Study Title: Effect of peripheral neuromodulation on vaginal blood flow

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University of Michigan IRBMED

Protocol HUM00148746

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1. Study Summary

1.1 Background and Significance

Female sexual health is an important determinant in quality of life, contributing to both increased meaning in life and general well-being [1]. Unfortunately, approximately 41% of women suffer from female sexual dysfunction (FSD) [2]. There are several domains that contribute to sexual dysfunction. Difficulty with genital arousal can arise from low activity in the nerves or blood vessels of the genitals. Problems with low sexual interest can stem from hyperactivity in the brain. Some women suffer from FSD due to neurological conditions such as spinal cord injury (SCI). After injury, neural connections between central sexual function neural circuits (e.g. desire) and peripheral sexual functions (e.g. genital arousal) are interrupted. Although not a factor in mortality, sexual function remains a critical component of quality of life after SCI and is frequently reported as a high priority for restoration [3], [4].

A challenge in studying sexual function in women is the complexity of sexual arousal, which includes both cognitive desire and genital arousal components [5]. Overall female sexual function is not well understood, which contributes to the lack of good treatment options for dysfunction, regardless of type. Pharmaceuticals such as sildenafil (viagra) have occasionally been reported to improve genital arousal [6] but results are inconsistent and frequently present with mild to moderate side-effects [7]. There is a need for an effective treatment for women who have genital arousal deficiencies without concurrent side-effects. The ultimate goal of this research is to provide improvement in genital sexual arousal for women FSD due to either neurogenic (i.e. SCI) or non-neurogenic causes.

One treatment avenue is the use of electrical stimulation on targeted nervous system pathways. Sacral neuromodulation (SNM) and percutaneous tibial nerve stimulation (PTNS) are common third-line treatments for irregularities in pelvic organ function, such as bladder incontinence, and have been used for decades [8]. Some patients undergoing SNM or PTNS to improve bladder function have also reported an improvement in their sexual health as an additional benefit [9]. This is not entirely unexpected, as organs of the pelvic floor share common nerve pathways and spinal circuits [10]. For example, the sacral root targeted by SNM gives rise to the pudendal nerve, of which a distal branch is the genital nerve. Each has been a target for electrical stimulation to treat bladder problems and may also be a treatment option for FSD. This neuro-functional overlap gives reason to believe that the nerves that innervate the organs associated with genital arousal and that have been previously targeted in bladder neuromodulatory studies are a viable treatment option for women with genital arousal deficiencies.

In order to explore the potential for electrical stimulation to modulate genital arousal, our lab has started a research focus of examining peripheral nerve stimulation to address female sexual dysfunction, targeting pudendal and tibial nerve pathways [11]–[14]. In animal studies we have shown that tibial and genital nerve stimulation can lead to increases in vaginal blood flow [11], [12], which is an indicator of sexual arousal [15]. A human subjects study from our group (HUM00101713) focused on non-neurogenic subjects with FSD and showed that stimulating the posterior tibial and dorsal genital nerves repeatedly across twelve weekly sessions are feasible approaches for improving sexual function based on improvements in clinically validated surveys [13]. The mechanisms that underlie this clinical effect, such as whether the applied nerve stimulation increases vaginal blood flow in women, are still largely unknown. This study aims to address this gap, to study the short-term effect of stimulation on vaginal blood flow. To potentially amplify any stimulation effects, this study will incorporate the use of sexually explicit films, a method that is standard in sexual function studies [16]-[18]. The inclusion of healthy

women and non-neurogenic women with FSD will also provide information about the underlying neural circuitry, based on whether either stimulation approach has better efficacy in spinal intact or damaged participants. While genital nerve stimulation is generally successful at improving bladder function in individuals with SCI, tibial nerve stimulation has had mixed results. These findings by other researchers suggest potential outcomes for our different study groups.

1.2 Objective

The overall purpose of this research is to improve sexual function in women with sexual dysfunction. The goal of this study is to see if either of two nerve stimulation interventions cause a short-term change in vaginal blood flow. The effect of this intervention will be compared between women who have neurogenic (spinal cord injury) or non-neurogenic dysfunction and healthy women, to reveal mechanisms underlying neural control over vaginal blood flow.

1.3 Specific Aims

The aims of this study are to:

- Aim 1: Compare the effect of skin-surface genital nerve stimulation and tibial nerve stimulation on vaginal blood flow in women with spinal cord injury caused neurogenic sexual dysfunction.
- Aim 2: Compare the effect of skin-surface genital nerve stimulation and tibial nerve stimulation on vaginal blood flow in women with non-neurogenic female sexual dysfunction.
- Aim 3: Compare the effect of skin-surface genital nerve stimulation and tibial nerve stimulation on vaginal blood flow in neurologically-intact women without sexual dysfunction.

