Study Title: Effect of peripheral neuromodulation on vaginal blood flow

PI: Tim Bruns, PhD

Study ID: HUM00148746

NCT#: NCT04384172

Protocol Version IRB Approval Date: 10/7/2021

UNIVERSITY OF MICHIGAN
CONSENT TO BE PART OF A RESEARCH STUDY

1. KEY INFORMATION ABOUT THE RESEARCHERS AND THIS STUDY

Study title: Effect of peripheral neuromodulation on vaginal blood flow

Company or agency sponsoring the study: International Society for the Study of Women's Sexual Health

Names, degrees, and affiliations of the principal investigator:

Principal Investigator: Tim Bruns, Ph.D., Department of Biomedical Engineering, University of Michigan
Co-Investigator: Priyanka Gupta, M.D., Department of Urology, University of Michigan
Co-Investigator: Gianna Rodriguez, M.D., Department of Physical Medicine & Rehabilitation, University of Michigan
Study Coordinator: Mackenzie Moore, MPH, Department of Biomedical Engineering, University of Michigan

1.1 Key Study Information

You may be eligible to take part in a research study. This form contains important information that will help you decide whether to join the study. Take the time to carefully review this information. You should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others such as your family, friends, or other doctors about joining this study. If you decide to join the study, you will be asked to sign this form before you can start study-related activities. Before you do, be sure you understand what the research study is about.

A research study is different from the regular medical care you receive from your doctor. Research studies hope to make discoveries and learn new information about diseases and how to treat them. You should consider the reasons why you might want to join a research study or why it is not the best decision for you at this time.

Research studies do not always offer the possibility of treating your disease or condition. Research studies also have different kinds of risks and risk levels, depending on the type of the study. You may also need to think about other requirements for being in the study. For example, some studies require you to travel to scheduled visits at the study site in Ann Arbor or elsewhere. This may require you to arrange travel, change work schedules, find childcare, or make other plans. In your decision to participate in this study, consider all of these matters carefully.

This research is studying nerve stimulation to learn about its safety as a treatment for sexual dysfunction. We want to understand how women's bodies will react to the nerve stimulation. This study will compare changes in vaginal blood flow between two types of nerve stimulation. One type of stimulation will be applied near your ankle. The other type will be applied near your clitoris. Subjects in the study may have sexual dysfunction after a spinal cord injury, may have sexual dysfunction without a

spinal cord injury, or may not have sexual dysfunction. In this study we will see if the nerve stimulation has a different effect for each subject group. As part of this study, we will collect information about your sexual function, bladder and bowel function, quality of life, and some demographical information including age, menopausal status, and sexual activity. You will need to have internet access to complete these surveys.

There can be risks associated with joining any research study. The type of risk may impact whether you decide to join the study. For this study, some of these risks may include a loss of privacy, skin irritation, or discomfort. More detailed information will be provided later in this document.

The researchers do not expect that this study will offer any benefit to you now. Others in the future may benefit if either nerve stimulation is shown to help with sexual function. More information will be provided later in this document.

We expect the amount of time you will participate in the study will be about five hours for two visits to a clinic and surveys to take at home.

You can decide not to be in this study. Even if you decide to join the study now, you are free to leave at any time if you change your mind.

More information about this study continues in Section 2 of this document.

2. PURPOSE OF THIS STUDY

2.1 Study purpose:

The goal of this study is to learn if electrical stimulation of certain peripheral nerves can affect vaginal blood flow. We are studying two nerve locations, the tibial nerve near the ankle and the genital nerve near the clitoris. Electrical stimulation of each nerve can improve bladder function for people with bladder problems like incontinence. It is possible that stimulation at one or both nerve location can help women with genital arousal sexual dysfunction. We know that electrical stimulation at each nerve location can increase vaginal blood flow in animals. This study will investigate whether the same affect can happen in women, and may support further study into their use to treat female sexual dysfunction.

