IRB NUMBER: 2022-168
IRB APPROVAL DATE: 07/31/2023
IRB EXPIRATION DATE: 04/20/2024

STUDY TITLE: PERCUTANEOUS TIBIAL NERVE STIMULATION (PTNS) THERAPY FOR FEMALE PATIENTS SUFFERING FROM MULTIPLE SCLEROSIS

This is a voluntary research study to find out the effects of percutaneous tibial nerve stimulations (PTNS) in treating overactive bladder (OAB) symptoms in Multiple Sclerosis patients. This is a pilot, single blind, randomized, sham-controlled trial, which means you will be randomly assigned to one of two treatment groups, and you will not know which group you have been assigned to. You will be assigned to receive either active PTNS treatments, or sham treatment (simulated treatment). Participation involves 14-27 visits which include a screening visit, treatment visits, and follow-up visits. If you are assigned to receive the PTNS treatments initially, your participation will last approximately 15 weeks. If you are assigned to receive sham treatments initially, your participation can last up to approximately 28 weeks. At the end of the first 15 weeks, you will be un-blinded to what treatment you received. Those participants who received sham treatment in the first portion of the study will be offered active PTNS treatments with the same schedule of visits as the first part of the study.

Your responsibilities include completing screening activities, completing questionnaires, completing voiding diaries, and informing the study staff of your current medical treatments and any changes to those treatments. You do not have to take part to receive treatment and you may quit at any time.

There are risks to this study that are described in this document. Some of the more common and/or serious risks include: Discomfort/pain/pressure/tingling at, or near, the stimulation site and possible worsening of OAB symptoms i.e. increased frequency, urgency, nocturia/leaking due to the procedure

The potential benefit may be improvement of bladder symptoms and improvement in quality of life however, there may be no direct benefit to you from taking part in this study. If you do not take part, or you withdraw from the study, you may receive the standard treatment. You do not have to take part in this study to receive treatment for your condition. One alternative may be to continue with your current treatment(s). Some other options for treatment may include behavioral modifications, such as decreased caffeine intake and timed voiding, and pelvic floor physical therapy. Additional options include taking certain oral medications, onabotulinumtoxinA (BTX) injection and sacral neuromodulation.

If you are interested in learning more about this study, please continue reading below.

IRB NUMBER: 2022-168
IRB APPROVAL DATE: 07/31/2023
IRB EXPIRATION DATE: 04/20/2024

CONSENT FORM AND AUTHORIZATION FOR DISCLOSURE OF PROTECTED HEALTH INFORMATION

STUDY TITLE: **PERCUTANEOUS TIBIAL NERVE STIMULATION (PTNS) THERAPY FOR FEMALE PATIENTS SUFFERING FROM MULTIPLE SCLEROSIS**

Principal Investigator: Priya Padmanabhan, MD
Address: 3535 W. Thirteen Mile Rd
Royal Oak, MI 48073

Hospital: William Beaumont Hospital (Royal Oak, Troy and Grosse Pointe)

INTRODUCTION

Why is this study being done?

You are being asked to participate in a research study. The purpose of research is to look at the nature of disease and try to develop improved methods to diagnose and treat disease. The doctor or clinician in charge of the study believes you meet the initial requirements to take part in the study. Before agreeing to participate, it is important for you to read and understand the following explanation of the research procedures. This Consent and Authorization form describes the purpose, procedures, benefits, risks and discomforts of the study. It also describes the alternatives available to you, and your right to withdraw (quit) from the study at any time.

Please read this information carefully and ask as many questions as you like before deciding whether or not you would like to take part in this research study.

The goal of this study is to determine if percutaneous tibial nerve stimulations (PTNS) therapy improves overactive bladder (OAB) symptoms in Multiple Sclerosis (MS) patients.

A total of 34 patients will take part in the study at Beaumont.

How long will I be in the study?

If you decide to take part in this study, your participation is expected to last approximately 28 weeks. Approximately, 15 weeks for **part 1**. If you are eligible and decide to participate in **Part 2** (open label phase), the duration will be an additional 13 weeks. You will have up to 1 week to opt to participate in part 2. You may not take part in this study if you are currently enrolled in another related research study which could alter or influence the study results.

DESCRIPTION OF THE STUDY

What will happen if I take part in the research study?

You are being asked to take part in this research study because you have been diagnosed with multiple sclerosis and are experiencing symptoms of overactive bladder.