1.4 Primary Outcomes

The primary outcome measure in this study is the maximum change in VPA from the average baseline value for each stimulation location across each stimulation participant group. To determine if participant type, stimulation location, and stimulation interval (i.e. timing within stimulation duration) has an effect on VPA, an ANOVA will be performed.

1.5 Secondary Outcomes

The secondary outcome measures will be the change in heart rate, blood pressure, and subjective arousal from baseline for each stimulation location and participant group.

1.6 Investigative team

Dr. Tim Bruns is an Associate Professor in the Biomedical Engineering Department. He leads a research lab that develops interfaces with the peripheral nervous system to restore function. He is an expert on the use of electrical stimulation to activate spinal circuits to control pelvic organs. During his doctoral and postdoctoral training, Dr. Bruns participated in human subjects research studies with spinal cord injured subjects and individuals undergoing spine surgery to examine nerve stimulation approaches to control bladder function and develop new nerve electrodes. At Michigan, Dr. Bruns was PI on HUM00101713, which studied the use of skin-surface electrical stimulation to improve sexual function in women with sexual dysfunction.

Dr. Priyanka Gupta is a Urologic Surgeon specializing in the diagnosis and management of voiding dysfunction and pelvic floor disorders. She completed a fellowship in Female Pelvic Medicine and Reconstructive Surgery at Beaumont Health in Royal Oak, Michigan. During her fellowship she gained additional expertise in the surgical management of pelvic organ prolapse, urinary incontinence, and the use of neuromodulation and robotic technology. Dr. Gupta's clinical practice includes both the surgical and non-operative management of pelvic organ

prolapse, incontinence, pelvic pain, voiding dysfunction, and pelvic floor disorders. Dr. Gupta's research interests include outcomes of pelvic organ prolapse treatments and neuromodulation, and surgical education in the developing world.

Dr. Gianna Rodriguez is an Associate Professor of Physical Medicine and Rehabilitation. Her clinical practice primarily revolves around evaluation and management of men and women with spinal cord injuries (SCI) and disorders. Dr. Rodriguez has a particular interest in pelvic organ function, studying bladder and bowel care management practices by patients in this community and has a strong history of working with urologists at the University of Michigan.

2. Research Procedures

We will conduct the proposed study in accordance with the requirements of the University of Michigan Medical School Institutional Review Board (IRBMED). All study visits will be conducted at University of Michigan Health System locations.

2.1 Pre-study surveys

Prior to the first visit, participants will complete five clinically validated surveys:

1. The American Urological Association Symptom Index (AUASI) bladder symptom index [19]
2. The Female Sexual Function Index (FSFI) [20]
3. Fecal Incontinence Severity Index (FISI) [21]
4. Patient Assessment of Constipation-Symptoms (PAC-SYM) [22]
5. The short-form (SF-36) quality of life survey [23], [24]

Surveys will be completed over the phone or online in REDCap, a standard clinical tool for survey data collection [25]. Each survey is included in section 29.1.

2.2 Study visits 1 & 2

The same steps will be followed for all three Aims. Participants will have two study visits. The interval between visits will be at least one month but not more than five months.
On each study day, subjects will complete a urine pregnancy test. Next, subjects will recline in a comfortable position on an elevated table, with pillows and blankets provided if desired. An MCRU staff member will be available to provide assistance, if needed, in addition to one or more clinical research team members. A vaginal plethysmography transducer (Biopac TSD204) will be inserted about 3 inches into the patient's vagina by a clinical staff member or by the patient with clinician supervision. The transducer measures vaginal pulse amplitude (VPA), the standard clinical technique for assessing genital sexual arousal in women [5], [26]–[28]. No energy is transmitted from the TSD204 to the participant. A heart rate monitor (e.g. electrocardiogram or pulse oximetry) and blood pressure monitor will be placed on the participant's arm, hand, or chest (as is appropriate per monitor) to monitor off-target autonomic responses.

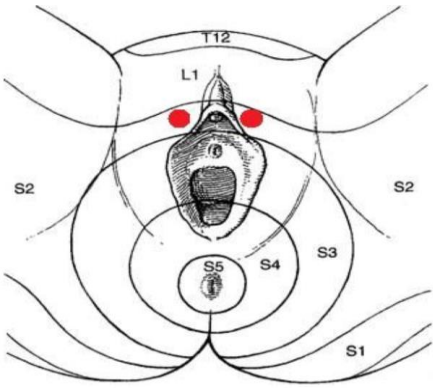

Figure 1. Electrode locations (red dots) for genital nerve stimulation, on either side of the clitoris.

