TITLE PAGE:

PROTOCOL TITLE:

INTENSE: INvestigation of TENS Efficacy versus Posterior Tibial Nerve Stimulation for overactive bladder

NCT NUMBER: Not yet assigned

Document Date: 2/11/2022

PROTOCOL TITLE:

INTENSE: INvestigation of TENS Efficacy versus Posterior Tibial Nerve Stimulation for overactive bladder

PRINCIPAL INVESTIGATOR:

Kate Meriwether, MD
Department of Obstetrics and Gynecology

ADMINISTRATIVE CONTACT:

Name: Karen Taylor

Department of OB/GYN

VERSION NUMBER:

3

DATE:

Include the date of submission or revision.

REGULATORY FRAMEWORK:

Please indicate all that apply (please note that the regulatory framework **does not** mean the funding source):

☐	DOD (Department of Defense)
☐	DOE (Department of Energy)
☐	DOJ (Department of Justice)
☐	ED (Department of Education)
☐	EPA (Environmental Protection Agency)
☒	FDA (Food and Drug Administration)
☒	HHS (Department of Health and Human Services)
☐	VA
☐	Other:

FUNDING:

This protocol is not currently funded.

CLINICAL TRIALS

Is this a clinical trial per the NIH definition of a Clinical Trial? ☒ Yes ☐ No

NIH Definition of a Clinical Trial:

"A research study in which one or more human subjects are prospectively assigned to one or more interventions. An "intervention" is defined as a manipulation of the subject or subject's environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints. Examples include: drugs/small molecules/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and, diagnostic strategies (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes."

Use the following four questions to determine the difference between a clinical study and a clinical trial:

1) Does the study involve human participants? ☒ Yes ☐ No
2) Are the participants prospectively assigned to an intervention? ☒ Yes ☐ No
3) Is the study designed to evaluate the effect of the intervention on the participants? ☒ Yes ☐ No
4) Is the effect being evaluated a health-related biomedical or behavioral outcome? ☒ Yes ☐ No

Note that if the answers to the 4 questions are yes, your study meets the NIH definition of a clinical trial, even if…

- You are studying healthy participants
- Your study does not have a comparison group (e.g., placebo or control)
- Your study is only designed to assess the pharmacokinetics, safety, and/or maximum tolerated dose of an investigational drug
- Your study is utilizing a behavioral intervention

If yes to all 4 questions, please confirm that the research team is familiar with and agrees to comply with the investigator requirement to register the study on the ClinicalTrials.gov database. Additionally, the approved consent document(s) must be uploaded to the ClinicalTrials.gov database ☒ Yes ☐ No

For any assistance with registration of your trial or the requirements, please contact HSC-CTSCResearchConcierge@salud.unm.edu

Table of Contents

1. Objectives 6
2. Background 6
3. Study Design 8
4. Inclusion and Exclusion Criteria 8
5. Number of Subjects 10
6. Study Timelines 11
7. Study Endpoints: 11
8. Research Setting 11
9. Resources Available 12
10. Prior Approvals 13
11. Multi-Site Research 13
12. Procedures 13
13. Data Analysis 17
14. Provisions to Monitor the Data to Ensure the Safety of Subjects 18
15. Withdrawal of Subjects 18
16. Data Management/Confidentiality 19
17. Data and Specimen Banking 19
18. Risks to Subjects 20
19. Potential Benefits to Subjects 20
20. Recruitment Methods 21
21. Provisions to Protect the Privacy Interests of Subjects 21
22. Economic Burden to Subjects 22
23. Compensation 22
24. Compensation for Research-Related Injury 23
25. Consent Process 23
26. Documentation of Consent 24
27. Study Test Results/Incidental Findings 25
28. Sharing Study Progress or Results with Subjects 25
29. Inclusion of Vulnerable Populations 25
30. Community-Based Participatory Research 25
31. Research Involving American Indian/Native Populations 25
32. Transnational Research 25
33. Drugs or Devices 25
34. Principal Investigator's Assurance 26
35. CHECKLIST SECTION 26
36. Partial Waiver of Consent for Screening/Recruitment 26
37. Partial Waiver of HIPAA Authorization for Screening/Recruitment 27
38. Waiver of Documentation of Consent 27
39. Alteration of Consent 27
40. Full Waiver of Consent/Parental Permission 27
41. Full Waiver of Consent/Parental Permission (Public Benefit or Service Programs) 27
42. Full Waiver of HIPAA Authorization (Checklist) 28
43. Other Waiver Types (Checklist) 28
44. Vulnerable Populations (Checklist) 28

45. Medical Devices (Checklist)..... 28
46. Export Control (Checklist)..... 29
47. Data Transfer/Sharing/Storage (Checklist) (required –do not delete even if the answer is "No") 29
48. Specimen Transfer/Sharing (Checklist) (required –do not delete even if the answer is "No") 30

1. Objectives

1.1. The objective of this research is to perform a non-masked, non-inferiority randomized controlled trial to assess the quality of life (QOL) of women with idiopathic overactive bladder (OAB) before and after treatment with percutaneous tibial nerve stimulation (PTNS) or transcutaneous electrical nerve stimulation (TENS) of tibial nerve. The target population is patients with OAB who previously failed first- and second-line treatments and desire non-surgical management.

1.2. Our central hypothesis is that a TENS unit is non-inferior to PTNS for improving the quality of life and symptom distress of women with OAB. The specific aims are:

1.2.1. To compare the effects on health-related quality of life (HRQoL) and symptom bother as measured by the change in score from baseline of the Overactive Bladder questionnaire (OAB-q) in women with urgency urinary incontinence or overactive bladder before and after PTNS versus TENS after 3 months of therapy. Secondary outcomes related to this aim include change in symptom bother alone, as measured by the OAB-q symptom subscale and change in HRQL alone, as measured by the OAB-q HRQL subscale from baseline. **Hypothesis:** TENS will demonstrate similar effects on symptoms and symptom-associated HRQoL in the treatment of women with OAB compared to PTNS.

1.2.2. To compare the rates of treatment success, as defined as 50% or more reduction of urinary incontinence episodes or 25% or more reduction in day or night voids in women with OAB before and after PTNS versus TENS after 3 months of therapy. The number of urinary incontinence episodes, number of voids per day and number of voids per night will be measured by a three-day voiding diary. **Hypothesis:** TENS will demonstrate similar rates of treatment success in women with OAB compared to PTNS.

1.2.3. To perform a comparative analysis of patient satisfaction and compliance between TENS and PTNS. Patient satisfaction will be measured by a patient satisfaction question (PSQ). Patient compliance will be measured by number of treatment sessions completed as verified by clinical records of completed PTNS treatments and TENS device interrogation. **Hypothesis:** Women will be satisfied with both TENS and PTNS treatment and will have greater treatment compliance with TENS compared to PTNS.

2. Background

OAB is a common condition affecting 16.9% of women in the US, with a marked increase in the prevalence of urgency urinary incontinence (UUI) after the age of 44[1]. The International Continence Society (ICS) and International Urogynecologic Association (IUGA) define OAB as a symptom syndrome characterized by urinary urgency, usually accompanied by frequency and nocturia, with or without UUI[2]. The burden of OAB is not only substantial but pervasive. The estimated annual cost of OAB in the US is over $12 billion[3]. On an individual level, it significantly impairs the quality of life of those who suffer from it, affecting social, psychological, occupational, domestic, physical and sexual aspects of their lives[4,5].

The 2019 American Urological Association/Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (AUA/SUFU) Guidelines for the management of OAB includes conservative first and second line treatments with behavior and pharmacologic therapies[6]. However, not all OAB patients respond to or tolerate conservative treatment. The discontinuation rate of anticholinergics is 58.8% at 6 months[7], worsening to 74.8% at 1 year and 87% at 3 years[8]. Hence, patients often seek alternate therapies. Third line options include PTNS, sacral neuromodulation (SNS) and intradetrusor onabotulinumtoxinA injections, while fourth line therapies are more invasive and morbid surgical treatments such as urinary diversion or augmentation cystoplasty[6]. SNS has a success rate of 54%[9] but requires the implantation of a permanent device, which may deter some patients. Additionally, there are frequent and moderately severe adverse effects associated with SNS, including pain, lead migration, infection/irritation, electric shock and the need for additional surgeries in over 30% of patients[6,10]. Costs for SNS are substantially higher than other treatments. A cost analysis comparing pharmacologic, SNS, PTNS and onabotulinumtoxinA by Kraus et al. found PTNS had the lowest mean costs at $6959 over 24 months, while SNS had the highest costs at $29,702[11]. Intradetrusor onabotulinumtoxinA is another effective treatment with success rates of 60-70%[12–14]. However it is expensive[11] and associated with adverse effects like urinary tract infections (19.7%) and urinary retention requiring temporary clean intermittent self-catherization (8.4%)[15].

