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Understanding the Impact of Cartridge-Based Electronic Cigarettes and Generated Aerosols on Cardiopulmonary Health

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RESEARCH PARTICIPANT INFORMATION AND CONSENT FORM
E-CIGARETTE USERS

STUDY TITLE: Understanding the Impact of Cartridge-Based Electronic Cigarettes and Generated Aerosols on Cardiopulmonary Health

VCU INVESTIGATOR: Paula Rodriguez Miguelez, PhD, NREMT, NCPT

SPONSOR: NIH & FDA Center for the Study of Tobacco Products

In this consent form, "you" always refers to the research participant.

ABOUT THIS CONSENT FORM

You are being invited to participate in a research study. **It is important that you carefully think about whether being in this study is right for you and your situation.** This consent form is meant to assist you in thinking about whether or not you want to be in this study. **Please ask the study doctor or the study staff to explain any information in this consent document that is not clear to you.** You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

Your participation is voluntary. You may decide not to participate in this study. If you do participate, you may withdraw from the study at any time. Your decision not to take part or to withdraw will involve no penalty or loss of benefits to which you are otherwise entitled.

AN OVERVIEW OF THE STUDY AND KEY INFORMATION

Why is this study being done?

Over the last decade, electronic cigarettes or e-cigarettes have become increasingly popular, due to their promotion as a healthy alternative to traditional tobacco cigarettes. However, there are large discrepancies of knowledge in understanding how these e-cigarettes affect the user's health and the way their body uses oxygen. The overall goal of this study is to evaluate e-cigarettes usage on users' health.

What will happen if I participate?

In this study, you will be asked to do the following things:

1. Visit the Department of Kinesiology and Health Sciences for a preliminary visit to verify if you qualify
2. Visit the laboratory (located in the Department of Kinesiology and Health Sciences) two times for two study visits. The visits will be around 5 hours
3. Use the e-cigarettes that we will provide for two weeks
4. Have your blood collected once during every experimental visit
5. Have your body measured and your heart function and blood flow tested in multiple ways
6. Complete questionnaires on health history and daily habits

Your participation in this study will last up to 2 weeks. Approximately a total number of 57adults, among them, 38 e-cigarette users, will participate in this study.
This study will not use your samples to sequence all or part of your DNA.

What are the risks and benefits of participating?
There are both risks and benefits of participating in research studies. We want you to know about a few key risks right now. We will give you more information in the "WHAT RISKS AND DISCOMFORTS CAN I EXPECT FROM BEING IN THE STUDY?" section.

Risks and Discomforts	Benefits to You and Others
1. For the participants assigned to use e-cigarettes without nicotine, there may be a process of withdrawal. You may experience symptoms including change in appetite, irritability, anxiety, restlessness, and difficulty sleeping. 2. Blood draws may cause pain, bleeding and/or bruising. You may faint and could develop an infection at the site where blood is drawn. 3. The flow mediated dilation vascular function tests may result in a small amount of pain, numbness, tingling, and/or loss of sensation (like when a body limb goes to sleep) in the portion of the arm or leg that is below the cuff during the 5 minutes of cuff inflation. 4. The iontophoresis test may result in a mild skin irritation on the hand or the forearm. 5. The local heating test may feel uncomfortably warm and may result in a mild skin redness in the portion of theforearm under the ring holders. 6. The study questionnaires ask personal questions that are sensitive in nature and may make you feel uncomfortable.	1. There is no guarantee that you will receive any medical benefits from being in this study. However, this study may help the investigators learn about the effects of e-cigarettes in user's health.

Now that you have a general overview of the study, we want to provide the details about what your participation involves. Please read, or have someone read to you, the rest of this document. If there is anything you don't understand, be sure to ask the study staff.

WHY IS THIS STUDY BEING DONE?
Over the last several decades tobacco consumption has seen a distinct decline in the US, and the alternative, electronic cigarettes has been on the rise due to its popularity amongst the

younger generation. With the increase in these tobacco alternatives, and the lack of regulations, further research surrounding the potential effects of these products on users' health is necessary.

WHAT WILL HAPPEN IF I PARTICIPATE IN THE STUDY?