On the first study day, one of the two stimulation approaches will be randomly selected and prepared. For dorsal genital nerve stimulation, two circular 1.25-inch diameter transcutaneous electrical stimulation (TENS)

electrodes (ValuTrode Fabric CF3200 or equivalent) will be placed on either lateral side of the clitoris (Figure 1). For tibial nerve stimulation, the two electrodes will be placed just above the medial malleolus and the ipsilateral calcaneus on one leg (Figure 2). The placement of TENS device will be performed by clinical study team members, specifically Dr. Priyanka Gupta, Dr. Gianna Rodriguez, or other clinical practitioners or fellows who are study team members. Each clinical study team member is a practicing MD physician trained in the use of neuromodulation including technology such as this. The conductivity of the electrodes may be tested with an impedance meter (Digitimer D175), which is connected to an electrode set and uses very low, imperceptible current levels. If the meter indicates poor conductivity, the electrodes may be repositioned.

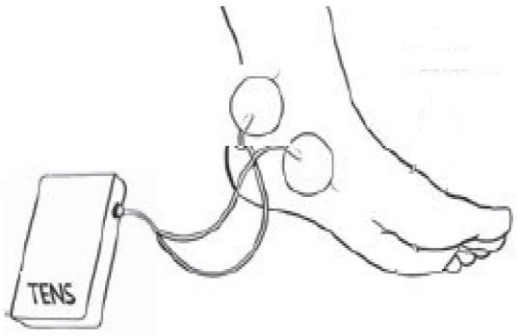

Figure 2. Electrode locations (white circles) for tibial nerve stimulation near the ankle.

Prior to starting stimulation with a TENS device (Empi Select, or similar), the stimulation amplitude will be determined. The current will be increased until the participant expresses discomfort and then reduced to a comfortable level, or a maximum level of 60 mA is reached. During stimulation, the set stimulation amplitude will be applied at a frequency of 20 Hz, which is standard for PTNS and the frequency we used in our previous human subjects' study (HUM00101713).

Participants will be shown a neutral video (nature film excerpt) and an erotic film clip featuring sexually explicit material at different intervals of the testing period. The use of videos in this manner is a standard method in studies of sexual function [16]–[18], and may help enhance an arousal response. Two videos will be loaded on a laptop computer in a fixed order that will not require patient intervention. Participants will choose a video based on their preference in viewing either two women or a woman and a man engaging in sexual activities.

As shown in Figure 4, during the testing period participants will first view a 5-minute neutral film depicting nature scenes to allow blood flow levels to stabilize. This will be followed by a 10-minute period while the subject watches an erotic film clip for assessment of arousal responses without electrical stimulation. The erotic film clip depicts sexually explicit material of two consenting adults engaging in sexual activities including manual and oral stimulation of breasts and genitals as well as penile-vaginal intercourse depending on the film chosen. A 10-minute clip of the same neutral film will follow, to allow blood flow levels to return to baseline. Five minutes into this film, electrical stimulation will be resumed at the previously determined amplitude. Finally, the subject will view another 10-minute erotic film clip depicting similar sexually explicit material as the first while electrical stimulation remains on as the last sequence in the testing.

At the beginning of the VPA recording sequence, in between each video transition, and at the end of the VPA recording sequence (a total of 5 times), participants will view a 15-30-second screen prompt asking them to record their agreement with the statement, "I feel sexually aroused (e.g. sexually excited, turned on) right now," according to a 5-point Likert scale: (1) *strongly disagree*, (2) *disagree*, (3) *neutral*, (4) *agree*, and (5) *strongly agree*. At the end of each session participants will be asked their general opinions of that stimulation session, whether it seemed to elicit any genital arousal responses such as lubrication, warmth, tingling, or any

sensations they would characterize as pleasurable, and whether they would consider further use of it.

At the second study day, stimulation using the same steps will be performed at the other location.

2.3 Pelvic function daily diaries

To look for off-target or carry-over stimulation effects, participants will be asked to complete a daily bladder, bowel, and sexual function diary from two days before until two days after a session, to provide objective measures across several parameters (e.g. incontinence episodes, regularity). The full diary is in section 44.1. Figure 3 shows the daily questions. Surveys will be completed in REDCap or over the phone. Spinal cord injured patients will also have a question asking if they had an autonomic dysreflexia event.

Bladder Function	
Did you have any leakage or incontinence?	• None • Some • A lot
Did you need to use the bathroom at night?	• No • Once • Multiple times
How did your bladder function compare to the prior day?	• Worse • The same • Better
Bowel Function	
Did you have a regular bowel event?	• No • Almost, or with help • Yes
Did you have fecal incontinence?	• No • Once • Multiple times
How did your bowel function compare to the prior day?	• Worse • The same • Better
Sexual Function	
Were you sexually active with a partner or by yourself?	• No • Self • Partner
If active, did you feel genital arousal or lubrication?	• No • Some • Yes
If active, did you have an orgasm?	• No • Yes
Changes in Pelvic Sensation	
Did you experience any atypical sensations from your pelvic region?	• No • Yes
If yes, please elaborate:	

Figure 3. Pelvic function daily diary questions

2.4 Patient timeline

Research Activity timetable summary:

1. Consent
2. Pre-session surveys
3. Study visit 1:
    - Days 1 & 2: At-home diary
    - Day 3: Test session and diary
    - Days 4 & 5: At-home diary
4. Interval of one to five months
5. Study visit 2:
    - Days 1 & 2: At-home diary.
    - Day 3: Test session and diary
    - Days 4 & 5: At-home diary

Figure 4 provides a visual summary of the timeline for each study participant.