3. WHO MAY PARTICIPATE IN THE STUDY

Taking part in this study is completely **voluntary**. You do not have to participate if you do not want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

3.1 Who can take part in this study?

We are recruiting three groups of adult (18 years of age or older) cis-gender women (women's whose gender identity matches the sex that they were assigned at birth) who are not pregnant: women with spinal cord injury (within C6-T10 at least six months prior if classified as Grade A or Grade B on the American Spinal Injury Association Impairment Scale (AIS), and within C4-T10 at least six months prior if classified as Grade C on the AIS) and sexual dysfunction, women without spinal cord injury but with sexual dysfunction, and women with neither spinal cord injury nor sexual dysfunction. Sexual dysfunction will be determined by a short-form Female Sexual Function Index (FSFI) score below 19 and

a low lubrication score. Women without spinal cord injury should be sexually active at least once per month. Participants should not be participating in another research study that may affect this study. People with certain conditions, such as epilepsy, implanted defibrillators, and others, may not be able to participate. Additionally, participants who currently have or tested positive for COVID-19 in the last 14 days or is symptomatic for COVID-19 will be excluded from this study. Participants are expected to speak English and be capable and willing to follow study procedures.

3.2 How many people are expected to take part in this study?
Up to 40 women will take part in this study; 10 women without spinal cord injury and without sexual dysfunction, 10 women without spinal cord injury and with sexual dysfunction, 20 women with spinal cord injury.

4. INFORMATION ABOUT STUDY PARTICIPATION

4.1 What will happen to me in this study?
If you meet eligibility criteria, you will be asked if you would like to enroll in the study, if you enroll, you will complete surveys and have two study visits.

Study Visits

You will have two study visits, separated by one to five months. The study visits will be at the Michigan Clinical Research Unit at the University of Michigan Health System in Ann Arbor. Each visit will last about one hour to an hour and fifteen minutes. At each visit, pre-menopausal subjects will complete a urine pregnancy test.

At both visits, a sensor that measures blood flow will be placed in your vagina to a depth of about three inches. Heart rate and blood pressure monitors will be placed on your arm or hand during the visit. The sensor and monitors will be in place for about thirty minutes. Small electrodes will be placed on a part of your skin in order to stimulate a nerve that may be associated with sexual function. In one visit two electrodes will be placed on either side of one ankle and a small current of electricity will stimulate the posterior tibial nerve. In the other visit, two electrodes will be placed on either side of the clitoris and a small current of electricity will stimulate the dorsal genital nerve. The order of stimulation will be randomized between the two visits. This stimulation will be below the level at which you experience any discomfort and will last for 20 minutes. At several times during the visit you will be asked about how sexually aroused you feel, including before the sensors are placed and during and after stimulation. After the sensors and electrodes have been removed, you will be free to leave.

It is the policy of Michigan Medicine to provide a chaperone during sensitive examinations and/or procedures. Using chaperones is part of Michigan Medicine's commitment for safe and responsible care. A chaperone acts as a witness for you and the healthcare provider during sensitive exams and procedures. This study will have a chaperone present during both study visits. The Michigan Clinical Research Unit (MCRU) will be providing the chaperone service for this research study. Specifically, MCRU staff members Jennifer Berry, Robbie Johnson, Chelsea Merillat, Alanna Harris, Tina Huffman, Alison Wellington-Quinn or Alexis Nelson are all Michigan Medicine-approved chaperones and may be present during one or both study visits, should you request a chaperone present.

During the study visits, the chaperone will stand in a location where they are able to observe the procedure. You are able to decline having a chaperone present during the visits if you so choose.

Surveys and Diaries

At the start of the study, you will be asked to take surveys on your sexual and bladder function, quality of life, and demographics. These surveys will be completed online or by phone and will take approximately 30 minutes to complete. From two days before until two days after each study visit, you will be asked to complete a diary, which will ask about normal bathroom and sexual activities. These diaries will be completed online and will take approximately 5 minutes to complete.

4.2 How much of my time will be needed to take part in this study?

Subjects will have three main study parts. First, subjects will complete online surveys. These surveys may need one or two hours to complete. Second, subjects will visit a research clinic two times for the study. Each clinic visit will last about one hour to one hour and fifteen minutes. Third, during the two days before each clinic visit and the two days afterwards, subjects will complete brief diaries. These diaries will need less than fifteen minutes to complete.

4.3 When will my participation in the study be over?

We expect that study participation will be six months or less. In this time, you will complete the study surveys and have both of the test visits.

4.4 What will happen with my information and/or biospecimens used in this study?

Your biospecimens and collected information may be shared with the International Society for the Study of Women's Sexual Health

With appropriate permissions, your biospecimens and collected information may also be shared with other researchers, here, around the world, and with companies.

