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Using Very Low Nicotine Cigarettes to Disrupt the Pain-smoking Reinforcement Cycle

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Duke University Health System

Consent To Participate In A Research Study
ADULT

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CONCISE SUMMARY

The purpose of this study is to evaluate the effects of switching to very low nicotine content (VLNC) cigarettes versus normal nicotine content (NNC) cigarettes on craving, withdrawal, and pain among individuals with chronic back pain who smoke cigarettes daily.

This study requires an initial screening visit, followed by an assessment/training visit, 5 weekly in-person visits, and a final assessment visit. You will be asked to not smoke for 24 hours before the training visit and final assessment visit. We will provide you with investigational study cigarettes during 4 weeks of the study, and you will be asked to smoke only the cigarettes that we provide you during that time. You will also be asked to install software on your smartphone and respond to questions about your smoking, craving, mood, and pain symptoms multiple times per day during 3 weeks of the study. All procedures can be completed within approximately 6 weeks.

Possible risks of the study include risks associated with continued smoking, possible increase in smoking rate during study cigarette use, withdrawal symptoms, and the possibility of worsening of pain or negative mood when using study cigarettes. There are no direct benefits to participating. We hope the information learned from the study will help improve treatments for smokers with pain who want to quit smoking.

You are being asked to take part in this research study because you smoke cigarettes every day and have recently experienced chronic back pain. Research studies are voluntary and include only people who choose to take part. Please read this consent form carefully and take your time making your decision. As your study doctor or study staff discusses this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. We encourage you to talk with your family and friends before you decide to take part in this research study. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are listed below.

Please tell the study doctor or study staff if you are taking part in another research study.

A grant from the National Institutes of Health (NIH) will sponsor this study. Dr. Sweitzer will be responsible for the conduct of the study and portions of Dr. Sweitzer's and her research team's salaries will be paid by this grant.

WHO WILL BE MY DOCTOR ON THIS STUDY?
If you decide to participate, Dr. Paolo Mannelli, our program's physician, will be your doctor for the study He will determine your initial medical eligibility and follow your progress through the study. If

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needed, he will be in contact with your regular health care provider throughout the time that you are in the study and afterwards.

WHY IS THIS STUDY BEING DONE?
The purpose of this study is to better understand how nicotine levels in cigarettes impact the relationship between smoking and pain. Pain and cigarette smoking have been shown to influence one another, such that people who smoke are more likely to have pain, and people with pain are more likely to smoke. Lowering the amount of nicotine in cigarettes may help to disrupt these associations and make it easier for people with pain to quit smoking. Looking at changes in smoking behavior, mood, and pain throughout the day and over several weeks of smoking normal nicotine content (NNC) versus very low nicotine content (VLNC) cigarettes will help us to better understand how nicotine impacts pain, which can ultimately lead to better smoking cessation treatments.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
Approximately 100 people will take part in this study at Duke.

WHAT IS INVOLVED IN THE STUDY?
If you agree to be in this study, you will be asked to sign and date this consent form. You will have the following tests and procedures to make sure that you are eligible:

- General information, including name, address, date of birth, demographics, and social security number will be collected. We will need your social security number to process your payment. If you do not provide this, we will be unable to pay you for participation.
- Interviews and questionnaires about medical history and tobacco use history
- Vitals, including blood pressure and heart rate
- Breath CO test to measure carbon monoxide (CO) level in your exhaled breath
- Urine sample collection to test for drugs of abuse. Some drugs can be detected for several weeks.
- If you test positive for illegal drug use (aside from marijuana) you will not be allowed to participate in the study. Participants are encouraged to avoid marijuana use during the study. If they decide to use marijuana in any form, they must avoid daily use, avoid additional tobacco, and abstain for 48 hours prior to study visits.
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- Psychiatric evaluation including a computer screening and follow-up interviewing to assess for psychiatric illness.

<u>Screening Session</u>
The screening session will take place after you have signed the consent form. The screening session will take approximately 3 hours to complete, including all interviews, questionnaires, and sample collection. We will ask you questions about your smoking behavior, medical history, and pain during this visit. Our team will verify your diagnosis of back pain through the option of your choice: you may grant us

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permission to contact your provider or view your medical record, if verification is necessary. There may be an option to complete the consent process and some of the screening procedures remotely.