Part 1

If you agree to take part in this study, you will be randomly assigned to one of 2 treatment groups. Randomization is like "the flip of a coin". However, you will not know which treatment you are assigned. This is called blinded. In case of an emergency, the treatment can be unblinded to determine which therapy you have been receiving.

The treatment groups are:

1. Sham group (You will receive a simulated treatment. You may feel the sensations of stimulation; however, your tibial nerve will not actually be stimulated).

   Or

2. PTNS group (You will receive active treatment where you will actually receive stimulation to your tibial nerve).

Both groups will receive 30-minute treatments, one time per week for twelve weeks.

IRB NUMBER: 2022-168
IRB APPROVAL DATE: 07/31/2023
IRB EXPIRATION DATE: 04/20/2024

If you are currently taking antimuscarinics/beta-3 agonists, you will be asked to discontinue your medication. You will need to be off this medication for a minimum of 2 weeks before your eligibility for study participation can be assessed. When discontinuing these medications, there is a chance that urinary symptoms may return to baseline. This may include but is not limited to an increase in urinary frequency, urgency, and urinary leakage. Medication may be resumed after study completion or in the event you do not meet study eligibility criteria.

The following activities will occur at the specified study visits:

Screening and Consent Visit 0: Week 0

The study will be explained to you in detail, and you will have as much time as you need to ask questions. You will be asked to read and sign this Consent and Authorization form before any study-related procedures are performed. The following tests and procedures will be done to determine if you qualify to participate in this study:

- Review demographic information (birth date, gender etc.)
- Review of your medical and surgical history, review of medications you are currently taking and medications that you have taken in the past
- Collection of urine sample for urinalysis and pregnancy, if applicable
- Complete a questionnaire about your urinary symptoms
- Receive a 3-day voiding (urination) diary to complete before Visit 1 – you will be instructed on how to complete the diary

Enrollment and Treatment 1: Visit 1: (within 3 weeks of visit 0 ± 3 days)

- The diary will be collected and reviewed
- Eligibility will be confirmed (if determined to be ineligible, you will not continue in the study and you will not receive study treatments)
- Randomly assigned to one of the two treatment groups
- A urinalysis via urine dipstick and pregnancy test (for women of child-bearing potential) will be performed
- Assess adverse events
- Review your medications
- Treatment 1 will be completed at this visit

Treatment Visits: 2 - 12: (1 week ± 3 days from last visit)

- 30-minute treatment
- A pregnancy test (for women of child-bearing potential) will be performed.
- Assess adverse events
- Review your medications
- PGI-I questionnaire will be completed at end of treatments 4, 8 and 12
- After treatment 12 a 3-day voiding diary will be dispensed with instructions for completion to be completed prior to visit 13

One week post treatment follow-Up visit: Visit 13: (1 week ± 3 days from treatment 12)

One-week after your last treatment (± 3 days), participants will return for an office visit.

- Completion of questionnaires (PGI-I, OABq-SF)
- 3-day voiding diary will be collected
- Collection of urine sample for urinalysis
- Assess for adverse events
- Review your medications
- Unblinding

  * Part 2 (open label phase): Open label treatment 1 may also begin the same day as visit 13 if the patient chooses

Part 2

At the completion of visit 13, you will be un-blinded to what treatment you have received. If you received sham treatment, you will be offered active PTNS treatment (**Part 2**) and follow the same schedule of visits as was completed for Visit 1 through Visit 13 in Part 1. If you receive sham treatment, you will have up to 7 days to decide and begin treatment if you would like to continue to the open label treatment phase. Open label treatment 1 may also begin the same day as visit 13 if the patient chooses.

Below is a table describing what will occur at each study:

	Consent and Screening	Enrollment and Tx 1	Tx 2	Tx 3	Tx 4	Tx 5	Tx 6	Tx 7	Tx 8	Tx 9	Tx 10	Tx 11	Tx 12	Follow up	Part 2 Tx1	Part 2 Tx2	Part 2 Tx 3	Part 2 Tx4	Part 2 Tx 5	Part 2 Tx 6	Part 2 Tx7	Part 2 Tx8	Part 2 Tx 9	Part 2 Tx10	Part 2 Tx 11	Part 2 Tx12	Follow up
Visit Window		Within 21days of screening +/- 3 days	Weekly +/- 3 days											7+/-3 days after last Tx	Within 7 days of follow up visit	Weekly +/- 3 days												7+/-3 days after last Tx
Visit	Visit 0	Visit 1	V 2	V 3	V 4	V 5	V 6	V 7	V 8	V 9	V 10	V 11	V 12	V 13	V 14	V 15	V 16	V 17	V 18	V 19	V 20	V 21	V 22	V 23	V 24	V 25	V 26
Consent	X																										
Eligibility	X																										
Demographics, medical history	X																										
OABq-SF	X													X													X
PGI-I					X				X				X	X				X				X				X	X
3-day Voiding Diary returned		X												X													X
Pregnancy test[a]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X	X												X													X
PTNS/SHAM treatment[c]		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Un-Blinding														X													