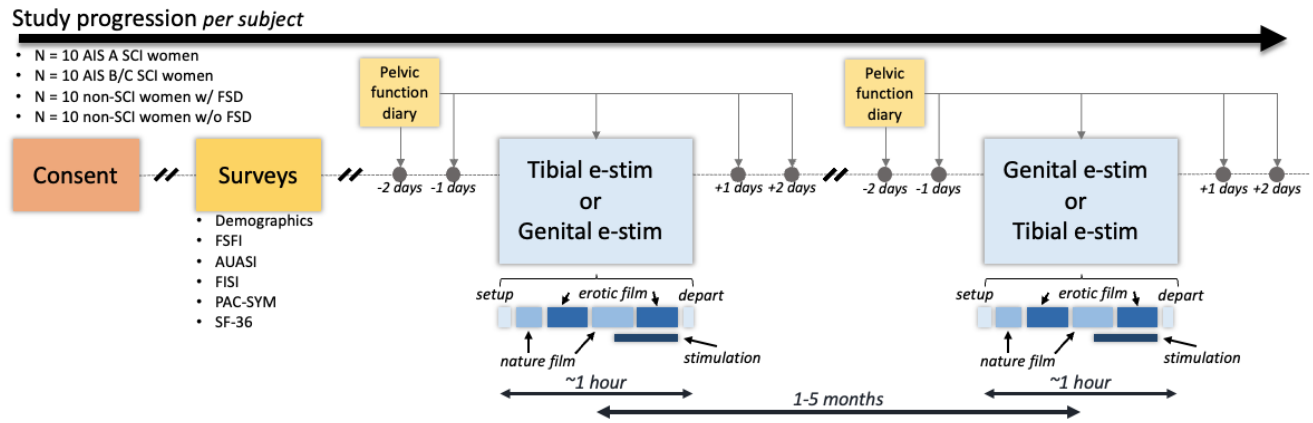

Figure 4. Timeline summary for each participant.

3. Study Statistics and Data Analysis Plan

3.1 Sample size

The target population size (N=40) is based on intended recruitment of 40 women; 10 normal women (e.g. without SCI nor FSD), 10 non-SCI women with FSD, and 20 women with SCI. Efforts will be made to recruit equal numbers between AIS A SCI and AIS B-C SCI participants, but it may be challenging to get exactly 10 in each SCI group. The AIS A SCI and AIS B-C SCI is based on the International Standards for Neurological Classification of Spinal Cord Injury. AIS A SCI refers to complete, no sensory or motor function SCI, while AIS B-C SCI refers to incomplete SCI (e.g. sensory but not motor function is preserved). This is a pilot study with no comparable studies for identifying an effect size and performing a power analysis. If we determine that a larger population size is needed for any participant groups, based on preliminary data analyses, then the target group size will be increased.

3.2 Data Analysis plan

VPA will undergo optimization, filtration, and a spectral analysis as in [11], [12], [15]. The change in VPA from the average baseline value will be determine for each stimulation at four-minute intervals, during which stimulation is paused for ten seconds. Although VPA will be recorded continuously, the genital nerve stimulation may cause a motion artifact and so equal pauses in stimuli will be used in each interval for both stimulation approaches. We may eliminate this pause if data analysis indicates that there are no artifacts or that filtration and spectral analysis eliminates artifacts. Similar calculations may be done for the heart rate and blood pressure. An ANOVA will be performed to determine whether participant type, stimulation location, and stimulation interval (i.e. timing within stimulation duration) has an effect on VPA. Wilcoxon signed rank tests will be used to test for differences within the groups. Similarly, changes in cardiovascular parameters will be assessed, to see if general autonomic responses are triggered with either stimulation location or patient group. We will also look for correlations between the pre-session survey scores (e.g. FSFI total score), patient demographics (e.g. age,

BMI), and changes in items (e.g. decrease in incontinence events) with the maximal VPA responses with a regression analysis.

4. Study Recruitment

This study addresses a potentially sensitive topic. During the recruitment and consenting processes, all study activities will be carefully explained with particular attention to matters of privacy and confidentiality. Many women with spinal cord injury (SCI) have had negative healthcare experiences with respect to reproductive health. Alternatively, grateful patients can feel compelled to participate out of a sense of loyalty. As such, for recruitment and consenting processes, we will emphasize that participation is entirely voluntary, and refusal or withdrawal will have no effect on any care they receive.