At the start of the in-person visit, we will collect breath and urine samples to test for recent smoking, alcohol, and drug use. If your breath sample does not indicate that you have smoked recently, or if you test positive for drug use (other than marijuana), you will not be allowed to participate in this study. You cannot participate in the study if you are a pregnant woman or a nursing mother. Depending on the results of other screening procedures you may also not eligible for the study. If you do not qualify for the study and you are diagnosed with a psychiatric illness during the psychiatric evaluation, Dr. Sweitzer and her team will provide you with appropriate referrals if you decide that you want to seek treatment. If you are determined to be ineligible during the in-person screening, your participation in the study will end and no additional information will be collected from you.

You will receive $30 for the in-person screening session, even if you are not eligible for the study or decide that you do not want to participate, as long as you pass the drug and breath sample tests. If you do not pass these tests you will be dismissed from the study without payment.

If you are determined to be eligible to participate after the in-person screening and you feel comfortable participating in the study, you will be scheduled to complete the training/assessment session.

Assessment/Training Session
The assessment/training session will take up to 90 minutes to complete. You will be instructed not to smoke any cigarettes for 24 hours before the session. At the start of the session we will ask you about your recent smoking and measure your breath CO level to confirm whether or not you have smoked. If your CO indicates that you have smoked prior to this visit, you may be asked to reschedule this visit.

You will be asked to complete a number of interviews and questionnaires about your healthcare, symptoms of withdrawal, and pain. We will install the MetricWire app on your smartphone, and you will be trained in how to use this to answer questions remotely.

Weekly Visits
Beginning 1 week after the training visit, you will be asked to attend 5 weekly visits, each lasting up to an hour. During each of these visits we will measure your breath CO and vitals (such as blood pressure), and we will ask you to complete interviews and questionnaires about your smoking, health, and pain. Depending on the week, we will provide you with study cigarettes or collect old packaging or cigarettes from you, as needed. We will also collect urine samples from you to measure your use of study cigarettes.

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Study Cigarettes
During the first weekly visit you will be randomly assigned (like the flip of a coin) to receive either very low nicotine content (VLNC) cigarettes or normal nicotine content (NNC) cigarettes to smoke instead of your usual brand for the next four weeks. You will be able to choose menthol or non-menthol cigarettes, but you will not be told which nicotine content you are assigned to. The study cigarettes have been obtained through the National Institute on Drug Abuse and the Food and Drug Administration has reviewed the study protocol. These cigarettes are manufactured in the same way as your usual brand cigarettes, but they may contain genetically modified tobacco to reduce the levels of nicotine.

Final Assessment Session
After you complete weekly visit 5, we will ask you not to smoke for the next 24 hours, and then to attend a final assessment visit. This visit will be the same as the initial assessment/training visit. We will measure your breath CO, ask you to complete interviews and questionnaires, and remove the MetricWire app from your smartphone.

Remote Assessment using the Metricwire App
We will ask you to complete remote assessments for 3 weeks of the study. Each day, you will be prompted at 6 random times throughout the day to answer a brief set of questions. You will also be asked to press a button each time you are about to smoke a cigarette, and occasionally you will be prompted to answer the questions at these times. Finally, you will be asked at the end of the day to tell us how many cigarettes you smoked.

All of the data and information collected through the Metricwire Mobile Application as part of your participation in this research is owned and controlled by the Research Team.

When the study is over, the research team will delete your data from the Metricwire servers. If you would like to access any of your data at any time during your participation in this study, please contact the research team or reach out to **privacy@metricwire.com** and we will help facilitate your request.

HOW LONG WILL I BE IN THIS STUDY?
This study includes the screening visit, followed by the assessment/training visit, 5 weekly visits, and a final assessment visit. You will also receive a phone call 3 months after you complete the study to answer some additional questions. You can complete in-person procedures in about 6 weeks. You can choose to stop participating at any time without penalty or loss of any benefits to which you are entitled.

Clinically relevant results of this research will be communicated with you. We plan to share what we learn from the study using the lab's website postings of early or published research findings. We may also send a newsletter mailed or emailed to you about our research discoveries unless you notify us in writing that you do not wish to receive such communication.