a. A urine pregnancy test will be completed for those of childbearing potential.
b. Urine culture required if urinalysis is positive for Leukocytes at screening, positive cultures will be treated by the study physicians per standard of care. Subsequent visits that require a urinalysis and are positive for leukocytes if the patient is symptomatic, a culture will be sent per the investigator's discretion.
c. All PTNS or sham sessions will be completed by an experienced Urology Research Nurse (treatments will be completed weekly +/- 3 days for 12 consecutive weeks

IRB NUMBER: 2022-168
IRB APPROVAL DATE: 07/31/2023
IRB EXPIRATION DATE: 04/20/2024

FDA Clinical Trial Information
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.

PARTICIPANT RESPONSIBILITIES
For any illnesses or injuries, you should contact the study doctor immediately at the number listed in this Consent and Authorization form or in an emergency situation call 911 (or go to the nearest hospital emergency room).
As a participant, your responsibilities include:

- Do not take part in any other research project while you are participating in this study.
- Follow the instructions of the study doctor and study staff.
- Keep your study appointments. If it is necessary to miss an appointment, please contact the study staff to reschedule as soon as you know you will miss the appointment.
- Tell the study doctor or study staff about any side effects, doctor visits, or hospitalizations that you may have.
- Tell the study doctor or study staff if you believe you might be pregnant.
- Keep your diaries as instructed.
- Complete your questionnaires as instructed.
- Ask questions as you think of them.
- Tell the study doctor or study staff if you change your mind about staying in the study.

RISKS, SIDE EFFECTS AND DISCOMFORTS
Ask your doctor what the standard of care risks are as well as the study risks.
What side effects or risks can I expect from being in the study?

Possible Risks*:*

Less frequent (occurring from 1% to 10% of the time):

- Discomfort/pain/pressure/tingling at, or near, the stimulation site, or the subject's lower leg or foot
- Redness/inflammation at, or near, the stimulation site
- Possible worsening of OAB symptoms (Stimulating the nerves can either improve, worsen, or have no effect on symptoms) i.e. increased frequency, urgency, nocturia/ leaking due to the procedure

Rare (occurring less than 1% of the time):

- Skin irritation
- Electrode burn
- Allergic reaction to adhesive pad gel
- Numbness of toes
- Allergic Reaction
- Possible increase in lower extremity pain or pelvic pain

IRB NUMBER: 2022-168
IRB APPROVAL DATE: 07/31/2023
IRB EXPIRATION DATE: 04/20/2024

There is a rare risk of breach of confidentiality (release of information, which personally identifies you).

Not all possible effects are known. With any *therapy*, unusual, unexpected or previously unreported side effects may occur. You will be informed of any significant new findings, which develop during the course of this research study, which may change your decision to continue participating in this study.

Pregnancy Warning

If you are a woman who is pregnant or becomes pregnant during the research study, there could be harmful effects to you or your unborn child. Women of childbearing potential must agree to practice approved birth-control methods (oral contraceptives, condom barrier, injection, diaphragm or cervical cap, vaginal contraceptive ring, IUD, implantable contraceptive, surgical sterilization (bilateral tubal ligation), vasectomized partner(s))

If you are a woman of childbearing potential you must have a negative pregnancy test before entering the study and prior to each treatment visit.

BENEFITS

What are the benefits of taking part in this study?

Benefits to the Participant

You could receive effective therapy for your symptoms of overactive bladder. Potential benefits you may receive include the following:

- Reduced number of urinary voids per day
- Reduced urgency to urinate
- Reduced number of urine leakage episodes
- Improved quality of life

However, there may be no direct benefit to you from taking part in this study. Your condition may improve, but this cannot be guaranteed. Information gained from the results of this study may be of benefit to others in the future, with a similar medical condition.

ALTERNATIVE OPTIONS

What are my choices other than taking part in this study?