All the participants will have identical study visits. The only difference will be that the e-cigarette users will complete the study visits twice, before and after the 2 weeks, while the non-e-cigarette users will complete one single visit. During the experimental visits, we will evaluate how your lungs, your heart, your blood vessels and your muscles work. The procedures are summarized below:

- **Physical Exam:** We will measure resting heart rate, resting blood pressure, and resting oxygen saturation.
- **Pregnancy Test:** Premenopausal females will complete a urine pregnancy test prior to the testing session.
- **Body Composition:** Both height and weight will be taken without shoes and wearing as few clothes as possible. Waist to Hip Ratio (WHR) will be measured using an inelastic vinyl tape measure. We will also complete a body impedance analysis (BIA) to evaluate your body composition. We will just stick small electrodes in your hand and ankle while you are laying down and a low electrical current that can't be felt will be used to measure how much fat, water, and muscle your body has.
- **Blood Samples**: A blood sample will be taken from a vein in the arm by a certified phlebotomist technician before and after each protocol. **You will be asked to fast overnight before these visits.** This means you should not consume any food or caffeine after 12AM (midnight) prior to your appointment. You may drink water but no other liquids. A total of about 40 ml of blood (~ 2-3 tablespoons) will be taken to normal biochemistry including cholesterol and hemoglobin and biomarkers of inflammation. You will also be asked to avoid exercise for at least 12 hours before the experiment and avoid taking any vitamins 3 days prior.
- **Breath**: We will also collect your breath in a tube. We will ask you to breathe through a specific tube during 7 minutes, while you are in a comfortable position.
- **Arterial Stiffness Evaluation:** A device will be used to measure how fast your blood travels. This test is called pulse wave velocity and gives us information on how stiff your arteries are. To start the test, we will ask you to lie still in a resting position for about 20 minutes. We will place some blood pressure cuffs in your arm and leg and a pen-like device on your neck to record how fast the blood flows. A device will be used to measure how fast your blood travels. This test is called pulse wave velocity or PWV. How fast your blood travels is also a measure of how stiff their arteries are. Stiff blood vessels/arteries are linked to heart disease. To start the test, you will be asked to lie still in a resting position for about 20 minutes. The research assistant will place white patches called electrode sensors on their body. A pen-like device is gently applied on the carotid artery (neck) and then the femoral artery (groin) and the radial artery (wrist) to record how fast their blood flows between each of the points.
- **Flow Mediated Dilation (FMD):** This test looks at how arteries expand with changes in blood flow. You will lie on your back for 20 minutes to rest. We will then measure the function of the artery by scanning an artery in the arm with an ultrasound. Following baseline measurements, a blood pressure cuff placed around your forearm will be inflated to temporarily stop blood flow (5 minutes). Blood flow and velocity and arterial diameters will be recorded for 2 minutes following the release of the cuff.

- **Skin Blood Flow:** We will use a special camera that shines a low energy laser light on the surface of your forearm to measure blood flow. The camera makes graphs, photos, and movies of the blood flow in your skin.
- **Iontophoresis:** Acetylcholine, sodium nitroprusside and L-NAME are substances that can dilate or constrict your blood vessels that will be used to study your skin blood flow in small regions of your forearm. These substances are not FDA approved for this use. We will place two rings in your forearm where we will add the solutions. The solutions are a very low electrical current that will change your skin blood flow at the surface and the drugs will not enter the body. The adjacent circulation will be monitored constantly with a special camera.
- **Local Heating:** We add water to a third ring on your forearm and measure the temperature of the skin. We will heat the water to increase blood flow in that localized area. The heating of the water will make the skin of the arm red just under that ring like when you take a hot bath. The redness will not last more than a few hours. Some people may be more sensitive to the heating than others. If your arm feels too hot, you will tell us, and we will reduce or stop the heating.
- **Cardiopulmonary Exercise Test:** This test is designed to measure how fit you are. You will be seated on a stationary bike to perform the exercise capacity test. During this exercise test, your effort of pedaling will become greater every minute, until you cannot continue to pedal any longer. You will breathe through a mouthpiece that collects all your expired air. Your heart rate and oxygen saturation will be monitored throughout the exercise. We will also place surface electrodes on your body (Physioflow) to monitor the heart and blood vessels through a wireless system. We will place an additional larger electrode on your thigh called near infrared spectroscopy (NIRS). This allows us to measure how saturated your thigh muscle is with oxygen while you exercise. This procedure will last approximately 60 minutes. If you experience any chest discomfort or pain, abnormal blood pressure and heart rate response, or electrocardiogram (ECG) signs of poor blood flow to the heart that limit your ability to complete the exercise test, you will not be permitted to continue the study.
- **Pulmonary Function Test***:* We will measure how well your lungs diffuse oxygen to the rest of the body. This involves taking a deep breath and then blowing into a tube as hard as you can, until you cannot blow any further. We will also measure how well the air crosses through the lungs by having you breathe a mixture of gasses (10% He, 21% O_2, 0.3% CO, and balance N_2) and having you hold your breath for 10 seconds.
- **Handgrip Exercise:** A test that will measure the health of a blood vessel in your upper arm in response to exercise will be done. You will do the handgrip exercise while lying flat on your back, arm slightly away from your body, at a rate of 1 hand squeeze per second while measures will be made in a blood vessel in your upper arm (brachial artery) using an ultrasound machine. You will continue increasing workloads until you are no longer able to complete a full 3-minute stage. We will place an additional small electrode on your arm called near infrared spectroscopy to measure how saturated your muscle is with oxygen while you exercise.
- **Questionnaires:** We will ask you how fatigue you feel as well as if you have any trouble breathing. We will also ask you to complete some question related to your lifestyle including how often you exercise, how your diet is, how many e-cigarettes you use and if you consume any alcohol or other substances.
- **Physical Activity**: We will ask you to wear a device that will measure how many steps you take during a period of seven days between the first and second experimental visit. The device to measure steps can be placed on the wrist as a watch or on the hip as a belt.