Your identifiable private information or identifiable biospecimens may be stripped of identifiers and used for future research studies or distributed to another researcher for future research studies without additional informed consent.

5. INFORMATION ABOUT STUDY RISKS AND BENEFITS

5.1 What risks will I face by taking part in the study? What will the researchers do to protect me against these risks?

The known or expected risks are:

- Your skin may be cleaned with a mild abrasive gel and an alcohol pad prior to placement of the electrodes. This procedure may cause some skin irritation.
- You may feel physical discomfort or pain due to the stimulation.
- Women with spinal cord injury could have an undesirable increase in blood pressure or other autonomic dysreflexia responses due to the stimulation.
- The intravaginal sensor could cause an infection if not properly cleaned prior to use.
- Women with a history of trauma may feel triggered by the research intervention.

Each of these risks is expected to be rare or uncommon (1-10% of patients). There are no known risks to a fetus, should you become pregnant after study participation.

The researchers will try to minimize these risks by:

- If skin cleaning causes discomfort it will be stopped and not performed in the second visit.
- The stimulation will be kept at a low level which usually does not cause discomfort. The researcher will talk with you as the stimulation is turned on, and will reduce or stop the stimulation if you feel any discomfort or pain. You will be instructed on how to turn the unit off yourself in case the stimulation becomes uncomfortable.
- Women recruited to participate in this study who have spinal cord injuries at a level within T6-T10 should have a low risk of autonomic dysreflexia, a syndrome in which there is a sudden onset of excessively high blood pressure, based on the study inclusion criteria. Women recruited to participate in this study who have spinal cord injuries at a level within C4-T6 are at an increased risk of autonomic dysreflexia. The clinical staff will monitor your blood pressure and heart rate before, during, and after stimulation, and will stop stimulation if you show undesirable symptoms. The clinical staff may require you to stay longer or seek further medical care if symptoms do not stop. Nitropaste will be available for use if autonomic dysreflexia occurs.
- Vaginal sensors will be properly sterilized between each session and placement of the sensor will be guided or performed by a clinical staff who is trained in sterile procedures such as clean intermittent catheterization.
- If psychological trauma is raised, patients will be referred to our sexual health therapists for treatment.

Additionally, there may be a risk of loss to confidentiality or privacy. See Section 9 of this document for more information on how the study team will protect your confidentiality and privacy.

As with any research study, there may be additional risks that are unknown or unexpected.

5.2 What happens if I get hurt, become sick, or have other problems as a result of this research?
The researchers have taken steps to minimize the risks of this study. Even so, you may still have problems or side effects, even when the researchers are careful to avoid them. Please tell the researchers listed in Section 10 about any injuries, side effects, or other problems that you have during this study. You should also tell your regular doctors. If problems occur during either visit, first aid will be provided, if needed. If problems occur before the second visit, you will be withdrawn from the study.

5.3 If I take part in this study, can I also participate in other studies?
Being in more than one research study at the same time, or even at different times, may increase the risks to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the researchers involved in each study.

5.4 How could I benefit if I take part in this study? How could others benefit?
You may not receive any personal benefits from being in this study. It is possible the stimulation session may give you short-term improvement in sexual function. Others may benefit from the knowledge gained from this study. Researchers may use the knowledge gained in this study to design treatments for sexual dysfunction.

5.5 Will the researchers tell me if they learn of new information that could change my willingness to stay in this study?
Yes, the researchers will tell you if they learn of important new information that may change your willingness to stay in this study. If new information is provided to you after you have joined the study, it is possible that you may be asked to sign a new consent form that includes the new information.

6. ALTERNATIVES TO PARTICIPATING IN THE STUDY

6.1 If I decide not to take part in this study, what other options do I have?
This is a voluntary study to help researchers understand how the body may respond to a potential treatment for sexual dysfunction. As the stimulation in this study is not being given as treatment, this is a non-therapeutic study, and there is not an alternative treatment to it. If you have sexual dysfunction, you can seek treatment from a Gynecologist or Sexual Health provider.

7. ENDING THE STUDY

7.1 If I want to stop participating in the study, what should I do?
You are free to leave the study at any time. If you leave the study before it is finished, there will be no penalty to you. You will not lose any benefits to which you may otherwise be entitled. If you choose to tell the researchers why you are leaving the study, your reasons for leaving may be kept as part of the study record. If you decide to leave the study before it is finished, please tell one of the persons listed in Section 10 "Contact Information".