PTNS is a cost effective and less invasive third line treatment option for OAB patients. Multiple studies have examined the efficacy and safety of PTNS for OAB in adults and children. The SUmiT Trial demonstrated PTNS was superior to sham for both objective (voids per day and incontinence episodes) and subjective (improvement in bladder symptoms) parameters of OAB[16] and was shown to have sustained safety and efficacy at 24 months[17,18]. The OrBIT Study comparing PTNS to extended release tolterodine demonstrated significant improvements in incontinence episodes, voids per day and nocturia in both arms. However, PTNS showed greater subjective improvement over tolterodine for overall health related quality of life (HRQOL)[18,19] with sustained effects at 12 months[18,20]. A meta-analysis of PTNS concluded improvement in OAB symptoms is comparable between PTNS and antimuscarinics, but PTNS offers a better adverse event profile[21]. PTNS has mild, transient and rare adverse effects occurring 1-2% and include bruising or bleeding at the needle site, tingling and mild pain with no serious adverse events reported[16,19,21]. In comparison, reported adverse events of antimuscarinics range from 9.7-63% and most commonly include constipation, dry mouth, voiding dysfunction, and urinary tract infection (UTI)[22]. Current standard treatment protocols involve weekly 30-minute treatments for 12 weeks total. This can pose a significant barrier for patients, requiring multiple clinic visits, time off work, and frequent transportation that can affect compliance and therefore treatment success and patient satisfaction.

A more patient-centered option for OAB with similar success rates may be TENS. TENS is commonly used in physical therapy to treat pain, but recent studies have demonstrated its effectiveness in treating OAB. When compared to controls, patients receiving TENS had significantly greater OAB symptoms improvement (48-93%), UUI cure rates (24-45%) and patient satisfaction[23–25]. TENS is an incredibly safe and non-invasive therapy with no adverse events reported by any study reporting use of TENS in a systematic review of 10

RCTs and 3 prospective cohorts [25]. Women also view TENS as a convenient, beneficial and acceptable treatment of OAB. A qualitative study by Daly et al. revealed TENS home treatment allowed for flexibility to accommodate lifestyle and work needs, unlike clinic visits, and provided a sense of control and empowerment over their OAB symptoms that facilitated their willingness and motivation to continue treatment and improve self esteem [26]. The home was viewed as a safe space for women to receive treatment without the stress and embarrassment of clinic visits for their condition. Women in the study often viewed TENS as both a mental and physical treatment[26]. The at home self-administration makes TENS treatment a viable way to reduce obstacles patients face accessing care. This is encouraging evidence that TENS may provide a safe, effective, convenient and possibly preferred alternative treatment to PTNS for OAB.

To date, there are very limited studies directly comparing PTNS and TENS for the treatment of OAB. Ramírez-García et al. compared PTNS to transcutaneous stimulation of the posterior tibial nerve for the treatment of OAB and demonstrated transcutaneous tibial nerve stimulation was non-inferior in decreasing daytime frequency, urinary incontinence episodes and quality of life[27]. However, both interventions in this study were performed in a clinical setting and once a week, overlooking the two significant advantages TENS provides over traditional PTNS: self-administered treatment at home and increased frequency of treatment. Another RCT comparing PTNS to TENS, in which the TENS group received daily treatments at home, did not demonstrate a difference between groups in reductions of incontinence episodes, number of voids or quality of life measures (unpublished data). However, this study was underpowered to determine equivalency or non-inferiority. The authors are unaware of any other trials directly comparing TENS and PTNS treatment for OAB. Given this gap in knowledge and the advantages TENS can offer to reduce barriers to accessing healthcare, we propose to study home TENS versus traditional, office-delivered PTNS for women with OAB. This innovative research shows promise in helping patients overcome a costly and embarrassing condition in the privacy of their own homes, on their own time.

3. Study Design

We plan to perform an unmasked, non-inferiority randomized controlled trial to determine if the quality of life is improved with the use of TENS compared to PTNS for urgency urinary incontinence and overactive bladder. The target population is patients with OAB and/or urgency urinary incontinence (UUI) who present to the urogynecology clinic either at the University of New Mexico Hospital (UNMH) or Sandoval Regional Medical Center (SRMC). Women will be informed of the arm of the study to which they are randomized, as the intervention is unable to be masked. Masking is not possible with this study design due to the nature of the interventions. All women will give written consent prior to enrollment.

4. Inclusion and Exclusion Criteria

4.1. We will recruit women with OAB and/or UUI who present to the University of New Mexico Urogynecology practice at UNM Eubank Clinic (UNM) or Sandoval Regional Medical Center (SRMC) with OAB, urgency urinary incontinence (UUI) without other types of incontinence, or mixed urinary incontinence with urge predominant-symptoms who have failed a trial of at least one medication. To confirm diagnosis and eligibility, we will conduct

a standard intake history and physical, complete with cough stress test, POP-Q pelvic examination, urinalysis and urine culture. If the potential participant predominantly complains of OAB or UUI, she will be introduced to the study and provided with written information that may help her decide if participation in the study is right for her. All potential participants will be counseled about possible treatment options for OAB and UUI including non-surgical and surgical techniques. If a woman is withdrawn from the study either by her desire or that of the research staff, or does not desire to participate, she will be offered the same treatment options. Her follow up appointments will be the same regardless of participation in the study. The rationale for targeting this population is that these are women who would routinely be offered third line treatments for OAB or UUI.

4.2. Patients will be enrolled if they meet the inclusion and do not meet the exclusion criteria.

4.2.1. Inclusion Criteria

- Female Subjects ≥18 years of age
- OAB, UUI or Mixed Urinary Incontinence with urgency predominant symptoms and more bother from UUI than stress urinary incontinence
- Failed trial of conservative therapy (including bladder training, fluid modification, diet modification, caffeine restriction, or pelvic floor training)
- Failed trial of at least one pharmacologic treatment (anticholinergics, β3-adrenoceptor agonist) either due to inability to take the medication, adverse reaction to medication, or no improvement on medication
- Willing to complete study questionnaires
- Willing to adhere to 12 office visits for PTNS over 3 months if randomized to that arm
- No contraindication to undergoing PTNS or TENS therapy

4.2.2. Exclusion Criteria

- Age < 18 years
- Presence of urinary fistula
- Male genital anatomy
- Undergoing evaluation or treatment of recurrent (2 or more infections in the last 6 months or 3 or more infections in the last 12 months) or current urinary tract infection
- Current Bladder stones
- Bladder cancer or suspected bladder cancer
- Gross Hematuria
- Pregnancy or planning to become pregnant during the study
- Cognitive impairment
- Central or peripheral neurologic disorders such as multiple sclerosis, Parkinson's disease, spina bifida, spinal cord lesions, etc.
- Metal implants such as pacemaker, implantable defibrillator, or metal implants where PTNS or TENS device needs to be placed (ankle/leg)
- Uncontrolled diabetes
- Diabetes with peripheral nerve involvement

- Current use of anticoagulants (excluding aspirin)
- Current use of anticholinergics or use within the last 4 weeks
- Current use of botox bladder injections or bladder botox injection within the last year (12 months)
- Current use of sacral neuromodulation therapy or currently implanted sacral neuromodulation device or leads
- Bladder outlet obstruction
- Urinary retention or gastric retention
- Painful Bladder Syndrome/Interstitial Cystitis
- Unable to be contacted for follow up by telephone
- Inability to speak/read/understand English or Spanish

4.3. We have decided to only include adults (age ≥ 18 years) who are capable of giving informed consent. Children, pregnant women and prisoners will be excluded.

4.4. We will include English and Spanish speaking populations only, as our primary outcome measures have not been validated in other languages. We are excluding men as we are a Urogynecology practice and therefore do not treat that population.

4.4.1. Because we are excluding pregnant women, during participant recruitment women will be asked if they are pregnant or have plans to become pregnant in the next 3 months. Their sexual activity, menopause status and surgical history (specifically hysterectomy or tubal ligation) will also be determined, which are standard questions asked in our practice for new patients. If there is concern for pregnancy, we will perform a urine pregnancy test of the participant on the day of enrollment.

5. Number of Subjects

5.1. This is a single-center study at the University of New Mexico, therefore the total number of subjects at the University of New Mexico is the total number of subjects for the study.

5.2. The total number of subjects to be recruited at this site is up to 130 patients.

5.3. *Sample size calculation:* The primary outcome for this study is the change in the OAB-q total score from baseline to 3 months. We used the means and standard deviation for this questionnaire from an unpublished pilot RCT study from Walter Reed that compares PTNS and TENS for the treatment of OAB (unpublished work). We have powered the study based on a 10-point difference as significant between groups. This 10-point difference used for the power calculation is based on the previously established minimum important difference[28]. To achieve power for this non-inferiority RCT study showing that the difference between groups is less than 10 points, we need 40 patients per group (80 total) to detect no difference with alpha = 0.05 and 80% power. Allowing for dropout of up to 30%, we will aim to randomize 114 patients, and will plan to recruit up to 130 to allow for potentially higher drop-out, as the study primary outcome is at the 12 weeks' time point. As we plan to perform both per-protocol and intention-to-treat analysis, the sample size must be met for both per-protocol and intention-to-treat analysis, with the per-protocol patients (those in the PTNS group completing at 12 treatments in a total of 13 weeks) being expected to be a lower sample size.