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WHAT ARE THE RISKS OF THE STUDY?
As a result of your participation in this study, you are at risk for the following potential side effects. You should discuss these with the study staff, study principal investigator, and your regular health care provider if you choose.

Reproductive Risks
Smoking during pregnancy increases the risks of a number of complications, including miscarriage, preterm birth, low birth weight, and stillbirth. In addition, pregnancy can affect back pain. For these reasons, women who are pregnant or actively planning a pregnancy are excluded from this study. If you are a woman who could possibly become pregnant (for example, you have not completed menopause, or you have not had a hysterectomy and/or both tubes and/or both ovaries removed) and you have a partner who is able to father children, you will have a urine pregnancy test before study cigarettes are provided to you. The urine pregnancy test must be negative (not pregnant) in order to continue with the study. You will be withdrawn from the study if you become pregnant during the study. If you wish to participate in all of the study visits, you and your partner are advised to abstain from all vaginal intercourse or use an effective method of birth control for the duration of the study.

Smoking Study Cigarettes:
You may experience some minor adverse health effects such as headaches or increased pain, or you may experience withdrawal symptoms, which are listed below. If you are assigned to cigarettes with lowered nicotine levels, there could be a change in your use of cigarettes including the manner in which you inhale the smoke or smoking more cigarettes per day. Smoking the study cigarettes do not provide any less risk than your usual brand of cigarette and could pose increased health risks. You may also experience increases in levels of carbon monoxide, a gas from smoke.

Smoking Withdrawal:
You may experience smoking withdrawal symptoms during this study. These symptoms can include anger, irritability, frustration, anxiousness, depressed mood, craving for a cigarette, difficulty concentrating, increased appetite, weight gain, sleep problems, restlessness, impatience, constipation, dizziness, coughing, nightmares, nausea and sore throat. These feelings can be uncomfortable but are of minimal risk. At each visit we will ask you how you feel, and if we think that being in this study is putting your health at risk, we may ask you to stop participating in the study.

Changes in Blood Pressure and/or Heart Rate:
Smoking and nicotine can affect the cardiovascular system which may result in changes in blood pressure and/or heart rate. Changes will be monitored by study staff and may result in stopping participation.

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Drug and Food Interactions:
For your safety, you must tell the study doctor about all the prescribed medical foods and drugs, herbal products, over-the-counter (OTC) drugs, vitamins, natural remedies, and alcohol that you are taking before you start the study and before starting to take any of these products while you are on the study. There may be unknown risks and side effects associated with these products while using study cigarettes.

Additional Risks:
There is also the potential risk of loss of confidentiality (your data could possibly be seen by someone without permission). Every effort will be made to keep your information confidential and private; however, this cannot be guaranteed. We will not contact your provider or view your medical record without your signed consent. Some of the questions we will ask you as part of this study may make you feel uncomfortable. You may decide not to answer any of the questions, and you may take a break at any time during the study. You may stop your participation in this study at any time.
There may be other risks, discomforts, drug interactions or side effects that are not yet known.

PHI Authorization
We may contact your provider or view your medical record to confirm a history of low-back pain. We will not do so without your consent. Our study team will only review medical information necessary for this study. Details of how we retrieve this information will be highlighted in our release form, reviewed and signed after your initial screening session. Please select one of the following options to let us know if we may review your medical history through your provider or medical record:

_____ The VLNC Pain study team **may** review my medical history through my provider or medical record.

_____ The VLNC Pain study team **may not** review my medical history through my provider or medical record.

If at any time during the study you change your mind about this decision, you can contact us at 919-907-9955.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
If you agree to take part in this study, there is no direct medical benefit to you. We hope that in the future, the information learned from this study will help to develop more effective treatments for smokers who may experience pain.

WHAT ALTERNATIVES ARE THERE TO PARTICIPATION IN THIS STUDY?
This study is not intended to help you quit smoking. If you are interested in quitting smoking, there are alternatives that can help you. You may talk with your doctor about prescription medicines or nicotine

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replacement products that can help with smoking cessation. Information about additional resources available to people trying to quit smoking is available through the North Carolina Tobacco Use Quitline at: quitnownc.org or by calling 1-800-784-8669.