You do not have to take part in this study to receive treatment for your condition. One alternative may be to continue with your current treatment(s). Some other options for treatment may include behavioral modifications, such as decreased caffeine intake and timed voiding, and pelvic floor physical therapy. Additional options include taking certain oral medications, onabotulinumtoxinA (BTX) injection and sacral neuromodulation.
You do not have to take part in this study to receive treatment for your condition.

ECONOMIC CONSIDERATIONS

What are the costs of taking part in this study?

IRB NUMBER: 2022-168
IRB APPROVAL DATE: 07/31/2023
IRB EXPIRATION DATE: 04/20/2024

There are no costs to you or your insurance company to participate in this study. The PTNS treatments will be provided to you at no cost. There will be no cost to you for the study procedures described in this consent (e.g. urinalysis and pregnancy test).

You will be reimbursed for your time and travel during the course of the study, as outlined in the table below. You will receive a stipend check (sent via US mail) after you have completed the scheduled visits. If you are unable to complete all the study visits, you will be paid only for the visits you were able to complete.

Visit	**Stipend**
Completion of Screening (visit 0)	$25.00
Completion of Treatment 1-12 (visits 1-12)	$25.00/visit
Completion of 1 week follow up (visit 13)	$25.00
Total	**$ 350.00**
Completion of Part 2: Treatment 1-12 (visits 14-25)	$25.00/visit
Completion of Part 2: 1 week follow up (visit 26)	$25.00
Total	**$325.00**
Maximum Stipend **(if all visits completed)**	**$675.00**

Income received as compensation for taking part in a research study is considered taxable income. Beaumont is required to report monetary reimbursement of $600 or more per year to the Internal Revenue Service (IRS). You will be required to provide your Social Security number for tax reporting. Beaumont does not withhold taxes from research stipend payments. At the end of the year you will receive a Form 1099 from Beaumont showing the amount reported to the IRS.

COMPENSATION

What happens if I am injured because I took part in this study?

Your involvement in this study is voluntary. The possible risks and side effects, which might occur during the course of the research study, have been described in this Consent and Authorization form.

A research injury is any physical injury or illness caused by the medications, devices, or procedures required by the study, which are administered, used, or performed appropriately. These medications, devices, or procedures are different from the medical treatment you would have received if you had not taken part in the study.

Should you experience a research injury, there are no designated funds provided for subsequent medical care or compensation by either the study doctor/clinician or Beaumont.

IRB NUMBER: 2022-168
IRB APPROVAL DATE: 07/31/2023
IRB EXPIRATION DATE: 04/20/2024

What are my rights if I take part in this study?
You are not giving up any of your legal rights by signing this form.

CONFIDENTIALITY, DISCLOSURE AND USE OF YOUR INFORMATION
Will my medical information be kept private?
We will keep your personal health information as confidential as possible. It is not likely your information will be given to others without your permission. In order for this research study to take place, you must also authorize the researchers to access and use some of your protected health information (PHI). PHI is information, which could identify you as an individual such as name, address, date of birth, etc. By signing this Consent and Authorization Form, you give Beaumont permission to use and/or disclose (release) your health information related to this research. Your medical and billing records collected for the purpose of the study will remain confidential, but may be disclosed (released) or used by the following and/or their representatives:

- The investigators (study doctor/clinician, research staff)
- Beaumont and its' parent, Beaumont Health and affiliated hospitals
- The Food and Drug Administration
- Other governmental regulatory agencies (domestic and/or foreign)
- Your health insurance company and/or group health plans and their intermediaries (companies contracted to process claims) may also have access to your medical and billing records of the study.

The purpose for this disclosure (release) or use is, for example, to assure compliance with the study protocol, to evaluate the effectiveness of the study, and/or to provide protection to you as a research study participant. The disclosure and use of your information will continue after your involvement in the study has ended. There is no expiration date for the use of your medical and billing records from the study. Any information about you disclosed to the parties identified above may be re-disclosed by them; however, such re-disclosure is not under the protections of this Consent and Authorization.

You will not be identified in any publication or other release of study results, data, and other information (such as in professional writings, at professional meetings, and in the study sponsor's product information, and/or advertising or other promotional materials).

If you decide to withdraw your authorization for the researchers to access and use your protected health information before the end of the study, you will be withdrawn from the research study. However, where the study relied on your Consent and Authorization for the time you participated in the study, your Consent and Authorization cannot be withdrawn and the information already collected may still be used and disclosed as you previously authorized.