6. Study Timelines

6.1. Based on the current clinic volume in the UNM division of Urogynecology, we estimate recruitment up to 130 patients will be feasible over 2 years. A review of our clinic calendar revealed in 1 months' time, the urogynecology division typically sees 10-20 patients who would meet criteria for our study. Assuming 25% enrollment (due to time commitment and eligibility criteria), we will be able to recruit our projected number of patients in less than 2 years. Participants will be followed for 3 months after randomization, so we expect an additional 3 months will be needed to collect follow up data. We estimate that data analysis and composition of the manuscript will take an additional 6 months.

7. Study Endpoints:

7.1. The **primary endpoint** of our study is to determine the change in OAB-q score in patients who undergo 12 weeks of PTNS compared to those who undergo TENS therapy for OAB. Our secondary endpoints include change in OAB-q Symptom Bother subscale score from baseline, change in OAB-q HRQL subscale score from baseline, number or urinary incontinence episodes, number of voids per day, number of voids per night, patient satisfaction question (PSQ) and patient compliance.

7.2. Due to the extremely low risk of the therapeutic interventions, we do not have any **safety endpoints**.

7.3. Our **exploratory endpoints** are to investigate compliance with treatment between groups and preference between therapeutic options.

8. Research Setting

8.1. The study will be performed at the University of New Mexico (UNM) Eubank Women's Primary Care Clinic and Sandoval Regional Medical Center (SRMC) Urogynecology clinics. These Urogynecology clinics are dedicated to care of women with pelvic floor disorders such OAB, the target population for this study.

8.2. Potential subjects will be recruited in the UNM Eubank and SRMC clinics when they present for care for OAB/UUI, either in person or virtually via telephone or Zoom care visits. All patients will have a history and physical taken to determine their study eligibility. Recruitment will take place either in private exam rooms at these clinics or over HIPAA-compliant telephone or Zoom conversation. After recruitment, they will undergo the informed consent via the same means as recruitment and complete initial questionnaires in clinic or will be sent a copy (digital or mail) to complete if enrolled virtually. Patients in the TENS group will be given their TENS device in clinic and research staff will assist in educating participants on proper placement and use of the device, as well as provide a standardized treatment protocol they will complete at home. The patients randomized to PTNS will have their sessions at the UNM Eubank Women's Primary Care Clinic.

8.3. There are no other laboratory tests in this trial beyond what would routinely be collected in the work up of OAB.

8.4. There will not be involvement of any community advisory board.

8.5. There will not be any research conducted outside of the UNM HSC and its affiliates.

9. Resources Available

9.1. Qualifications of PI and study staff: Dr. Kate Meriwether is a board-certified subspecialist in Urogynecology and will serve as the primary investigator (PI) for this study. She is an experienced researcher at UNM and eligible PI at UNM, in addition to serving on an HRRC at the UNM HSC Institutional Review Board, which makes her familiar with ethical and compliant practices. She has been the PI on multiple research trials and has successfully completed randomized control trials both as a fellow and now as faculty at UNM. Dr. Sarah Jeney, a co-investigator on this project, is a board-certified in Obstetrics and Gynecology and is board-eligible for Urogynecology, as she recently completed her fellowship. She is an experienced researcher who has completed multiple research projects in Urogynecology, including a randomized control trial, as a resident and fellow. She recently joined as faculty at UNM. Dr. Angela Dao, a co-investigator on this project, is the fellow who has a total of 12 months of protected research time during her fellowship in order to complete this study.

9.2. This trial does not require any medical decision-making or ordering of therapeutics due to research protocols.

9.3. Resources available to conduct the research: The University of New Mexico (UNM) Urogynecology division operates at two main locations. UNM Eubank Urogynecology Clinic, located in Northeast Albuquerque, provides a full range of services for women with pelvic floor disorders. The Eubank clinic consists of 8 examination rooms, 2 treatment rooms, and 2 physical therapy rooms. Our second location is at Sandoval Regional Medical Center (SRMC), a community-based facility located in Rio Rancho, New Mexico, a large suburb located outside of Albuquerque.

Research Staff: The Urogynecology Division employs a clinical research specialist as well as research coordinators. Our research staff has extensive experience conducting multi-center investigations and recruiting patients to clinical studies, with special expertise in community-based research and quality of life studies.

Research Experience: The Urogynecology Division at UNM has a strong history of conducting high quality research and collaboration with other investigators in the US and abroad, and has consistently met or exceeded recruitment goals on time. We have been members of the NICHD-sponsored Pelvic Floor Disorders Network (PFDN), and have met recruitment goals with high rates of follow-up and accurate data collection. In addition to PFDN research, Dr. Kate Meriwether has mentored and has been the PI on multiple clinical trials and contributes multiple publications in peer-reviewed journals. Her Curriculum Vitae is attached.

Our group is well versed in the importance of adherence to protocols, timely completion of regulatory requirements, effective recruitment strategies, and the importance of the inclusion of minority subjects. Research is integral to all aspects of Divisional work; importantly, all members of the clinical team participate in research efforts. There are weekly research meetings to discuss the progress of the ongoing studies within the department, and it is an excellent forum to ensure that all involved are adequately informed of their duties, of the protocol, and of the procedures.

We do not anticipate that emergency care will be needed for this study, as the interventions are low-risk. However, the urogynecology physicians are available on a 24 hour basis, 7 days per week for their patients requiring emergency care for any reason, including those relating to study participation.

10. Prior Approvals

10.1. There will not be any approvals obtained prior to commencing the research. The study was presented to Dr. Yuko Komesu for approval, and the signed Departmental Review Form can be found in the "Supporting Documents" section.

10.2. This study does not include any ionizing radiation, biological specimens, or drugs.

11. Multi-Site Research

This is not a multi-site research study.

12. Procedures

This non-blinded, non-inferiority randomized controlled trial will be conducted at the UNM Eubank Clinic and SRMC Urogynecology clinic. Each site will recruit participants and we will plan to obtain up to 130 women between the two sites. Collaborating investigators will be members of the Urogynecology Division at UNM HSC.

The primary aim of our study is to determine if symptoms and quality of life related to overactive bladder are improved similarly with TENS use versus PTNS in women with OAB/UUI. The target population will be patients with OAB or UUI who are seeking care after failing first- and second-line therapies. According to the American Urologic Association, first line therapy includes conservative treatments like bladder training, bladder-control strategies, pelvic floor muscle training or fluid management. Second-line treatment includes pharmacologic management with anti-muscarinic and β3-adrenoceptor agonist medications[6,29]. Subjects must have failed a trial of at least one medication (use with no improvement in symptoms for at least 8 weeks, or a contraindication to taking medication such as narrow angle glaucoma, use of other medications that would interact with anticholinergics, uncontrolled hypertension, allergic reaction or adverse side effect to an anticholinergic medication). The subject may have stress urinary incontinence, but urinary urgency or urgency urinary incontinence must be a bothersome complaint or symptom. The current standard-of-care recommendation for those with refractory OAB or UUI who have failed first- and second-line therapies is to offer patients third-line treatment with PTNS, sacral neuromodulation, or intradetrusor injection of onabotulinumtoxinA[6,29]. For patients who present for treatment of refractory OAB or UUI, we will take a thorough history and physical and counsel the patient on all of her options including medical and surgical interventions.

If the patient is interested in non-surgical management with PTNS and fulfills study inclusion criteria, we will then offer her the choice of volunteering for the study. All women will give written and/or electronic consent prior to their enrollment at this time and fill out baseline questionnaires in the clinic. Research staff and clinicians will obtain consent and administer study. After enrollment, participants will fill out a baseline OAB-q and will be

given a 3-day voiding diary to complete prior to starting their intervention. Urinalysis and urine culture will be obtained to rule out urinary tract infection. This is routinely done on all new patients in our clinic and would be performed on patients not participating in the study as well. Data collected in addition to the above outcome measures includes patient demographics, medical/surgical history, and contact information, which are attached as supporting documents. This information will be collected from the patient on the day of enrollment and we will review the patient's medical record if information is missing or unclear.

The randomization sequence will be generated by computer-based randomization in a sequence that preserves 1:1 randomization and also preserves allocation concealment (likely with randomly alternating block sizes of 6-10 in blocked randomization). Randomization assignments will be completed via REDCAP by a research coordinator. Randomization will only occur after consent has been signed and all baseline data has been obtained.