7.2 Could there be any harm to me if I decide to leave the study before it is finished?
There is no harm that may come to you if you decide to leave the study before it is finished.

7.3 Could the researchers take me out of the study even if I want to continue to participate?
Yes. There are many reasons why the researchers may need to end your participation in the study. Some examples are:

- The researcher believes that it is not in your best interest to stay in the study.
- You become ineligible to participate.
- Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- You do not follow instructions from the researchers.
- The study is suspended or canceled.

8. FINANCIAL INFORMATION

8.1 Who will pay for the costs of the study? Will I or my health plan be billed for any costs of the study?
The study will pay for research-related items or services that are provided only because you are in the study. If you are not sure what these are, see Section 4.1 above or ask the researchers for a list. If you get a bill you think is wrong, call the researchers' number listed in section 10.1.

You or your health plan will pay for all the things you would have paid for even if you were not in the study, like:

- Health care given during the study as part of your regular care

- Monitoring for side effects or other problems
- Deductibles or co-pays for these items or services.

If you do not have a health plan, or if you think your health plan may not cover these costs during the study, please talk to the researchers listed in Section 10 below or call your health plan's medical reviewer. By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

The study team has given you instructions about this research study. It is important that you follow these instructions carefully. If you get sick, have a medical complication, or are injured as a result of your being in the study, call Dr. Priyanka Gupta immediately, at 734-836-7030. The doctor will either treat you or send you to another doctor for treatment. You will get free medical care at the UMHS for any hospitalization or ER visits directly caused by the study procedure. The UMHS and the study doctor are responsible for determining whether your condition was the result of your participation in the study. The UMHS will pay for your treatment only if the need for treatment has been caused by the study procedure. This means that you or your health plan must pay for any treatment that is part of your usual medical care or that is related to a medical condition you had before participating in the study.

8.2 Will I be paid or given anything for taking part in this study?
You will be compensated $100 for full participation in the study. This will be separated into two separate time points throughout the study:

- Completion of the first study visit and the before and after visit diaries: $50
- Completion of the second study visit and the before and after visit diaries: $50

We will reimburse parking expenses for each study visit at study facilities, if needed.

8.3 Who could profit or financially benefit from the study results?
No person or organization involved in the conduct of this study has a financial interest in the outcome of the study. Research can lead to new discoveries, such as new tests, drugs, or devices. Researchers, their organizations, and other entities, including companies, may potentially benefit from the use of the data or discoveries. You will not have rights to these discoveries or any proceeds from them.

9. CONFIDENTIALITY OF SUBJECT RECORDS AND AUTHORIZATION TO RELEASE YOUR PROTECTED HEALTH INFORMATION

The information below describes how the confidentiality of your research records will be protected in this study, and any sub-studies described in this document.

9.1 How will the researchers protect my information?
Research records are stored in a secure, locked location and will not be made a part of your regular medical record. Data will be kept in a separate research file that does not include names, registration numbers, or other information that is likely to allow someone other than the researchers to link the information to you. Identifiable data (such as the screening and consent forms) are stored separately. If the researcher orders any tests, the order and results may become part of your regular medical record.

If you tell us or we learn something that makes us believe that you or others have been or may be harmed, we may be required to report that information to the appropriate agencies.

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

9.2 What protected health information (PHI) about me could be seen by the researchers or by other people? Why? Who might see it?

Signing this form gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study.

Medical information and billing records are protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA). This type of information is called protected health information (PHI). PHI about you may be obtained from any hospital, doctor, and other health care provider involved in your care, including:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)
- All records relating to your condition, if applicable, the treatment you have received, and your response to the treatment
- Billing information
- Demographic information
- Personal identifiers
- Other information

There are many reasons why information about you may be used or seen by the researchers or others during or after this study. Examples include:

- The researchers may need the information to make sure you can take part in the study.
- The researchers may need the information to check your test results or look for side effects.
- University, Food and Drug Administration (FDA) and/or other government officials, auditors, and/or the IRB may need the information to make sure that the study is done in a safe and proper manner.
- Study sponsors or funders, or safety monitors or committees, may need the information to:
    - Make sure the study is done safely and properly
    - Learn more about side effects
    - Analyze the results of the study
- Insurance companies or other organizations may need the information in order to pay your medical bills or other costs of your participation in the study.
- The researchers may need to use the information to create a databank of information about your condition or its treatment, if relevant.
- If you receive any payments for taking part in this study, the University of Michigan accounting department may need your name, address, Social Security number, payment amount, and related information for tax reporting purposes.
- Federal or State law may require the study team to give information to government agencies. For example, to prevent harm to you or others, or for public health reasons.