SCI participants will primarily be recruited through direct interactions with clinicians on the study team, Drs. Rodriguez and Gupta, in their clinical practice. We will also seek referrals from clinical colleagues who work with SCI women. Additionally, colleagues of Dr. Gupta and Dr. Rodriguez may distribute or post the study flyer in their urogynecology or SCI clinics. Women with female sexual dysfunction (FSD) may also be recruited from urogynecology or sexual health clinics run by a member of the study team or a colleague. If this occurs, these colleagues will have a general understanding of the study and will refer any patient questions to study investigators or the study coordinator. We will place flyers in relevant Physical Medicine & Rehabilitation, Urology, and Obstetrics & Gynecology clinics. We will also advertise the study on an online University of Michigan health research portal (umhealthresearch.org). Additionally, we will place flyers at several clinics outside of the UM healthcare system in Southeast Michigan, specifically, Detroit Medical Center/Wayne State, PM& R/Novi Rehab Institute of Michigan) and John D. Dingell VA Medical Center. Furthermore, this study will recruit via social media platforms (Facebook and Instagram). The study will be advertised via these social media platforms and direct interested people to the umhealthresearch.org website.

Non-SCI participants will be primarily recruited through the online health portal and we will place flyers in Obstetrics & Gynecology clinics, particularly Dr. Gupta's clinics.

5. Study Population

5.1 Inclusion Criteria

- All participants will need internet access to complete the initial surveys and the diaries.

Non-dysfunction participants
Inclusion criteria:

- Adult (over 18 years old) cis-gender female
- Neurologically stable
- Sexually active at least once per month
- Able to understand consent and communicate effectively with research team

Non-SCI dysfunction participants
Inclusion criteria:

- Adult (over 18 years old) cis-gender female
- Neurologically stable
- Sexually active at least once per month

- Sexual dysfunction, per short-form FSFI score below 19
- Lubrication difficulties, per short-form FSFI lubrication subdomain score below or equal to 3
- Able to understand consent and communicate effectively with research team

Spinal cord injured participants
Inclusion criteria:

- Adult (over 18 years old) cis-gender women
- Clinically diagnosed spinal cord injury (AIS A-B) at vertebral level within C6-T10 at least six months prior or clinically diagnosed spinal cord injury (AIS C) at vertebral level within C4-T10 at least six months prior
- Nominally sexually active, but at minimum interest in sexual pleasure even if fully self-induced
- Sexual dysfunction, per short-form FSFI score below 19
- Able to understand consent and communicate effectively with research team

5.2 Exclusion Criteria

Non-dysfunction participants
Exclusion criteria:

- Male
- Pregnancy or planning to become pregnant during study period
- Sexual dysfunction, per short-form FSFI score below 19
- Lubrication difficulties, per short-form FSFI lubrication subdomain score below or equal to 4, or per investigator's discretion.
- Clinically diagnosed bladder dysfunction, pelvic pain, or other pelvic organ symptoms
- Suspected or diagnosed epilepsy
- Active infection or active pressure sores in the perineal region
- Implanted pacemaker or defibrillator
- Currently has or tested positive in the last 14 days for COVID-19 or is symptomatic for COVID-19.

Non-SCI dysfunction participants
Exclusion criteria:

- Male
- Pregnancy or planning to become pregnant during study period
- Clinically diagnosed bladder dysfunction, pelvic pain, or other pelvic organ symptoms
- Suspected or diagnosed epilepsy
- Active infection or active pressure sores in the perineal region
- Implanted pacemaker or defibrillator
- Currently has or tested positive in the last 14 days for COVID-19 or is symptomatic for COVID-19.

Spinal cord injured participants
Exclusion criteria:

- Male

- Spinal cord injury at or above C5 level (C1-C5) if AIS A or B, or spinal cord injury at or above C3 level (C1-C3) if AIS C
- Spinal cord injury below T10 vertebral level or reflexes not preserved
- Acute worsening in motor or sensory function in the last month
- Suspected or diagnosed epilepsy
- Pregnancy or planning to become pregnant during study period
- Active infection or active pressure sores in the perineal region
- Implanted pacemaker or defibrillator
- Currently has or tested positive in the last 14 days for COVID-19 or is symptomatic for COVID-19.

6. Study Sites

All research activities will be performed at University of Michigan Health System locations, also known as Michigan Medicine. The two electoral stimulation sessions will be performed at MCRU sites at Domino's Farms or the Cardiovascular Center in Ann Arbor. These sites are normal clinical sites for studies of this nature. All clinical team members have full clinical privileges at both locations and see patients at both locations. All members of the research team hold primary appoints within the University of Michigan Medical School.

