of all persons and materials entering the MRI scanning room. You will be asked to change into a standard hospital gown to further minimize this risk. The door to the room will be closed when the study starts to minimize the risk of someone accidentally walking into or bringing an object into the magnet room. Some of the pulse sequences (a series of radio wave signals) and/or radio frequency coils (device used to receive the radio wave signals) are not FDA approved but are considered to pose no more than minimal risk.

It is possible that during the course of the research study the research staff may notice an unexpected finding. The appropriate personnel will consider the finding if this occurs and the principal investigator will inform you if necessary. Any possible findings may or may not be significant but may lead to anxiety about your condition and to further work-up by your physician.

Reproductive Risks: If you are pregnant, you should not take part in this study. Although there are no known risks of MRI on pregnant women or a fetus, there is a possibility of yet undiscovered pregnancy related risks. Since there is no direct benefit from participating in this protocol for a pregnant woman, we will exclude pregnant women. A negative urine pregnancy test will be required before a woman of childbearing potential can participate in this study.

Blood Draw: There are minor risks that are associated with drawing blood, which include pain, a bruise at the point where the blood is taken, redness, swelling of the vein, infection, and a rare risk of fainting.

Blood Pressure Cuff: There is a risk of discomfort during the blood pressure cuff inflation. You may feel an uncomfortable tingling or prickling similar to when a part of your body “falls asleep”.

Aerosol Inhalation: There are also some minimal risks associated with aerosol inhalation. These risks include dry mouth, cough, sore throat, eye irritation, taste differences, dizziness and an increase in heart rate heart rate.

Hypercapnia: The symptoms of mild hypercapnia are generally mild or undetectable, but can include: flushed skin, faster heart rate, increased blood pressure, muscle twitches, hand flaps, exhaustion, anxiety, headache, and confusion. If this happens at any time, the emergency stop button on the RespirAct will be used. Mild to moderate hypercapnia induced by a gas mixture through a breathing mask is often used in scientific research to study the blood flow in the brain.

Privacy and/or Confidentiality: Every effort will be made to protect your privacy and confidential information. However, this cannot be guaranteed.

Unforeseen Risks: The long-term risks of electronic cigarette use are unknown at this time.

What if new information becomes available about the study?
During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

What are the possible benefits of the study?
While there is no direct benefit to an individual participant, this study has the potential to affect society as a whole.

What other choices do I have if I do not participate?
The alternative is not to participate in the study.

Will I be paid for being in this study?
You will be compensated for your time and travel after you have completed the entire study with $200, via ClinCard by Greenfield. It is important that you do not lose the University of Pennsylvania debit card (your ClinCard). Costs for replacing lost or stolen University of Pennsylvania debit cards will be your responsibility. The cost to replace the debit card is $3.00 and that amount will be deducted from your study visit payment. To be compensated for your participation in this study, you must provide your social security number. The University of Pennsylvania is

required to report to the IRS any cumulative payments for participation in research studies that exceed a total of $600 in a calendar year.

Will I have to pay for anything?
All of the tests or procedures performed during this study will be free of charge to you and will not be billed to your insurance company. You are responsible for any deductibles or applicable co-pays for routine office visits, scans and blood work that are not related to this research study.

What happens if I am injured from being in the study?
We will offer you the care needed to treat injuries directly resulting from taking part in this research. We may bill your insurance company or other third parties, if appropriate, for the costs of the care you get for the injury, but you may also be responsible for some of them.

There are no plans for the University of Pennsylvania to pay you or give you other compensation for the injury. You do not give up your legal rights by signing this form.

If you think you have been injured as a result of taking part in this research study, tell the person in charge of the research study as soon as possible. The researcher's name and phone number are listed in the consent form.

When is the study over? Can I leave the study before it ends?
This study is expected to end after all participants have completed all visits, and all information has been collected. This study may also be stopped at any time by your physician, the study sponsor, or the FDA without your consent because:

- The principal investigator feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- You have not followed study instructions.
- The sponsor, the study principal investigator, or the Food and Drug Administration has decided to stop the study.

If you decide to participate, you are free to leave the study at any time. Withdrawal will not interfere with your future care.

How will my personal information be protected during the study?
We will do our best to make sure that the personal information obtained during the course of this research study will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. The Institutional Review Board (IRB) at the University of Pennsylvania will have access to your records. If this study is being overseen by the Food and Drug Administration (FDA), they may review your research records. Your study results will be filed using a unique subject identification number rather than your name. This identification number will be destroyed after all data from the study has been collected and analyzed. Research records and information from your examinations will be kept on a secure computer available only to the study investigators, and if necessary, for your medical management. You will have access to this information if you desire. Any paper files containing your information will be stored in a locked cabinet in the study coordinator's office during the study. Data from this study will be kept for at least six years per regulations set by the Department of Health and Human Services. Paper files from the study may be archived at the University of Pennsylvania Archives and Records Center following completion of the study.

Will information about this study be available to the public?
A description of this clinical trial will be available on wwww.clinicaltrials.gov, as required by U.S. law. This website will not include information that can identify you.

What may happen to my information and samples collected in this study?
Your information will be de-identified. This means that all identifiers have been removed. The information could be stored and shared for future research in this de-identified fashion. It would not be possible for future researchers to identify you as we would not share any identifiable information about you with future researchers.