After completing the first experimental visits, we will give you a number of e-cigarettes to substitute

the ones you normally use. Randomly, you will receive e-cigarettes with or without nicotine, but we will not know which ones you received until we have completed the study. We will ask you to use them daily, in substitution of your own ones. During the 2nd visit, we will ask you to bring back the ones you have not used. If you are unable to use the study e-cigarettes for more than two days, we will ask you to let us know and we may withdraw you from this study.

WHAT ARE THE BENEFITS OF BEING IN THE STUDY?

There is no guarantee that you will receive any medical benefits from being in this study. However, this study may help the investigators learn about the effects of e-cigarettes on heart and lung health which may help people in the future. You will also get information about your labs (lipid panel, glucose, hemoglobin), pulmonary (lung) function, and overall cardiovascular (heart) health.

WHAT RISKS AND DISCOMFORTS COULD I EXPERIENCE FROM BEING IN THE STUDY?

Possible Risks Associated with the use of E-cigarettes

The effect of e-cigarettes is still unknown. The consumption of e-cigarettes can be associated with shortness of breath, fatigue, chest pain, cough, anorexia, nausea, diarrhea, and weight loss, with symptoms worsening over days or weeks with some dying from this condition. It has been also hypothesized that they may impact the epithelium inflammatory responses in the lungs and contribute to the onset, progression, and proliferation of lung cancer. Since you will be taking home the provided e-cigarettes, they must be kept out of reach of children and persons who many not be able to read or understand the label. In addition, only you can use the provided e-cigarettes.

For the participants assigned to use e-cigarettes without nicotine, there may be a process of withdrawal. You may experience symptoms including change in appetite, irritability, anxiety, restlessness, and difficulty sleeping. For participants assigned to use e-cigarettes with nicotine, the e-cigarettes may have a higher or lower level of nicotine than you are used to consuming.

To note, e-cigarette companies have to apply to the Food and Drug Administration (FDA) and be approved for sale in U.S. markets. In June 2022, the FDA denied the marketing application from JUUL, the manufacturer of the e-cigarettes used in this study. The FDA determined that JUUL did not provide enough evidence about the toxicity of its e-cigarette device and pods in its application. However, the FDA has not received clinical information to suggest an immediate hazard associated with the use of JUUL devices or JUUL pods. The FDA decision to ban the sale of JUUL is not final yet due to ongoing legal disputes. When and if the FDA's decision to ban JUUL is final, it will be illegal to sell JUUL products. However, it will still be legal for researchers to study these products and for participants to use them.

Possible Risks Associated with the tests:

- *Cardiopulmonary exercise capacity:* there is extremely low risk of serious complications such as heart attack or stroke (less than 1 in 1,000). Abnormal cardiovascular response during exercise testing (i.e. markedly elevated blood pressure or heart rate) may occur (approximately 1 in 10), which may require to stop the test early and/or rest for a few minutes to catch your breath. At all times, an exercise physiologist and a national certified emergency medical technician will supervise the cardiopulmonary exercise test. Minor arm or discomfort/pressure may occur during blood pressure measurement.