12.1. Interventions:

12.1.1. **PTNS**: Women randomized to the PTNS group will begin therapy after their baseline evaluation is complete. They will be scheduled for PTNS treatment sessions once weekly for 30 minutes, for 12 weeks total. PTNS treatment will be performed as follows:

- The patient sits in a reclining chair, with their legs elevated on a foot rest. The area for needle placement is cleaned with an alcohol swab. A 34 gauge needle is inserted percutaneously approximately 5 cm cephalad to the medial malleolus of the right or left ankle (patient's choice) at a 60 degree angle. A surface electrode is placed on the medial aspect of the ipsilateral calcaneus. The needle and electrode are connected to a low voltage (9V) electrical stimulator (brand name). Stimulation current with a fixed frequency of 20 Hz and a pulse width of 200 μsec is increased until flexion of the big toe or fanning of all toes visualized, or until the woman reports a tingling sensation across the heel or sole of the foot. The current is then set to the highest level of tolerable to the patient (0-10 mA) and then she undergoes therapy for 30 minutes. If no response is seen (no fanning of toes or flexion of big toe or no report of a tingling sensation across the heel or bottom of the foot), the needle is replaced on the same or opposite side until the appropriate response is seen. The needle placement sites will be monitored for bleeding, bruising, irritation or a hematoma. This will be repeated each week, until the completion of 12 weeks of treatment.
- If women assigned to the PTNS arm miss one of their weekly office PTNS sessions, they will be permitted to "make up" the missed session at the end of the 12 weeks, and their "12 week" outcome measures will be performed following that last session (13 weeks following randomization). Women that have missed this one session and made up the session at the end of the treatment course will be considered "fully compliant" with treatment and analyzed in the "per protocol" analysis as having completed the PTNS treatment course per protocol.
- If women assigned to the PTNS arm miss more than one of their weekly office PTNS sessions, they will not be allowed to make up the extra sessions and their

participation in the study or outcome measurement will not be extended further than 13 weeks after randomization. However, they will not be withdrawn from the study for missing sessions, and will be followed for outcomes and adverse events despite missing sessions of PTNS. Women that miss more than one session of PTNS or miss one session and do not make it up at the end will be considered "not fully compliant" with PTNS treatment, and will be analyzed in the "intention-to-treat" analysis in the PTNS arm but not in the "per protocol" analysis in the PTNS arm.

Prior to their week 6 session, women will be asked to complete a 3-day voiding diary in the three days before their scheduled PTNS treatment and bring it to clinic. At their week 6 session, women will complete the UDI and PSQ questionnaires via REDCAP on an iPad in clinic. The same will be conducted for their week 12 session. Patient compliance of attending PTNS sessions will be recorded.

12.1.2. **TENS**: Women randomized to the TENS groups will begin therapy after their baseline evaluation is complete. They will be asked to purchase a TENS 7000 device (estimated cost $30) and will administer self-treatment at home, daily for 20 minutes, for 12 weeks total. Current practice in the Urogynecology clinic is to offer TENS therapy to women as an alternative to in-person maintenance therapy for after completing PTNS 12 sessions. TENS 7000 device is off label for its use in the treatment of OAB. If funding is secured, women in both PTNS and TENS group will be reimbursed with a merchandise card. Participants will be asked to bring their device to clinic to the ensure the correct device is used, standardize settings and provide the following patient education:

- Proper TENS device set up and pre-set standardized settings, detailed below
- Proper electrode pad placement that will be demonstrated. Electrodes will be traced with a skin marker during this clinic visit and pictures will be provided to ensure correct placement at home. If the patient has a camera, they can photograph electrode placement while in clinic.
- Determine intensity level
- Patients will be notified that they can go about their regular daily activities with the TENS device in place, so that treatment does not interfere with normal work or household duties. However, they will be instructed to not use the device while exercising due to sweat causing reduced adhesive function of electrodes and possible displacement.
- If a caretaker will be assisting the participant in use of the TENS unit due to physical limitations, they too will be instructed in set-up and use.
- An information handout with device settings, surface electrode placement, and treatment schedule will be provided at this initial clinic visit.

TENS treatment will be performed as follows (adapted from the most common setting from a s systematic review of TENS for OAB)[25]:

- Surface electrodes, 2 x 2 in diameter, will be placed 5 cm cephalad to the medial malleolus of the right or left ankle (patient's choice). The second surface electrode is placed on the medial aspect of the ipsilateral calcaneus. The electrodes are connected to the TENS device with the following pre-set settings:
- Mode: "M" or modulation

- Frequency: 10 Hz
- Pulse width: 200 µsec
- Intensity: to patient comfort level, as determined at clinic visit when device is verified. This is variable and participants will be told that as they use the device regularly, it is anticipated that they will become accustomed to stimulation and may need to change this setting.
- Women will then complete 20-minute daily TENS treatment using the settings above, for 12 weeks total.
- If women assigned to the TENS arm miss more than 2 daily sessions in a week on one of their weeks of treatment, they will be permitted to "make up" the missed sessions with an extra week of treatment at the end of the 12 weeks, and their "12 week" outcome measures will be performed following that week of make-up (13 weeks following randomization). Women that had this one "deficient week" with less than 5 treatments in a week and made up a week (with 5 or more daily treatments in the last week), their treatment course will be considered "fully compliant" with treatment and analyzed in the "per protocol" analysis as having completed the TENS treatment course per protocol.
- If women assigned to the TENS arm miss more than 2 days a week averaged over the course of the study thus far, they will not be allowed to make up the extra sessions and their participation in the study or outcome measurement will not be extended further than 13 weeks after randomization. However, they will not be withdrawn from the study for at-home TENS, and will be followed for outcomes and adverse events despite missing sessions of at-home TENS. Women that miss more than 2 daily sessions a week of TENS, as averaged over the 12 weeks, will be considered "not fully compliant" with TENS treatment, and will be analyzed in the "intention-to-treat" analysis in the TENS arm but not in the "per protocol" analysis in the PTNS arm.

Participants in the TENS group will receive weekly phone or email reminders to complete treatment program and inquire about any adverse effects. During their week 6 of treatment, women will be contacted by telephone to check concordance with treatment program, discuss any issues and ask them to complete a 3-day voiding diary, UDI and PSQ questionnaires via REDCAP. A log to track TENS use will be provided to participants. They will be able to access this via REDCAP. The same will be conducted at the end of week 12.

Table 1: Outcomes collected at various time points

	Baseline	6 weeks	12 weeks
Demographic and medical history	X		
OAB-q	X	X	X
3 day voiding diary	X	X	X
PSQ		X	X
Number of treatment sessions completed		X	X

12.2 Outcome measures:

12.2.1 **OAB-q:** The Overactive Bladder questionnaire is a validated tool to assess the patient's perceptions of symptom bother and impart on HRQL among patients with both continent and incontinent OAB. It is comprised of 8 symptom bother questions and 25 HRQL questions that form 4 subscales (coping, concern, sleep, and social interaction) and a total HRQL score. OAB-q is widely utilized in OAB/UUI[16,22,25,28,30–34].

12.2.2 **Voiding diary**: This is a patient completed record of micturition behavior to obtain objective data on subjective symptoms. The International Continence Society (ICS) recommends use of voiding diaries in the clinical assessment of patients with lower urinary tract symptoms[2]. It is a chart where patients record their urinary habits for at least 24 hours and is widely used in OAB/UUI[2,21,23,27,30,35–39].

12.2.3 **PSQ**: The Patient Satisfaction Question is a validated tool to assess patient satisfaction of treatment. It is comprised of a single question and is widely used in OAB/UUI[30,40,41].

13.Data Analysis

13.1. Data Analysis: Between and within group differences will be evaluated using Fisher's exact test for categorical variables and t-tests for continuous variables, as we expect the data will be normally distributed. Wilcoxon rank-sum test will be used for continuous variables that are not normally distributed. If there are any baseline differences between groups, a multivariate analysis will determine the contribution of these differences to observed differences (if any) between groups.

13.2. Intention-to-treat analysis: We plan to perform the primary analysis as "intention-to-treat" indicating that patients will be analyzed in the group to which they were randomized, regardless of compliance with study procedures, unless they asked to be withdrawn or were withdrawn by investigators due to safety or validity concerns. For example, PTNS patients that miss more than one session or do not make up a missed session of their office PTNS would still be analyzed in the "intention-to-treat" analysis as being in the PTNS group.

13.3. Per protocol analysis: We plan to perform a secondary analysis as "per protocol" indicating that patients will be analyzed in the group to which they were randomized only if they complete a full 12 weeks of treatment in compliance with study procedures, meaning that women assigned to the PTNS arm completed 12 weekly PTNS session in the office in 13 weeks or less, and women in the at-home TENS arm performed TENS stimulation at least 5 days per week for 12 weeks, as averaged over 12 weeks. For example, PTNS patients that miss more than one session or do not make up a missed session of their office PTNS will not be analyzed in the "per protocol" analysis as being in the PTNS group.

13.4. Power Analysis: Power analysis was performed based on previously reported means and standard deviation for the OAB-q. The primary outcome of this study is improvement in HRQL and symptom bother of OAB/UUI as measured by the OAB-q. We used the means and standard deviation for this questionnaire from a prior unpublished pilot RCT from Walter Reed comparing PTNS and TENS for the treatment of OAB. We have assumed a change score of greater than 10 points to be significant between groups based on the minimally important difference that has been previously established[28]. To achieve significance for a non-inferiority study using these assumptions we would need 80 patients,

40 per group to detect this difference with alpha = 0.05 and 80% power. To allow for a dropout of up to 30% we will enroll up to 130 patients to account for participants who are lost to follow up. As noted above, we plan to perform both per-protocol and intention-to-treat analysis, and adequate power much be achieved for both per-protocol and intention-to-treat analysis, with the per-protocol patients (those in the PTNS group completing at 12 treatments in a total of 13 weeks) being expected to be a lower sample size and take more recruitment and study follow-up to achieve power.