7. Informed Consent

We will explain the study verbally and in writing, and we will provide the informed consent form to the participant for review before signing. We will inform participants that the purpose of the study is to learn if electrical stimulation of certain peripheral nerves can affect vaginal blood flow. We will also explain to each participant that there will be no expected benefit to them by participating in this research study. However, it is possible (although not anticipated) that during the stimulation session participants may experience short-term improvement in sexual function. Additionally, we will also explain that the knowledge gained from this research may be beneficial for others, society, and/or science.

The research team will adopt an optional electronic informed consent procedure using SignNow. This option will be our preferred method for obtaining consent. Once an interested participant is identified, the study coordinator who will reach out to the participant over the telephone to discuss the study and either obtain consent or schedule a time call the participant after they have had a time to review the consent form. In the instance a potential participant does not have access to the internet or is not inclined to use the internet, research staff will revert back to using the standard procedure for obtaining consent on paper during the first study visit. We will recruit all potential and eligible subjects who can speak, read, and understand English.

8. Waiver of Informed Consent

We are seeking a waiver of informed consent as there are a set of surveys that get completed at the very beginning of the study and daily diaries for the two days prior to the first study visit. Subjects will be able to complete their surveys and diaries at home and at their leisure. We prefer that they are completed before the test session in order to ensure that their answers won't be affected by the treatment and so that the time spent by the participant at that session is not too long. In order to do this expeditiously, it would be simplest to send them the surveys and diaries if they agree to take part during their initial recruitment call. This means, though, that a participant could be completing surveys and diaries before formally signing the consent form if

they are not being recruited during a visit at a clinic with a study team member or if they are not doing electronic consent.

9. Confidentiality of Data

Proper, standard procedures will be followed to protect participant identities. Each subject will be assigned an identification number. Only this number will be used to identify subjects in any individual tabulation. The surveys that the patients are required to fill out as part of the study will also only use this identification number as the piece of identifying information. These surveys will only be administered and collected by the study coordinator or other research team staff. The study coordinator will have access to the patient information and code key. The study coordinator's office will have a locked door. Paper research records will be stored in a locked cabinet in the study coordinator's office. No patient-identifying information will be shared outside the research team.

Only group data is expected to be published. If individual subject data is published, then no identifying information will be included. Study files will also be maintained in a secured location. Access to computerized data will be restricted to IRB approved study personnel and password authorization will be enforced. Data collection will be limited to the study investigators and research staff. All study personnel who have access to the data will be educated regarding the need to protect confidentiality and the procedure to be followed to ensure such protection. All staff will also be required to sign a standard medical record confidentiality agreement.

10. Data Safety and Monitoring

10.1 Data Safety and Monitoring Board

All research personnel involved in this study will have completed training in the protection of human research participants. A full Data and Safety Monitoring Board will not be used for this study as it is a small study. Once data collection has begun, Drs. Bruns and Gupta will discuss project progression, participant safety, and overall data on a monthly basis via phone, email correspondence, or an in-person meeting. Adverse Events (AEs) will be reported promptly to the IRB and to the Medical Monitor. If multiple patients experience adverse events related to research procedures, then the Medical Monitor will be consulted to discuss whether the study should be stopped or reassessed. If there is any evidence of a pattern of unanticipated AEs (regardless of causality), or Serious Adverse Events (SAEs), then the Medical Monitor will immediately the data.

10.2 Severity

The investigator will grade any Adverse Event signs and symptoms as mild, moderate, severe, or life threatening according to the following definitions in Table 1.

Table 1. Adverse events severity scale.

Grade	Definition
Mild:	Causing no limitation of usual activity
Moderate:	Causing some limitations of usual activities
Severe:	Causing inability to carry out usual activities
Life Threatening:	Patient was at immediate risk of death from the event

10.3 Serious Adverse Event

Serious Adverse Events (SAEs) will be identified as any adverse event (AE) that:

- Is fatal;

- Is life threatening, meaning the patient was, in the view of the investigator, at
- immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more serious form or progressed, might have caused death;
- Causes a persistent or significant disability or incapacity;
- Requires or prolongs inpatient hospitalization. Inpatient hospitalization will be considered a hospitalization if is longer than 24 hours or requires an intervention to treat emergent symptomatology (non-diagnostic);
- Is a congenital anomaly or birth defect;

Other important medical events may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes as listed in this definition. We will report all SAEs to the IRBMED, including death, due to any cause which occurs during this study and until 30 days after the last participation in the study, whether or not expected and regardless of causality.

10.4 Termination of Subjects

10.4.1 Subject Decision

Participation is strictly voluntary, and the research is strictly knowledge driven; therefore, a subject may withdraw from further participation in the study without penalty or harm. Any reason(s) the subject may give for terminating his or her participation will be kept confidential. We will store the study documents according to the procedures outlined in the Confidentiality of Data section of this protocol (Section 9). We will require no further information of the subject and the subject will be compensated for their completed study visits prior to termination.