- *Blood Samples:* Potential risks related with taking a blood sample are few but include slight bruising, pain, a temporary feeling of faintness, and phlebitis. Rarely, there may be a small blood clot or infection at the site of the needle puncture. All blood draws will be performed following sterile techniques by a research team member or a nurse who is a phlebotomist certified.

- *Flow-mediated dilation (FMD)*. The risks associated with the flow-mediated dilation are minimal, if not none. Potential risks include redness of the skin, bruising, numbness, pain, tingling of the fingers and discomfort while the cuff is inflated (5 minutes). The risks associated with the lubricant gel used with the ultrasound probe are skin irritation and possible break out of rash.
- *Skin Blood Flow*: There are no known risks associated with the laser imaging camera. The small skin probes can hurt the eyes if you stare into the light for a long time. We do not turn on the laser until the probes are taped to a surface of the arm.
- *Iontophoresis*. Some people may be more sensitive to the current than others. If the subject feels skin irritation on the hand or the forearm where the chambers are placed, the subject has been instructed to tell us, and we will reduce or stop the current.
- *Local Heating:* We measure the temperature of your skin under the ring holders. The skin will feel very warm but should not hurt. The heating of the water will make the skin of your arm under the holders red like when taking a hot bath. The redness will not last more than a few hours. Some people may be more sensitive to the heating than others. If your arm feels too hot, the subject has been instructed to tell us, and we will reduce or stop the heating
- *Pulmonary Function Test.* Rarely, some participants may feel dizzy or lightheaded that it will be resolved after finishing the test.
- *Questionnaires:* May contain questions that are sensitive in nature. You may refuse to answer any question that makes you feel uncomfortable.
- *Non-Physical Risks*: Participation in research might involve some loss of privacy. There is a small risk that someone outside the research study could see and misuse information about you.
- *Unknown or Unforeseeable Risks*: The researchers will let you know about any significant new findings (such as additional risks or discomforts) that might make you change your mind about participating in the study. Any unforeseen adverse events that occur throughout the course of the study will be immediately reported to the principal investigator for further review.
- *Reproductive Risks*: As the study procedures might injure an unborn child, pregnant women may not participate. Women who might become pregnant should use a medically accepted form of birth control such as total abstinence, birth control pills, an IUD, diaphragm, progesterone injections or implants, or condoms plus a spermicide. Methods of birth control other than total abstinence are not 100% effective, and should a women become pregnant there is a risk of injury to an unborn child. For similar reasons, women who are nursing an infant may not participate. For men, the study procedures might increase the risks for birth defects of any child conceived during treatment and several months after treatment is stopped. Men in this study who have the potential of fathering children should be aware of this possibility and consider using a medically accepted form of birth control. For men this would include total abstinence and condoms plus a spermicide, or for the female partner, birth control pills, an IUD, diaphragm, progesterone injections or implants. Methods of birth control other than total abstinence are not 100% effective, and should a women become pregnant there is a risk of injury to an unborn child.

WHAT ARE THE COSTS?

You will not be charged for any study visits, tests, or procedures.

WILL I BE PAID TO PARTICIPATE IN THE STUDY?

You will be paid $250 in cash or by check or by gift card for your time to complete the study. You will receive $50 after completing the first experimental visit and another $200 after the completion of the second and final experimental visit.

Total payments within one calendar year that exceed $600 will require the University to report these payments annually to the IRS and you. This may require you to claim the compensation you receive for participation in this study as taxable income. VCU is required by federal law to collect your social security number. Your social security number will be kept confidential and will only be used to process payment.

WHAT HAPPENS IF I AM INJURED OR BECOME SICK BECAUSE I TOOK PART IN THE STUDY?

If you are injured by, or become ill, from participating in this study, please contact the principal investigator, Dr. Rodriguez Miguelez, immediately. Medical treatment is available at the Virginia Commonwealth University Health System (VCU Health System). Your study doctor will arrange for short-term emergency care at the VCU Health System or for a referral if it is needed.

Fees for such treatment may be billed to you or to appropriate third party insurance. Your health insurance company may or may not pay for treatment of injuries or illness as a result of your participation in this study. To help avoid research-related injury or illness, it is very important to follow all study directions.

CAN I STOP BEING IN THE STUDY?

You can stop being in this research study at any time. Leaving the study will not affect your medical care, employment status, or academic standing at VCU or VCU Health. Tell the study staff if you are thinking about stopping or decide to stop. To withdraw from the study, please notify the PI, Dr. Rodriguez Miguelez in writing. The data collected as part of the study will need to be kept for regulatory purposes.