The results of this study could be published in an article or presented at scientific meetings, but would not include any information that would let others know who you are.

9.3 What happens to information about me after the study is over or if I cancel my permission to use my PHI?

As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission or the study is over.

Examples of reasons for this include:

- To avoid losing study results that have already included your information
- To provide limited information for research, education, or other activities. (This information would not include your name, social security number, or anything else that could let others know who you are.)
- To help University and government officials make sure that the study was conducted properly

As long as your information is kept within the University of Michigan Health System, it is protected by the Health System's privacy policies. For more information about these policies, ask for a copy of the University of Michigan "Notice of Privacy Practices". This information is also available on the web at http://www.uofmhealth.org/patient+and+visitor+guide/hipaa. Note that once your information has been shared with others as described under Question 9.2, it may no longer be protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

9.4 When does my permission to use my PHI expire?

Your permission expires at the end of the study, unless you cancel it sooner. You may cancel your permission at any time by writing to the researchers listed in Section 10 "Contact Information" (below). If you withdraw your permission, you may no longer be eligible to participate in this study.

10. CONTACT INFORMATION

10.1 Who can I contact about this study?

Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Talk about study-related costs to you or your health plan
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator: Tim Bruns, Ph.D.
Mailing Address:
Biointerfaces Bruns Group
2800 Plymouth Road. NCRC B10-A169
Ann Arbor, MI 48109
Telephone: 734-647-8727

Co-Investigator: Priyanka Gupta, M.D.
Mailing Address:
Taubman Center, Floor 2 Reception C
1500 E Medical Center Dr. SPC 5330
Ann Arbor, MI 48109
Telephone: 734-836-7030

Study Coordinator: Mackenzie Moore, MPH
Mailing Address:
Biointerfaces Bruns Group
2800 Plymouth Road. NCRC B14-186
Ann Arbor, MI 48109
Telephone: 734-647-8568

You may also express a question or concern about a study by contacting the Institutional Review Board listed below:

University of Michigan Medical School Institutional Review Board (IRBMED)
2800 Plymouth Road
Building 520, Room 3214
Ann Arbor, MI 48109-2800
Telephone: 734-763-4768
Fax: 734-763-1234
e-mail: irbmed@umich.edu

If you are concerned about a possible violation of your privacy or concerned about a study you may contact the University of Michigan Health System Compliance Help Line at 1-866-990-0111.
When you call or write about a concern, please provide as much information as possible, including the name of the researcher, the IRBMED number (at the top of this form), and details about the problem. This will help University officials to look into your concern. When reporting a concern, you do not have to give your name unless you want to.

11. RECORD OF INFORMATION PROVIDED

11.1 What documents will be given to me?

Your signature in the next section means that you have received copies of all of the following documents:

- This "Consent to be Part of a Research Study" document. (*Note: In addition to the copy you receive, copies of this document will be stored in a separate confidential research file and may be entered into your regular University of Michigan medical record.)*
- Other (specify): Study diaries to complete before and after each study visit

12. SIGNATURES

Sig-A

Consent/Assent to Participate in the Research Study

I understand the information printed on this form. I have discussed this study, its risks and potential benefits, and my other choices with _____. My questions so far have been answered. I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 10 (above). I understand that I will receive a copy of this form at the time I sign it and later upon request. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

Print Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Sig-D

Consent/Assent to Collect for Unspecified Future Research

This project involves the option to allow the study team to keep your identifiable specimens/data for use in future research. I understand that it is my choice whether or not to allow future use of my specimens. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

_____ Yes, I agree to let the study team keep my specimens for future research.

_____ No, I do not agree to let the study team keep my specimens for future research.

Print Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Sig-G

Principal Investigator or Designee

I have provided this participant and/or her legally authorized representative(s) with information about this study that I believe to be accurate and complete. The participant and/or her legally authorized representative(s) indicated that she understands the nature of the study, including risks and benefits of participating.

Printed Legal Name: _____

Title: _____

Signature: _____

Date of Signature (mm/dd/yy): _____