This can be done without again seeking your consent in the future, as permitted by law. The future use of your information only applies to the information collected on this study.

Collection of Identifiable Specimens
Your samples may be used to create products, 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.

Whole genome sequencing will not be conducted on your samples. Whole genome sequencing involves analyzing your entire personal genetic code.

Future Use of Data and/or Specimens
Specimens will not be stored or distributed for future research studies. Data from your imaging exam and blood serum analysis will be de-identified. De-identified means that all identifiers have been removed. This data could be stored and shared for future research in this de-identified fashion. It would not be possible for future researchers to identify you as we would not share any identifiable information about you with future researchers. This can be done without again seeking your consent in the future, as permitted by law. The future use of your information only applies to the information collected on this study.

Electronic Medical Record and Release of Study Related Information

What is an Electronic Medical Record?
An Electronic Medical Record (EMR) is an electronic version of your medical chart within a health system. An EMR is simply a computerized version of a paper medical record.

If you have never received care within Penn Medicine and are participating in a University of Pennsylvania research study that uses Penn Medicine healthcare related services, an EMR will be created for you for the purpose of maintaining any information produced from your participation. The creation of this EMR is a requirement of your participation in this study. In order to create your EMR, the study team will need to obtain basic information about you that would be similar to the information you would provide the first time you visit a hospital or medical facility. If you have been a patient at Penn Medicine in the past, information from your research participation will be added to your existing medical record.

What may be placed in the EMR?
Information related to your participation in the research (e.g., laboratory tests, imaging studies) will be placed in your EMR maintained by Penn Medicine.

Once placed in your EMR your information may be accessible to appropriate Penn Medicine workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by Penn Medicine to be appropriate to have access to your EMR (e.g. health insurance company, disability provider, etc.).

Penn Medicine also participates in automated information sharing through Health Information Exchanges (HIEs). HIEs securely share parts of your electronic health record, including research information, with other healthcare organizations involved in your care. This information is shared to improve the quality, safety, and efficiency of your healthcare. To request that your health information not be shared through HIEs, please call 215-662-4484.

Will I, as a subject, have access to research related information within the EMR?
The 21st Century Cures Act requires healthcare institutions to allow patients increased access to their electronic medical record. As part of your participation in this research, you will have access to research related information within your EMR through Penn Medicine's patient portal – called MyPennMedicine (MPM).

Will I receive the results of research testing that may be relevant to my health?
Many of tests done in research studies are only for research and have no clear impact on your healthcare. Research results for this study will not be returned to you because they would not be relevant to your healthcare.

What information about me may be collected, used or shared with others?
The following personal health information will be collected and may be disclosed for this research study:

- Name, address, telephone number, email
- Birthdate, medical record number, medical history, current and past medications or therapies
- MRI images
- Social security number is required for payment only and is stored in a separate file

Why is my information being used?
Your information is used by the research team to contact you during the study. Your information and results of tests and procedures are used to:

- do the research
- oversee the research
- to see if the research was done right
- to evaluate and manage research functions.

Where may my information be stored?
Information related to your participation in clinical research will be contained in a clinical trial management system (CTMS). A clinical trial management system (CTMS) is used to register your information as a participant in a study. This allows for your research data to be entered and stored for the purposes of study operational and financial applications and other activities required as part of the conduct of the research. Once placed in the CTMS your information may be accessible to other authorized personnel at Penn Medicine that support research operations. Your information may be held in other research databases.

Who may use and share information about me?
The following individuals may use or share your information for this research study:

- The investigator for the study and the study team
- Other authorized personnel at Penn Medicine and the University of Pennsylvania, including offices that support research operations
- Other research personnel with access to the databases for research and/or study coordination and as otherwise approved by the IRB

Who, outside of Penn Medicine, might receive my information?
The following oversight organizations might receive your information:

- The Food and Drug Administration
- The National Institutes of Health
- The Office of Human Research Protections

Once your personal health information is disclosed to others outside the School of Medicine, it may no longer be covered by federal privacy protection regulations.

The principal investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to University of Pennsylvania procedures developed to protect your privacy.

How long may Penn Medicine use or disclose my personal health information?
Your authorization for use of your personal health information for this specific study does not expire.

However, Penn Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization

- The University of Pennsylvania's Institutional Review Board grants permission
- As permitted by law

Can I change my mind about giving permission for use of my information?
Yes. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the investigator for the study. If you withdraw your permission, you will not be able to stay in this study.

What if I decide not to give permission to use and give out my health information?
Then you will not be able to be in this research study.

You will be given a copy of this Research Subject HIPAA Authorization describing your confidentiality and privacy rights for this study.

By signing this document, you are permitting Penn Medicine to use and disclose personal health information collected about you for research purposes as described above.

Who can I call with questions, complaints or if I'm concerned about my rights as a research subject?
If you have questions, concerns, or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, you should speak with the principal investigator listed on page one of this form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the IRB at the number on page one of this form.

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania to use the personal health information collected about you for research purposes within our Institution. You are also allowing the University of Pennsylvania to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this consent form will be given to you.

_____	_____	
Name of Subject (Print)	Signature	Date
_____	_____	
Name of Person Obtaining Consent (Print)	Signature	Date