14. Provisions to Monitor the Data to Ensure the Safety of Subjects

There is no DSMB that will be monitoring safety of these procedures as the study risks are low. PTNS is a common treatment modality for OAB and UUI and standard of care[6,29] with minimal adverse effects[16,18,19,21,36]. TENS for OAB and UUI has been shown to be a low-risk intervention with minimal adverse effects[23–25,27,38,42,43]. Skin irritation, a "shocking" sensation, or temporary pain with stimulation could be experienced. Additionally, we will keep track of adverse events by asking patients about adverse effects at each weekly treatment session for the PTNS group and in weekly phone or email reminders for the TENS group during the course of the study. Because neither of the studied treatments are experimental or associated with above average risk we do not anticipate any significant adverse events. Participants will have access to a 24/7 phone number to reach research or clinical staff with concerns. All adverse events will be recorded in REDCap and reported to the study PI.

We do not anticipate any conditions that would trigger a suspension or termination of the research.

15. Withdrawal of Subjects

Participants may withdraw from the study at any time without penalty and will continue to receive the clinical standard of care. A subject may be withdrawn from the study without her consent at the discretion of the physician and study staff if they believe she no longer meets study inclusion criteria or if she meets exclusion criteria, if they believe that it is not in her best interest to continue study participation i.e., desire to undergo alternative treatment, or if they stop the study early due to scientific reasons. Investigators may withdraw a subject if the subject is not following the study protocol. If a woman is withdrawn from the study either at her own discretion or that of the research staff, she may continue with conservative or surgical management of her OAB/UUI in the usual fashion. If a participant chooses to withdraw from the study, the study intervention and PTNS device will no longer be provided to the participant and may not be available for purchase. If a participant withdraws from the TENS group, the TENS device they purchased will be kept by the participant.

To minimize withdrawal from the study, patients will be randomized after they have had what they feel to have been adequate time to consider whether or not they would like to participate in the study and they provide consent. According to the 2010 CONSORT guidelines, we will analyze all participants assessed for eligibility within the study. We will document reasons for withdrawal from the study if the participant willingly provides this

information. We will report eligibility criteria not met or reasons for declining participation in the study if the participant willingly provides this information. The withdrawal procedure is clearly documented in the study consent.

16. Data Management/Confidentiality

Participants will be given a de-identified study subject number. Data collection sheets and questionnaires will contain the subject number. No other patient identifiers will be collected on study forms. PHI including patient name, date of birth, phone number, email address and medical record number will be collected to track appointments and ensure patient follow-up. The data collection, HIPAA and consent forms will be maintained in a locked file cabinet in the locked Eubank research office or via REDCap. A separate folder will be designated for each participant. PHI will not be entered into the study database. The link between PHI and study IDs will be kept on a password protected computer on a secure UNM OBGYN department server.

The study database does not include sensitive information or information requiring additional protection.

Study binders will be kept in a locked cabinet in the research administrative area. In order to further ensure patient confidentiality, the identifying information will be kept separately from the numbered study files in a locked cabinet.

Electronic data entry will be performed on REDCAP, using the de-identified subject study number. The electronic data and subject link will be encrypted, password protected, and stored on the secure UNM OBGYN department server. This server's electronic security is monitored / maintained by the Health Sciences Library and Informatics Center (HSLIC). A REDCAP database will be created to collect, store and manage the data. REDCAP databases are reposed securely and all data entered is de-identified. The REDCAP database is only accessible using an individual unique login and password and access is only provided to co-investigators. Access is restricted to co-investigators and research staff and will be protected using the unique REDCAP login and password provided to each co-investigator.

Access to the files and REDCAP will be restricted to research personnel and Investigators and will be locked or password-protected using the unique REDCAP login and password provided to each co-investigator. The data will be stored for 6 years after completion of analysis and study closure and then will be destroyed.

A Certificate of Confidentiality will not be used to protect data from forced release. No identifying or study related data will be transported to outside locations. There will be no audio or video recordings or photographs taken.

17. Data and Specimen Banking

As stated above, the data collection, HIPAA and consent forms will be maintained in a locked file cabinet in the Eubank research area. A separate file will be designated

for each participant. A key matching study number to subject's name will be stored on a password protected computer on a secure UNM OBGYN department server. In order to further ensure patient confidentiality, the identifying information will be kept separately from the numbered study files in a locked cabinet. The data will be maintained for 6 years after completion of the study and then destroyed.

18. Risks to Subjects

Risks of enrollment in the study include loss of confidentiality. We will take every measure to try to ensure the security and confidentiality of participants. Participants will be recruited in a private room or in a private location via phone or HIPAA compliant ZOOM and will have ample time to consider whether they want to participate in the study. Also, locked cabinets will be used to protect patient consent information and collected data. The link identifying patients and their study numbers will be also stored on a password protected computer on a secure UNM OBGYN department server.

Additionally, each patient who will be offered enrollment will already have agreed to non-surgical management of her OAB. There are minimal risks with being assigned to either study intervention in this RCT. PTNS could cause pain, bruising, tingling or bleeding at the insertion site,leg cramps, numbness/pain under the sole of the foot, generalized swelling, worsening of incontinence, generalized headache and vasovagal response to needle placement, but these are rare or occasional[21,43]. No serious adverse effects, like permanent or irreversible nerve damage or permanent or long-term loss of muscle function, have been reported for PTNS. TENS could cause temporary skin irritation, leg cramping or numbness/pain, however no adverse events, such as permanent or long term nerve damage or loss of muscle function, have been reported[23,25,27]. Emotional discomfort due to the reflective nature of the questionnaires or lack of symptom improvement is also possible. Both treatment randomizations in this study are well established as options for OAB with an excellent safety profile.

Participants may also have to pay for the cost of transport to clinic visits and data charges for mobile devices for phones call or ZOOM visits.

Pregnant women will not be included in the study, so there is no risk to embryos/fetuses. If there is concern for pregnancy, we will test the participant on the day of enrollment. If they are pregnant, the patient meets exclusion criteria and will be ineligible to participate.

There are no risks to those who are not subjects.

19. Potential Benefits to Subjects

The patients enrolled are already opting for third line, non-surgical treatment of their OAB. Participation in this study may help to improve an individual participant's condition, but it is also possible that the condition may not improve. There is no guarantee that any individual will personally benefit by participating in this research study. Women randomized to TENS

will potentially get benefit from having a personal device they can keep and use on their own time. Women randomized to TENS will not require weekly in-person office visits, which will save time on travel, office visits, and potential COVID-19 or other viral exposures as compared to the PTNS group. Participation in this study may provide information that may help other people who have a similar medical problem in the future. The literature supports improvement of QOL with improved OAB symptoms. PTNS and TENS have both been successfully used to treat OAB and UUI in the past.

20. Recruitment Methods

The Urogynecology clinics at UNM Eubank, and SRMC have a large referral population of patients with pelvic floor conditions such as OAB. Subjects will be identified in the clinics at UNM Eubank clinic and SRMC by investigators when they present either in person or virtually (telephone or Zoom visits) for visits for OAB care. The patients will be counseled about possible treatment options for OAB and they will be introduced to the study and provided with written information that may help them decide if participation in the study is right for them. Subjects are encouraged to consult with family, friends, and primary health care providers, as well as communicate any questions they may have before beginning the consent process. We will request a waiver of HIPAA authorization for recruitment purposes.

If a woman declines to participate or is withdrawn from the study either by her desire or that of the research staff, she will be offered the same treatment options. Her follow up appointments will be the same regardless of participation in the study.

Potential participants may also self-identify through a recruitment material flyer that will be placed in Eubank clinic restrooms, waiting area and in the OB/GYN department at UNM. The proposed recruitment flyer is uploaded in the supplemental materials section.

21. Provisions to Protect the Privacy Interests of Subjects

Privacy concerns are considered with every patient seen at the UNM and SRMC clinics. Participants approached and/or interviewed in the clinic setting will be in either private offices or examination rooms in the clinics, personal Zoom or on telephone calls that are HIPAA compliant. All staff, including research staff, are well-versed in sensitive health care discussions and procedures. Telephone interviews for recruitment and study data gathering are conducted in the research staff area or private physician offices, where all staff have received CITI Training. The office area designated for the entire Urogynecology research staff is isolated from the clinical administrative staff area, providing protection for participants and potential participants during screening, recruitment, study-designated calls, and data entry. All study sheets used to collect patient information will be de-identified.

At all times throughout the clinical investigation, confidentiality will be observed by all parties involved. All data will be secured against unauthorized access. Privacy and confidentiality of information about each subject will be preserved in study reports and in any publication. Each subject participating in this study will be assigned a unique identifier. An IRB-approved HIPAA authorization within the consent is required to be given to the

patient. All documents containing personal health information (screening logs, consent documents, data forms) are maintained in locked cabinets with access available only to research staff and investigators. Data is entered into a password protected system. No individual identifiers, other than email to send consent and questionnaire forms, are entered into the system. The sole link with personal information is maintained by the research team on a password protected computer on a secure UNM OBGYN department server with access limited to authorized research staff and investigators. This information is only to be used at the study center.