WILL MY INFORMATION BE KEPT CONFIDENTIAL?
Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total confidentiality. Your personal information may be viewed by individuals involved in this research and may be seen by people including those collaborating, funding, and regulating the study. We will share only the minimum necessary information in order to conduct the research. Your personal information may also be given out if required by law.

As part of the study, results of your study-related laboratory tests and procedures may be reported to the National Institutes of Health and its affiliates. In addition, your records may be reviewed in order to meet federal or state regulations. Reviewers may include representatives from the Food and Drug Administration, representatives and affiliates of the National Institutes of Health, the Duke University Health System Institutional Review Board, and others as appropriate.

The Department of Health and Human Services (HHS) has issued a Certificate of Confidentiality to further protect your privacy. With this Certificate, the investigators may not disclose research information that may identify you in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings, unless you have consented for this use. Research information protected by this Certificate cannot be disclosed to anyone else who is not connected with the research unless:

1) there is a law that requires disclosure (such as to report child abuse or communicable diseases but not for legal proceedings);

2) you have consented to the disclosure, including for your medical treatment; or

3) the research information is used for other scientific research, as allowed by federal regulations protecting research subjects.

Disclosure is required, however, for audit or program evaluation requested by the agency that is funding this project or for information that is required by the Food and Drug Administration (FDA).

You should understand that a Confidentiality Certificate does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it. This means that you and your family must also actively protect your own privacy.

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Finally, you should understand that the investigator is not prevented from taking steps, including reporting to authorities, to prevent serious harm to yourself or others.

The study results will be retained in your research record for at least six years after the study is completed. At that time either the research information will be destroyed or information identifying you will be removed from such study results at DUHS.

This information may be further disclosed by the sponsor of this study. If disclosed by the sponsor, the information is no longer covered by federal privacy regulations.

If this information is disclosed to outside reviewers for audit purposes, it may be further disclosed by them and may not be covered by federal privacy regulations.

While the information and data resulting from this study may be presented at scientific meetings or published in a scientific journal, your identity will not be revealed.

Some people or groups who receive your health information might not have to follow the same privacy rules. Once your information is shared outside of DUHS, we cannot guarantee that it will remain private. If you decide to share private information with anyone not involved in the study, the federal law designed to protect your health information privacy may no longer apply to the information you have shared. Other laws may or may not protect sharing of private health information.

Risks Specific to Mobile Apps

Information collected by mobile applications or 'apps' is subject to their terms of use, which you should read carefully. Many apps make claims that they are very secure, compliant with federal privacy regulations, and used and tested by other academic centers. However, any mobile app that is downloaded carries potential security risks, and Duke cannot guarantee that these mobile apps are free of risk. Some apps may be able to perform hidden functions or may have security flaws that allow unauthorized access to information. We are unable to fully tell you what information these mobile apps are able to access or change on your device or what information from your device may be stored outside of Duke. You are encouraged to limit personal identifiers you enter into mobile applications (particularly your name, date of birth, address, place of employment, and other details that could allow someone to identify you) only to those that you wish to voluntarily share with others. These apps may send/receive information with other mobile apps, including social networking apps or websites (for example, Facebook). If you give permission for this, the terms of use for those apps/websites apply and you should read them carefully.

It is recommended that you run a current operating system (OS) on your device, review the privacy/security settings often, and restrict any unnecessary access. These applications may run in the background of your device. Mobile apps may have unanticipated impact on the operations of your

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device (e.g., battery drainage). If you do not have an unlimited data/text plan, you may incur additional charges. At the conclusion of the study, we will provide you instructions on how to remove the mobile apps from your device.

We are not asking you to make any health decisions based on the use of these mobile apps. You should discuss health decisions directly with your healthcare provider.

As with all technology, we ask you to wait until you are in a safe environment, use good judgment and follow prevailing laws. Do not perform study-related activities while you are driving.

WHAT ARE THE COSTS?
There will be no additional costs to you as a result of being in this study. The study sponsor (National Institutes of Health) has agreed to pay for services and procedures that are done solely for research purposes. However, you will be responsible for data charges on your smartphone during use of the Metricwire application for remote assessments.