10.4.2 Investigator Decision

Study personnel (principal investigator, co-investigators, and study coordinator) will be authorized to release a subject from further study participation according to the following guidelines:

- The researcher believes that it is not in the subject's best interest to stay in the study.
- Subject becomes ineligible to participate.
- Subject's condition changes such that she needs treatment that is not allowed while taking part in the study.
- Subject does not follow instructions from the researchers.
- The study is suspended or canceled.

Upon termination of a subject, the investigators will ensure the subject is dismissed with any study documents to which he or she is entitled, as well as guidance for resuming medications safely. Subjects will be compensated for their completed study visits prior to termination. Investigators will require no further obligation or participation from a terminated subject.

11. Protection of human subjects

11.1 Potential benefits of this research

11.1.1 Potential benefits to society

This study will provide new knowledge about the effect of peripheral nerve stimulation on vaginal blood flow for women with intact and damaged spinal cords. These findings may lead to new methods of treating female sexual arousal disorder for women with and without SCI.

11.1.2 Potential benefits to participants

We do not expect participants to benefit directly from this study. It is possible the stimulation session may give participants 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.

11.2 Risks to Human subjects

Potential risks include release of identifying information, physical discomfort or pain during stimulation, skin irritation from gel and alcohol pad prior to electrode placement, women with SCI could have an increase in blood pressure (autonomic dysreflexia), infection from intravaginal sensors, and women with a history of trauma may feel triggered by the research intervention.

11.2.1 Potential Risks and Protection against risks

See sections 11.2.2 through 11.2.7 for a complete list of potential risks and protections against each risk.

11.2.2 Identifying information

A risk to participating in the study is an increased risk of loss of privacy. Participants personal information will be protected per HIPAA guidelines. Only the study coordinator will keep the necessary PHI (name, address) to recruit and schedule the participant session. Otherwise all references to each participant will be coded. Thus, only one person beyond each participant's normal clinical team (for UMHS patients) will have access to their PHI. If individual subject data is published, then no identifying information will be included. Study files will be maintained in a secure location. Access to computerized data will be restricted to IRB-approved study personnel and will be password protected. Data collection will be limited to the study investigators and study staff. All study personnel who have access to the data will be educated regarding the need to protect confidentiality and the procedures to follow to ensure such protection. The likelihood of this risk is rare.

11.2.3 Electrical stimulation

Electrical stimulation can result in pain at site of stimulation. We will keep stimulation current levels at or below the perception threshold, which is normally below the pain threshold. Subjects will be able to report any discomfort or pain associated with the stimulation and current levels will be decreased until the discomfort is no longer observed. The likelihood of this risk is rare to infrequent.

11.2.4 Skin irritation

Participants skin may be cleaned with a mild abrasive gel and an alcohol pad prior to the placement of electrodes. If this procedure causes discomfort and/or skin irritation, it will be stopped and not performed in the second visit. We anticipate the likelihood of this risk to be rare.

11.2.5 Intravaginal sensor

The intravaginal sensor could cause an infection if it is not properly sterilized or improper sterile technique is used. Vaginal sensors will be properly sterilized between each session and placement of the sensor will be performed by a clinical staff who is trained in sterile procedures such as clean intermittent catheterization. If the sensor shows any signs of damage due to reuse or repeated sterilizations, then it will be replaced. We will have back-up sensors on hand throughout the study. The sensor is specifically designed to be human use only and reused. As sensor placement will be guided by clinical staff who are trained in sterile methods including the

standard clean intermittent (urethra) catheterization procedure, we expect that the likelihood of this risk is rare to infrequent.

11.2.6 History of trauma

Subjects with a history of trauma may feel triggered by the research intervention. To reduce the risk of trauma triggering, patients will be fully informed about the treatment regimen and that their participation is voluntary. If psychological trauma occurs, patients will be referred to our sexual health therapists for treatment. The likelihood of this risk is rare to infrequent.

11.2.7 Spinal cord injured participants

In spinal cord injured participants, electrical stimulation of nerves can lead to autonomic dysreflexia (AD) responses such as increased blood pressure that could have serious consequences to the subject. Risk of autonomic dysreflexia, or syndrome in which there is a sudden onset of excessively high blood pressure is generally limited to patients with injuries at the cervical and upper-thoracic levels. Patients with injuries in levels C4 to T5 have a risk of autonomic dysreflexia, however patients are typically well-educated about it and mitigation for it is well established. These patients have nitroglycerine paste in their regimen already, to mitigate against AD, and we will provide it for any patients who do not have it. During the session, we will have cardiovascular monitors (heart rate, blood pressure) that will be watched for any abnormal increases. The MCRU staff member and clinical research team member(s) present will be aware of these parameters, and will respond as needed by terminating stimulation, helping the subject to relax, applying nitroglycerine paste, and seeking further medical care if needed. Prior to the session we will ask spinal cord injured participants to try to empty their bladder, or if they have done it recently, to help further reduce the likelihood of autonomic dysreflexia. In the at-home daily pelvic diary, spinal cord injury participants will be asked if they have symptoms of AD including headaches, flushing, sweating, or goose bumps (see Section 2.3). The likelihood of this risk is rare (T6-T10 patients) to infrequent (C4-T5 patients).