22. Economic Burden to Subjects

The cost of the TENS 7000 device and associated materials will be the responsibility of the subject if randomized to the TENS group. If funds become available, we will plan to compensate participants in both the PTNS and TENS arms with a $50 merchandise card. Participants will not be billed for any other study materials.

Participants have already chosen to undergo third line, non-surgical treatment of their OAB/UUI and will receive prior authorization from their third-party payers if randomized to PTNS or will have worked out financial assistance if needed. These costs will be billed to their insurance provided and costs may range from copay only to full cost of treatment.

Research Procedures	**Number of Samples/Procedures**	**Responsible Party**	
		Study	**3rd Party Payer or Participant**
TENS Device	1	☐	☒
_____	_____	☐	☐
Standard of Care Procedures	**Number of Samples/Procedures**	**Responsible Party**	
		Study	**3rd Party Payer or Participant**
PTNS Treatment	12	☐	☒
Clinic visit	1-2	☐	☒
Transportation to PTNS treatment	0-12	☐	☒
Transportation to Clinic Visits	1-2	☐	☒
Phone Visit – remote	2	☐	☒
_____	_____	☐	☐
_____	_____	☐	☐
_____	_____	☐	☐

23. Compensation

At this time, no compensation will be provided to study participants. If funds become available, each participant will be compensated with a merchandise cards worth $50: a $25 merchandise card when they complete 6 weeks of treatment (6 weekly sessions in the case of the PTNS group) and another $25 merchandise card when they complete 12 weeks of treatment (12 weekly sessions in the case of the PTNS group). These compensations will be

provided to patients when they complete 6 sessions or 12 sessions and the resulting outcomes measures, regardless of when they complete them. So, for example, if a PTNS patient does 6 sessions of PTNS in an 8-week period, they will get the $25 merchandise card when they complete the 6 sessions (after 8 weeks). A modification will also be submitted to the IRB to update the protocol and consent with compensation amounts. This payment will be reasonable compensation for the purchase of a TENS device and the inconvenience of participating in a research study due to the additional time the study questionnaires will require from the participant.

24. Compensation for Research-Related Injury

If participants are injured or become sick as a result of this study, which is extremely unlikely given the nature of the interventions, UNMHSC will provide emergency treatment at the study participant's cost. No commitment is made by the University of New Mexico Health Sciences Center to provide free medical care or money for injuries to participants of the study. Reimbursement for treatment for all related costs of care will be sought from the participant insurer, managed care plan, or other benefits program. The participant will be responsible for any associated co-payments or deductibles required by the insurance. Participants will be encouraged to report any illness or injury they believe to be related to the study to the investigator or research staff. Participants will be given telephone contact information for the Urogynecology office for the purpose of asking any questions or stating any concerns about the study or treatment as a research subject. They may also be directed toward the HRPO. This language will be stated in the consent document, and reviewed during the informed consent process.

25. Consent Process

Patients will be approached about the research study at the Urogynecology clinic or via virtual consultation at UNM Eubank or SRMC during a discussion for the management of OAB/UUI. Each patient undergoes counseling in a private room with a closed door to ensure privacy. The physicians in the Urogynecology division and research staff will be able to give a paper or electronic consent to patients to allow for inclusion. REDCap will be utilized to eConsent participants with the HRRC approved PDF consent uploaded into REDCap. Our division routinely treats this condition and are highly qualified to counsel patients regarding the risks, benefits, alternatives for the treatment. Care will not be withheld if they decide not to participate. If the patient prefers, she may also be counseled about study participation via ZOOM or phone following her clinic appointment by providers or study personnel.

The patients who would like to participate in the study will be consented during their new or return visit in the Urogynecology clinic. Participants will have these multiple opportunities to ask any questions and they will also be provided with the clinic's contact information to get in touch with research investigators to address any additional questions or concerns.

Subjects will be reassured that participation is completely voluntary and does not affect their treatment, their relationship with their providers, or the university to minimize the possibility of coercion or undue influence. The patients will be asked that they understand the opportunity to participate and their complete freedom to decline. This will also be asked if they understand and if they have any questions. There is no minimum time period needed between informing the patient of the study and time of consent. Subjects will be encouraged to take as much time as they need.

This study will obtain HIPAA authorization prior to enrollment. HIPAA authorization will be reviewed with all participants by the physician or research staff obtaining consent. Specific information that will be obtained includes prior medical history, surgical history, reproductive health history including child bearing, drug allergies, age, and ethnicity. This information will be obtained by health care providers, not research coordinators, as deemed necessary for a more complete and accurate medical history of the patient.

Subjects not fluent in English:

Patients will be consented with a certified translator if Spanish speaking. Spanish-speaking patients will be offered information about risks, benefits, and alternatives to study participation in a private setting and given adequate time to consider the risks and benefits of the study prior to offering consent or declining to participate. The Spanish consent will be translated from the English consent once the English consent is approved, and we will submit a modification in Huron IRB to update the study with Spanish materials in the future.

Cognitively Impaired Adults/Adults Unable to Consent/Use of a Legally Authorized Representative:

NA. Cognitively impaired subjects will not be included in this study.

Subjects who are not yet adults (infants, children, teenagers):

NA. Only subjects ≥ 18 years of age will be included in this study.

Waiver or Alteration of Consent Process (consent will not be obtained, required element of consent will not be included, or one or more required elements of consent will be altered)

NA. There will be no waiver or alteration of the consent process.

26. Documentation of Consent

26.1. We plan to document consent and the consent form is attached.

26.2. We do not plan on collecting or storing tissue samples.

27. Study Test Results/Incidental Findings

We do not anticipate that the research being conducted will result in incidental findings. Every patient will receive the practice's standard of care regarding workup of OAB, which may include different laboratory tests, urine culture or urodynamic testing if unclear cause of incontinence, or imaging studies, as determined by their other active medical issues. These results are not directly a part of the research being conducted and will hence be disclosed to the patient. They will not, however, affect randomization.

28.Sharing Study Progress or Results with Subjects

We do not intend to share study progress with participants while the study is underway as not to introduce bias. We do not intend to seek out study participants to disseminate information once the study is complete. Women who are interested in the results will be provided the information where to read the manuscript once it is published. Study results for individual participants will not be shared.

29. Inclusion of Vulnerable Populations

NA. There will not be any vulnerable populations included in this study.

30. Community-Based Participatory Research

NA. There will be no involvement of the community in this research.

31. Research Involving American Indian/Native Populations

NA. This research does not specifically target this population. If an American Indian woman is a candidate for the study, she will be offered participation if she is able to speak/read/write in English or Spanish.

32. Transnational Research

NA. This study is domestic.

33.Drugs or Devices

The devices used in this study are considered standard of care for the use and treatment of OAB. Urgent PC® Neuromodulation Device made by Uroplasty was FDA approved for use 10/17/2005 with the updated leads and device approved 10/21/2010 (see FDA website https://www.accessdata.fda.gov/cdrh_docs /pdf10/K101847.pdf). The PTNS device is stored at the UNM Eubank Urogynecology clinic and only handled and administered by trained healthcare providers. TENS 7000® device made by Roscoe Medical was approved by the FDA on 03/24/2008 for use for pain therapy(See FDA website https://www.accessdata. fda.gov/cdrh_docs/pdf8/K080661.pdf). The TENS system is available over the counter (FDA 501(k) Summary provided in Supplemental documents) and routinely used for overactive bladder therapy, but is considered an off-label use. Recently, a TENS device specifically marketed for treatment of OAB was FDA cleared as Substantially Equivalent on 03/19/2021 (see FDA website https://www.accessdata.fda.gov/cdrh_docs/pdf19/K192731.pdf). However, the device is not

currently available for purchase, therefore we will use the TENS device described above. Participants will be educated on its use, storage and maintenance at their clinic visit.

34.Principal Investigator's Assurance

By submitting this study in the Huron IRB system, the principal investigator of this study confirms that:

☒ The information supplied in this form and attachments are complete and correct.

☒ The PI has read the Investigator's Manual and will conduct this research in accordance with these requirements.

☒ Data will be collected, maintained and archived or destroyed per HSC Data Security Best Practices, including:

1. **Best Practice for data collection** is to be directly entered onto a data collection form that is stored in a secured access folder on HSC central IT managed network storage (such as the N:\Research-Studies drive), or in a secure HSC Information Security approved system such as REDCap.
2. **Temporary storage -- de-identified data collection**, if done in a clinical setting or other setting that does not allow direct entry into a secured system, may be temporarily stored using encrypted removable (e.g. CD-ROM (a compact disc used as a read-only optical memory device for a computer system), USB flash/thumb drive (a small external flash drive that can be used with any computer that has a USB port), etc.) media or a university owned electronic storage device or hard copy document. This temporarily stored data must be transferred to HSC central IT managed network storage and deleted from the temporary device as soon as possible. **The important security safeguard is that no identifiers be included if the data is entered or stored using a storage container that is not managed by HSC central IT.**
3. **Permanent (during data analysis, after study closure) storage** must reside on HSC central IT managed network storage (such as the N:\Research-Studies Drive). Processing of data (aggregation, etc.) are to be carried out in such a way as to avoid creating/retaining files on untrusted or unsecure storage devices/computers (an example of an unapproved storage location would be storing the data locally on your HSC computer hard drive rather than on the HSC network drives). Trusted devices are HSC managed and provide one or more of following safeguards: access logs, encryption keys, backups, business continuity and disaster recovery capabilities.
4. **Alternate storage media** must be approved by HSC IT Security as meeting or exceeding HSC central IT provided security safeguards.