STOPPING STUDY PARTICIPATION
What if I decide to stop taking part in the study?
Taking part in this research study is completely voluntary. You may choose not to take part or to stop being in the study (withdraw) at any time without penalty or loss of benefits to which you are otherwise entitled, or without jeopardizing your medical care by your doctor at

IRB NUMBER: 2022-168
IRB APPROVAL DATE: 07/31/2023
IRB EXPIRATION DATE: 04/20/2024

Beaumont. However, if you do not agree to sign this Consent and Authorization form, you will not be able to take part in this study.

If you decide to withdraw from the study you will need to notify the study doctor/clinician of your decision to stop taking part in the study. Written notification is preferred. This notice may be sent to Dr. Priya Padmanabhan at Beaumont 3535 West Thirteen Mile Road, Suite 438, Royal Oak, MI 48073.

Your participation in this study may be stopped by the study doctor/clinician or study sponsor, without your consent, for any reason, which will be explained to you. Examples include:

- The study medication or procedures appear to be medically harmful to you.
- You fail to follow directions for participating in the study.
- It is discovered you do not meet the study requirements.
- The study is canceled.
- It is determined to be in your best interest (for example, your disease has progressed despite treatment).

If this is a placebo controlled or otherwise blinded study you may not review your research medical records during the course of the study, regardless of whether or not you continue in the study. If your study doctor/clinician stops your participation, or you decide not to continue, you may be asked to have a final study visit or examination, in order for you to be discontinued from the study in a safe and orderly manner. In addition, the type of treatment you are getting will not be able to be disclosed to you/your doctor until the study is completed.

CONTACTS

Who can answer my questions about the study?

You may talk to the study doctor/clinicians about any questions or concerns regarding your study participation, or you think you may have suffered a research-related injury. The doctor/clinician in charge of the study, Priya Padmanabhan MD may be reached at: 248-551-9238 to answer your questions.

Your contact person is Amanda Schonhoff, RN. You may contact her at 248-551-1225

If you have questions regarding your rights as a research participant, or have problems, concerns, complaints, want information or would like to offer input, you may contact the Institutional Review Board Chairperson at (248) 551-0662. The Institutional Review Board is charged with the oversight of all human participant research conducted at Beaumont facilities.

IRB NUMBER: 2022-168
IRB APPROVAL DATE: 07/31/2023
IRB EXPIRATION DATE: 04/20/2024

STATEMENT OF VOLUNTARY PARTICIPATION

I have read the above, have asked questions and have received answers about this study to my satisfaction. I understand what I have read and willingly give my consent to participate in **PERCUTANEOUS TIBIAL NERVE STIMULATION (PTNS) THERAPY FOR FEMALE PATIENTS SUFFERING FROM MULTIPLE SCLEROSIS**. I understand I will receive a signed copy of this document and will be promptly informed of any new findings regarding this study. I further authorize the use or disclosure of my health and personal information contained in records as described above.

_____
RESEARCH PARTICIPANT NAME (PLEASE PRINT)

_____ _____ _____
RESEARCH PARTICIPANT SIGNATURE DATE TIME

ALTERNATIVE SIGNATURE (for use only when participant is a minor, cognitively impaired or critically ill**)**
AS THE PERSONAL/LEGAL REPRESENTATIVE OF THE STUDY PARTICIPANT, PLEASE PRINT PARTICIPANTS NAME ON THIS LINE_____, AND CHECK ONE OF THE BOXES BELOW AS THE BASIS FOR YOUR AUTHORITY TO SIGN THIS CONSENT AND AUTHORIZATION:

☐ COURT-APPOINTED GUARDIAN
*COURT LETTER IS REQUIRED

☐ DURABLE POWER OF ATTORNEY
*ATTORNEY LETTER MUST BE PRESENT & VERIFIED BY 2 PHYSICIANS

☐ NEXT OF KIN

_____ _____
NAME (PLEASE PRINT) RELATIONSHIP TO PARTICIPANT

_____ _____ _____
SIGNATURE DATE TIME

***WITNESS TO THE ENTIRE CONSENT PROCESS AND SIGNATURE ARE REQUIRED IF THE PARTICIPANT IS VISUALLY IMPAIRED, ILLITERATE OR NON-ENGLISH SPEAKING ONLY**

_____
WITNESS NAME (PLEASE PRINT)

_____ _____ _____
WITNESS SIGNATURE DATE TIME

AUTHORIZED CONSENT PROVIDER STATEMENT:

I have explained this study and have offered the study participant an opportunity for any further discussion or clarification.

_____ _____ _____
NAME (PLEASE PRINT) CREDENTIALS PHONE NUMBER

_____ _____ _____
SIGNATURE DATE TIME