11.2.8 Reasonableness of risks

The risks of participation in the study are minimal, and if there is pain caused by the stimulation it can be stopped by reducing the stimulation amplitude or stopping stimulation completely. Autonomic dysreflexia risk will be limited based on our subject recruitment, cardiovascular vitals will be tracked, and clinical team members will be prepared to respond if necessary. Psychological discomfort can be reduced with psychological support. Infection can be treated with antibiotics. Study team members are fully trained on protection of human private information, and thus the odds of privacy loss occurring are minimally greater than the participant already faces while getting their normal clinical treatment. The study will provide new human data that has never been addressed before. This presents a significant scientific benefit that may lead to new treatment for a patient population that is significantly underserved.

12. Research Costs

All research-specific costs will be covered by research accounts overseen by the research team. Study participants will not be billed for any research study procedures. Participants will be reimbursed for each study visit and travel expenses.

13. Investigational Drug

There is no involvement of any investigational drug in this study.

14. Investigational Device

There is no involvement of any investigational device in this study.

15. Marketed Drugs/Device

15.1 Device
Transcutaneous electrical nerve stimulator (Empi Select TENS)

15.2 PMA Number
K061650

15.3 Purpose of the device
The Empi TENS unit is used to apply electrical stimulation to the skin, to provide relief for pain through electrodes that accompany the unit. We will use the unit and accompanying electrodes to apply stimulation over cutaneous nerves that may modulate vaginal blood flow - the posterior tibial nerve and the dorsal genital nerve. The selection of stimulation parameters will be similar to normal use of the device for pain.

15.4 Frequency and total duration of use for an individual subject
The TENS device will be used once per subject, for 20 minutes of total stimulation during the test session.

15.5 FDA classification of device
Class 2

15.6 How research use departs from the FDA-approved indication
The Empi SELECT Transcutaneous Electrical Nerve Stimulator Device is used for the symptomatic relief and management of chronic, intractable pain and relief of pain associated with arthritis. It is also used as an adjunctive treatment for post-surgical and post-trauma acute pain. The purpose of using the device in this study is to evaluate whether or genital nerve or tibial nerve stimulation will modulate autonomic neural circuits and vaginal blood flow.

15.7 Purpose of evaluation
Our goal is to determine support for a possible new indication for use of the device.

15.8 Risk designation for device
Non-significant risk

15.9 Justify risk level and evaluate safety risk
The device is not an implant. The device does not sustain human life or present a potential for serious health risk. The device does not have a substantial importance in diagnosing, curing, mitigating, or treating disease. The device is used in one short-term skin-surface stimulation sessions. The device applies electrical stimulation through electrodes placed on the skin. It is battery-powered, and thus does not have a ground-fault risk. As noted elsewhere in the protocol, stimulation could lead to pain or discomfort below the electrodes. This is not expected to be significant pain. If observed, stimulation will be reduced or terminated such that the discomfort ceases. Each electrode placement will be performed be study personnel familiar with

proper use of the device.

15.10 Procedures for controlling device

The PI (Dr. Bruns) will have ultimate responsibility for receiving, labeling, storing, and dispensing the device. Once the study begins, study personnel will coordinate storage and use of the device, with oversight by Dr. Bruns. The PI or co-I Dr. Gupta will be present for initial use of the device, verifying that it will be done in a manner consistent with the protocol. Any use of the device, in a session that either does not attend, will include study team personnel that have been previously overseen by Dr. Bruns or co-I Dr. Gupta. Dr. Gupta has clinical experience with the device. After such a session, a report will be sent to Dr. Bruns verifying appropriate device usage. At the end of the study the device will be retained by the PI (Dr. Bruns) in their office for potential use in a future study.

16. Additional Requirements

16.1 Biosafety

This research does not involve the use of infectious agents, recombinant DNA, or gene transfer.

16.2 Point of care testing

This research does not involve laboratory testing of the patient.

16.3 Tissue procurement

This research does not involve use of redundant/residual biological specimens.

16.4 Clinical research unit

This research will involve the use of the Michigan Clinical Research Unit (MCRU) Clinical Support Services includes space and support of clinical personnel for each visit. MCRU has been consulted during the planning of this study, and a budget estimate was obtained.

16.5 Nurse or student nurse research

No one participating in this research study is a nurse or student nurse.

16.6 Pregnant women and newborns

This research does not involve pregnant women and/or newborns.

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