35.CHECKLIST SECTION

This section contains checklists to provide information on a variety of topics that require special determinations by the IRB. Please complete all checklists relevant to your research.

36. Partial Waiver of Consent for Screening/Recruitment

NA. We are not requesting a partial waiver of consent for screening/recruitment.

37. Partial Waiver of HIPAA Authorization for Screening/Recruitment

We are requesting a partial waiver of HIPAA authorization for screening/recruitment.

A. Will you be recording any PHI when conducting the records review to identify potential subjects and/or determine eligibility?

☒ Yes. Describe: We will review medical records of participants to ensure they are eligible for the study. In particular, we will confirm if they have a diagnosis of OAB or UUI and ensure they do not have an alternative diagnosis that would make them ineligible.

☐ No

B. If you answered "Yes" to question 6 above, please describe when you will destroy identifiers (must be the earliest opportunity consistent with the conduct of the research) or provide justification for why they must be retained:

If women are enrolled in the study after recruitment and informed consent, their PHI will be maintained in a locked file cabinet in the locked Eubank research office, in a separate folder designated for each participant. PHI will not be entered into the study database. The data will be stored for 5 years after completion of analysis and then will be destroyed.

If women are not enrolled, PHI collected for the purpose of screening and recruitment will be immediately destroyed.

C. The PHI accessed or recorded for identification/screening purposes will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.

☒ True

☐ False

38. Waiver of Documentation of Consent

NA. We are not requesting a waiver of documentation of consent

39. Alteration of Consent

NA. We are not requesting an alteration of consent.

40. Full Waiver of Consent/Parental Permission

NA. We are not requesting a full waiver of consent/parental permission.

41. Full Waiver of Consent/Parental Permission (Public Benefit or Service Programs)

NA. We are not requesting a full waiver of consent/parental permission.

42. Full Waiver of HIPAA Authorization (Checklist)

NA. We are not requesting a full waiver of HIPAA authorization.

43.Other Waiver Types (Checklist)

NA. We are not requesting other waiver types.

44.Vulnerable Populations (Checklist)

A. Adults with Cognitive Impairments
NA. Adults with cognitive impairments will not be included in this study.

B. Children
NA. Children will not be included in this study.

C. Pregnant Women and Fetuses
NA. Pregnant women and fetuses will not be included in this study.

D. Neonates of Uncertain Viability or Nonviable Neonates
NA. Neonates of uncertain viability and nonviable neonates will not be included in this study.

E. Nonviable Neonates
NA. Nonviable neonates will not be included in this study.

F. Biomedical and Behavioral Research Involving Prisoners
NA. Prisoners will not be included in this study.

45.Medical Devices (Checklist)

Complete this checklist if the research evaluates the safety or effectiveness of a medical device. If more than one medical device is being evaluated, provide the requested information for each.

A. Device Name: TENS 7000

B. Manufacturer: Roscoe Medical

C. Does the research involve a Significant Risk Device under an IDE?

☐Yes. Include documentation of the FDA approval of the IDE with your submission. *Acceptable methods of documentation include: (1) FDA letter noting IDE number and approval status; (2) Industry sponsor letter noting IDE number and FDA*

approval status; or (3) FDA-approved industry sponsor protocol with IDE number noted

☒No

D. Is the research IDE-exempt?

☐Yes. Include a FDA letter with your submission noting the determination that the research is IDE-exempt or a letter from the sponsor (or sponsor-investigator) justifying why they believe the research is IDE-exempt*.

☒No

E. Does the research involve a Non-Significant Risk (NSR) Device?

☒Yes. Include a FDA letter with your submission noting the determination that the research is NSR or a letter from the sponsor (or sponsor-investigator) justifying why they believe the research is NSR**.

☐No

* This FDA guidance includes a description for when a device study is exempt from the IDE requirements:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127067.pdf

**This FDA guidance includes information on how to differentiate between Significant Risk and Non-Significant Risk device studies:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf

46. Export Control (Checklist)

NA. There will not be any export control concerns.

47.Data Transfer/Sharing/Storage (Checklist) (required –do not delete even if the answer is "No")

Data Use Agreement (DUA) Contacts:

Sponsored Projects Office

- Aida Andujo, Manager, AAndujo@salud.unm.edu
- Siiri Wilson, Contract Specialist, SiWilson@salud.unm.edu

Privacy Office

- Laura Putz, Privacy Officer, LPutz@salud.unm.edu
- Gayle Shipp, Privacy Specialist, GShipp@salud.unm.edu

Information Security Office

- Information Security Office, HSC-ISO@salud.unm.edu

Provide all information requested if the research involves transferring/sharing of data with an external entity (institution, company, etc.).

A. Will UNM data be transferred/shared with an external entity (i.e. another institution, company, etc.) or will an external entity's data be transferred/shared with UNM?

☐Yes. **If yes, all questions must be answered congruently based on protocol provisions.**

☒ No. **If no, the remainder of this section does not apply.**

48.Specimen Transfer/Sharing (Checklist) (required –do not delete even if the answer is "No")

Provide all requested information if the research involves transferring/sharing of specimens with an external entity (institution, company, etc.).

A. Will specimens be transferred/shared with an external entity (institution, company, etc.)?

☐ Yes. **If yes, all questions must be answered congruently based on protocol provisions.**

☒No. **If no, the remainder of this section does not apply.**

References

1. Stewart W, Van Rooyen J, Cundiff G, et al. Prevalence and burden of overactive bladder in the United States. *World J Urol*. 2003;20(6):327-336. doi:10.1007/s00345-002-0301-4

2. Haylen BT, de Ridder D, Freeman RM, et al. An international urogynecological association (IUGA)/international continence society (ICS) joint report on the terminology for female pelvic floor dysfunction. *Neurourol Urodyn*. 2010;29(1):4-20. doi:10.1002/nau.20798

3. Hu TW, Wagner TH, Bentkover JD, et al. Estimated economic costs of overactive bladder in the United States. *Urology*. 2003;61(6):1123-1128. doi:10.1016/S0090-4295(03)00009-8

4. Abrams P, Kelleher CJ, Kerr LA, Rogers RG. Overactive Bladder Significantly Affects Quality of Life. *Am J Manag CARE*. 2000;6(11):11.

5. Tubaro A. Defining overactive bladder: Epidemiology and burden of disease. *Urology*. 2004;64(6, Supplement 1):2-6. doi:10.1016/j.urology.2004.10.047

6. Gormley EA, Lightner DJ, Burgio KL, et al. Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: AUA/SUFU Guideline. *J Urol*. 2012;188(6S):2455-2463. doi:10.1016/j.juro.2012.09.079

7. Gopal M, Haynes K, Bellamy SL, Arya LA. Discontinuation rates of anticholinergic medications used for the treatment of lower urinary tract symptoms. *Obstet Gynecol*. 2008;112(6):1311-1318. doi:10.1097/AOG.0b013e31818e8aa4

8. Kalder M, Pantazis K, Dinas K, Albert US, Heilmaier C, Kostev K. Discontinuation of Treatment Using Anticholinergic Medications in Patients With Urinary Incontinence. *Obstet Gynecol*. 2014;124(4):794-800. doi:10.1097/AOG.0000000000000468

9. Monga AK, Tracey MR, Subbaroyan J. A systematic review of clinical studies of electrical stimulation for treatment of lower urinary tract dysfunction. *Int Urogynecology J*. 2012;23(8):993-1005. doi:10.1007/s00192-012-1691-5

10. Sutherland SE, Lavers A, Carlson A, Holtz C, Kesha J, Siegel SW. Sacral nerve stimulation for voiding dysfunction: One institution's 11-year experience. *Neurourol Urodyn*. 2007;26(1):19-28. doi:10.1002/nau.20345

11. Kraus SR, Shiozawa A, Szabo SM, Qian C, Rogula B, Hairston J. Treatment patterns and costs among patients with OAB treated with combination oral therapy, sacral nerve stimulation, percutaneous tibial nerve stimulation, or onabotulinumtoxinA in the United States. *Neurourol Urodyn*. 2020;39(8):2206-2222. doi:10.1002/nau.24474

12. Nitti VW, Dmochowski R, Herschorn S, et al. OnabotulinumtoxinA for the Treatment of Patients with Overactive Bladder and Urinary Incontinence: Results of a Phase 3, Randomized, Placebo Controlled Trial. *J Urol*. 2013;189(6):2186-2193. doi:10.1016/j.juro.2012.12.022