Your participation in this study may be stopped at any time by the study doctor without your consent. The reasons might include:

- the primary investigator thinks it necessary for your health or safety
- you are found to not be eligible for the study
- the sponsor has stopped the study
- you have not followed study instructions

If you withdraw from the study, data that has already been collected about you will remain part of the study database and may not be removed.

HOW WILL INFORMATION ABOUT ME BE PROTECTED?

VCU and the VCU Health System have established secure research databases and computer systems to store information and to help with monitoring and oversight of research. Your information may be kept in these databases according to VCU's policies (i.e. for a minimum of 5-6 years). It is only accessible to individuals working on this study or authorized individuals whohave

access for specific research related tasks.

Identifiable information in these databases are not released outside VCU unless stated in this consent or required by law. Although results of this research may be presented at meetings or in publications, identifiable personal information about participants will not be disclosed. Personal information about you might be shared with or copied by authorized representatives from the following organizations for the purposes of managing, monitoring and overseeing this study:

- The study Sponsor, representatives of the sponsor and other collaborating organizations
- Representatives of VCU and the VCU Health System
- Officials of the Department of Health and Human Services or the Federal Food and Drug Administration

In general, we will not give you any individual results from the study. If we find something of medical importance to you, we will inform you, although we expect that this will be a very rare occurrence. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Web site at any time.

Project findings and reports prepared for dissemination will not contain information that can reasonably be expected to be identifiable.

There are no plans to share any money or profits with you if the use of your sample(s) results in inventions or discoveries that have commercial value. In the future, identifiers might be removed from the information and samples you provide in this study, and after that removal, the information/samples could be used for other research studies by this study team or another researcher without asking you for additional consent.

Certificate of Confidentiality

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. It will offer the protections described here. A Certificate of Confidentiality helps the researchers keep your information private. For example, researchers can refuse to give out your information in a court case. Researchers may have to give your information if the study is audited, or if the information is required by the Food and Drug Administration (FDA).

The researchers cannot prevent you or others, for example a member of your family, from sharing information about you or your involvement in this research. If you give an insurer, employer, or other person permission to receive research information, then the researchers may not use the Certificate to withhold that information.

OPTIONAL STORAGE FOR FUTURE RESEARCH STUDIES

As part of this study, we would like to keep the samples that you provide, along with your name and contact information (phone and email) in a registry/repository to be available for other research studies in the future. Your contact information and samples would be stored at VCU by the PI of this study (Dr. Rodriguez Miguelez) that will have sole control and management of the registry and could be used for other research studies focused specifically on e-cigarette usage

research. Your data/samples will be protected, but there is always a possibility that information could be accessed by individuals without authorization. There is no limit on the length of time we will store your information/samples. In the future, if you decide that you do not want to be part of this registry, you can request that your information/samples be removed and destroyed by contacting Dr. Rodriguez Miguelez. However, information that has already been shared with other researchers will continue to be used.

Permission to Store Data and/or Samples for Future Research Studies
Please circle your answer: I agree that my data and/or samples may be stored and used for future research as described above.

YES NO

WHOM SHOULD I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY?

The investigator and study staff named below are the best person(s) to contact if you have any questions, complaints, or concerns about your participation in this research:

Paula Rodriguez Miguelez, PhD
Office Phone (804) 396- 4498
prodriguezmig@vcu.edu

If you have general questions about your rights as a participant in this or any other research, or if you wish to discuss problems, concerns or questions, to obtain information, or to offer input about research, you may contact:

Virginia Commonwealth University Office of Research

800 East Leigh Street, Suite 3000, Box 980568, Richmond, VA 23298

(804) 827-2157; https://research.vcu.edu/human_research/volunteers.htm

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

STATEMENT OF CONSENT

I have been provided with an opportunity to read this consent form carefully. All of the questions that I wish to raise concerning this study have been answered. By signing this consent form, I have not waived any of the legal rights or benefits to which I otherwise would be entitled. My signature indicates that I freely consent to participate in this research study. I will receive a copy of the consent form for my records.

Signature Block for Enrolling Adult Participants	
Adult Participant Name (Printed)	
Adult Participant's Signature	Date
Name of Person Conducting Consent Discussion (Printed)	
Signature of Person Conducting Consent Discussion	Date
Principal Investigator Signature (if different from above)	Date