WHAT ABOUT COMPENSATION?
The total amount of money that you could earn for all completed study activities is $1235. This includes:

- $30 for the screening session
- $50 for assessment/training session
- $30 for each weekly visit ($150 total)
- $50 for the final assessment visit
- $5/day for completing ≥ 4 remote prompted assessments and $50/week for completing 4 out of 5 remote assessments and the end of day survey each day (up to $255 total)
- $100 completion bonus for attending all study visits
- $600 bonus for using only study cigarettes as directed *or* $200 for truthful reporting of non-study cigarette use

Compensation for completing study procedures will be provided after each study visit and weekly for the remote assessment. If you start but do not finish the study, you will be compensated for the sessions that you do complete at the same rate.

Bonus payments will be paid after urine samples from weekly visits have been analyzed, which could take 1 to 2 months after study completion. We will randomly select 2 urine samples from weekly visits during study cigarette use to measure nicotine levels. If these samples confirm that you have only smoked study cigarettes, you will receive a bonus payment of $600. If these samples indicate you have smoked non-study cigarettes, but you truthfully reported this during your weekly visits, you will receive a bonus payment of $200. If you tell us that you have used only study cigarettes, but the nicotine levels in your urine samples are above the cutoff indicating non-study cigarette use, you will not be eligible for a bonus payment.

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Payment received as compensation for participation in research is considered taxable income to the research subject. If payment to an individual totals $600 or more in any one calendar year, Duke University is required to report this information to the Internal Revenue Service (IRS). Research subject payments to a non-employee of Duke University adding up to $600 or more during any calendar year will result in a 1099 (Miscellaneous Income) form being issued to the individual and a copy sent to the IRS.

WHAT ABOUT RESEARCH RELATED INJURIES?
Immediate necessary medical care is available at Duke University Medical Center in the event that you are injured as a result of your participation in this research study. However, there is no commitment by Duke University, Duke University Health System, Inc., or your Duke physicians to provide monetary compensation or free medical care to you in the event of a study-related injury.

For questions about the study or research-related injury, contact Dr. Maggie Sweitzer at 919-668-0094 during regular business hours or at [redacted] after hours and on weekends and holidays.

WHAT ABOUT MY RIGHTS TO DECLINE PARTICIPATION OR WITHDRAW FROM THE STUDY?
You may choose not to be in the study, or, if you agree to be in the study, you may withdraw from the study at any time. If you withdraw from the study, no new data about you will be collected for study purposes other than data needed to keep track of your withdrawal.

Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled, and will not affect your access to health care at Duke. If you do decide to withdraw, we ask that you contact Dr. Sweitzer in writing and let her know that you are withdrawing from the study. Her mailing address is Duke University Medical Center, 2608 Erwin Road, Suite 300, Durham, NC 27705. You may be asked to complete a brief telephone exit interview.

Nonparticipation or withdrawal from this study will not affect your job status if you are a Duke employee and will not affect your grades if you are a Duke student. We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

Your data may be stored and shared for future research without additional informed consent if identifiable private information, such as your name and medical record number, are removed. If your identifying information is removed from your samples or data, we will no longer be able to identify and destroy them.

We will tell you about any new information that may affect your health, welfare, or willingness to stay in this study. Dr. Sweitzer also reserves the right to remove you from the study at any time.

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A description of this clinical trial will be available on http://www.ClinicalTrials.gov. 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.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
For questions about the study or if you have problems, concerns or suggestions about the research, contact Dr. Maggie Sweitzer, Ph.D. at 919-668-0094 during regular business hours. For questions about a research related injury you should contact Dr. Paolo Mannelli at [redacted] during regular business hours and at [redacted] after hours and on weekends and holidays.

For questions about your rights as a research participant, or to discuss problems, concerns or suggestions related to the research, or to obtain information or offer input about the research, contact the Duke University Health System Institutional Review Board (IRB) Office at 919-668-5111.

STATEMENT OF CONSENT
"The purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have been told whom to contact if I have questions, to discuss problems, concerns, or suggestions related to the research, or to obtain information or offer input about the research. I have read this consent form and agree to be in this study, with the understanding that I may withdraw at any time. I have been told that I will be given a signed and dated copy of this consent form."

_____	_____	_____
Signature of Subject	Date	Time
_____	_____	_____
Signature of Person Obtaining Consent	Date	Time