13. Kuo HC. Bladder base/trigone injection is safe and as effective as bladder body injection of onabotulinumtoxinA for idiopathic detrusor overactivity refractory to antimuscarinics. *Neurourol Urodyn*. 2011;30(7):1242-1248. doi:10.1002/nau.21054

14. Davis NF, Burke JP, Redmond EJ, Elamin S, Brady CM, Flood HD. Trigonal versus extratrigonal botulinum toxin-A: a systematic review and meta-analysis of efficacy and adverse events. *Int Urogynecology J*. 2015;26(3):313-319. doi:10.1007/s00192-014-2499-2

15. Cui Y, Zhou X, Zong H, Yan H, Zhang Y. The efficacy and safety of onabotulinumtoxinA in treating idiopathic OAB: A systematic review and meta-analysis. *Neurourol Urodyn*. 2015;34(5):413-419. doi:10.1002/nau.22598

16. Peters KM, Carrico DJ, Perez-Marrero RA, et al. Randomized Trial of Percutaneous Tibial Nerve Stimulation Versus Sham Efficacy in the Treatment of Overactive Bladder Syndrome: Results From the SUmiT Trial. *J Urol*. 2010;183(4):1438-1443. doi:10.1016/j.juro.2009.12.036

17. Peters KM, Carrico DJ, MacDiarmid SA, et al. Sustained therapeutic effects of percutaneous tibial nerve stimulation: 24-month results of the STEP study. *Neurourol Urodyn*. 2013;32(1):24-29. doi:10.1002/nau.22266

18. Staskin DR, Peters KM, MacDiarmid S, Shore N, de Groat WC. Percutaneous Tibial Nerve Stimulation: A Clinically and Cost Effective Addition to the Overactive Bladder Algorithm of Care. *Curr Urol Rep*. 2012;13(5):327-334. doi:10.1007/s11934-012-0274-9

19. Peters KM, MacDiarmid SA, Wooldridge LS, et al. Randomized Trial of Percutaneous Tibial Nerve Stimulation Versus Extended-Release Tolterodine: Results From the Overactive Bladder Innovative Therapy Trial. *J Urol*. 2009;182(3):1055-1061. doi:10.1016/j.juro.2009.05.045

20. MacDiarmid SA, Peters KM, Shobeiri SA, et al. Long-Term Durability of Percutaneous Tibial Nerve Stimulation for the Treatment of Overactive Bladder. *J Urol*. 2010;183(1):234-240. doi:10.1016/j.juro.2009.08.160

21. Burton C, Sajja A, Latthe P m. Effectiveness of percutaneous posterior tibial nerve stimulation for overactive bladder: A systematic review and meta-analysis. *Neurourol Urodyn*. 2012;31(8):1206-1216. doi:10.1002/nau.22251

22. Chapple C, Khullar V, Gabriel Z, Dooley JA. The Effects of Antimuscarinic Treatments in Overactive Bladder: A Systematic Review and Meta-Analysis. *Eur Urol*. 2005;48(1):5-26. doi:10.1016/j.eururo.2005.02.024

23. Schreiner L, dos Santos TG, Knorst MR, da Silva Filho IG. Randomized trial of transcutaneous tibial nerve stimulation to treat urge urinary incontinence in older women. *Int Urogynecology J*. 2010;21(9):1065-1070. doi:10.1007/s00192-010-1165-6

24. Schreiner L, Nygaard CC, dos Santos TG, Knorst MR, da Silva Filho IG. Transcutaneous tibial nerve stimulation to treat urgency urinary incontinence in older women: 12-month follow-up of a randomized controlled trial. *Int Urogynecology J*. 2021;32(3):687-693. doi:10.1007/s00192-020-04560-6

25. Booth J, Connelly L, Dickson S, Duncan F, Lawrence M. The effectiveness of transcutaneous tibial nerve stimulation (TTNS) for adults with overactive bladder syndrome: A systematic review. *Neurourol Urodyn*. 2018;37(2):528-541. doi:10.1002/nau.23351

26. Daly CME, Loi L, Booth J, Saidan D, Guerrero K, Tyagi V. Self-management of overactive bladder at home using transcutaneous tibial nerve stimulation: a qualitative study of women's experiences. *BMC Womens Health*. 2021;21(1):374. doi:10.1186/s12905-021-01522-y

27. Ramírez-García I, Blanco-Ratto L, Kauffmann S, Carralero-Martínez A, Sánchez E. Efficacy of transcutaneous stimulation of the posterior tibial nerve compared to percutaneous stimulation in idiopathic overactive bladder syndrome: Randomized control trial. *Neurourol Urodyn*. 2019;38(1):261-268. doi:10.1002/nau.23843

28. Coyne KS, Matza LS, Thompson CL, Kopp ZS, Khullar V. Determining the Importance of Change in the Overactive Bladder Questionnaire. *J Urol*. 2006;176(2):627-632. doi:10.1016/j.juro.2006.03.088

29. Lightner DJ, Gomelsky A, Souter L, Vasavada SP. Diagnosis and Treatment of Overactive Bladder (Non-Neurogenic) in Adults: AUA/SUFU Guideline Amendment 2019. *J Urol*. 2019;202(3):558-563. doi:10.1097/JU.0000000000000309

30. Dyer KY, Xu Y, Brubaker L, et al. Minimum important difference for validated instruments in women with urge incontinence. *Neurourol Urodyn*. 2011;30(7):1319-1324. doi:10.1002/nau.21028

31. Surbala L, Khuman P, Mital V, Devanshi B, Shah C. NEUROMODULATION FOR OVERACTIVE BLADDER WITH TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION IN ADULTS - A RANDOMIZED CLINICAL STUDY. *undefined*. Published online 2014. Accessed November 9, 2021. https://www.semanticscholar.org/paper/NEUROMODULATION-FOR-OVERACTIVE-BLADDER-WITH-NERVE-A-Surbala-Khuman/70627eb1a2593d87baa80bde09fe062ecca9d345

32. Coyne KS, Matza LS, Thompson CL. The responsiveness of the Overactive Bladder Questionnaire (OAB-q). *Qual Life Res*. 2005;14(3):849-855. doi:10.1007/s11136-004-0706-1

33. Coyne K, Revicki D, Hunt T, et al. Psychometric Validation of an Overactive Bladder Symptom and Health-Related Quality of Life Questionnaire: The OAB-q. *Qual Life Res*. 2002;11(6):563-574.

34. Matza LS, Thompson CL, Krasnow J, Brewster-Jordan J, Zyczynski T, Coyne KS. Test-retest reliability of four questionnaires for patients with overactive bladder: The overactive bladder questionnaire (OAB-q), patient perception of bladder condition (PPBC), urgency questionnaire (UQ), and the primary OAB symptom questionnaire (POSQ). *Neurourol Urodyn*. 2005;24(3):215-225. doi:10.1002/nau.20110

35. Salatzki J, Liechti MD, Spanudakis E, et al. Factors influencing return for maintenance treatment with percutaneous tibial nerve stimulation for the management of the overactive bladder. *BJU Int*. 2019;123(5A):E20-E28. doi:10.1111/bju.14651

36. Van Der Pal F, Van Balken MR, Heesakkers JP f. a., Debruyne FM j., Bemelmans BL h. Percutaneous tibial nerve stimulation in the treatment of refractory overactive bladder syndrome: is maintenance treatment necessary? *BJU Int*. 2006;97(3):547-550. doi:10.1111/j.1464-410X.2006.06055.x

37. Locher JL, Goode PS, Roth DL, Worrell RL, Burgio KL. Reliability Assessment of the Bladder Diary for Urinary Incontinence in Older Women. *J Gerontol Ser A*. 2001;56(1):M32-M35. doi:10.1093/gerona/56.1.M32

38. de Sèze M, Raibaut P, Gallien P, et al. Transcutaneous posterior tibial nerve stimulation for treatment of the overactive bladder syndrome in multiple sclerosis: Results of a multicenter prospective study. *Neurourol Urodyn*. 2011;30(3):306-311. doi:10.1002/nau.20958

39. Bright E, Drake MJ, Abrams P. Urinary diaries: Evidence for the development and validation of diary content, format, and duration. *Neurourol Urodyn*. 2011;30(3):348-352. doi:10.1002/nau.20994

40. Burgio KL, Goode PS, Richter HE, Locher JL, Roth DL. Global ratings of patient satisfaction and perceptions of improvement with treatment for urinary incontinence: Validation of three global patient ratings. *Neurourol Urodyn*. 2006;25(5):411-417. doi:10.1002/nau.20243

41. Goode PS, Burgio KL, Kraus SR, et al. Correlates and predictors of patient satisfaction with drug therapy and combined drug therapy and behavioral training for urgency urinary incontinence in women. *Int Urogynecology J*. 2011;22(3):327-334. doi:10.1007/s00192-010-1287-x

42. Ammi M, Chautard D, Brassart E, Culty T, Azzouzi AR, Bigot P. Transcutaneous posterior tibial nerve stimulation: evaluation of a therapeutic option in the management of anticholinergic refractory overactive bladder. *Int Urogynecology J*. 2014;25(8):1065-1069. doi:10.1007/s00192-014-2359-0

43. Lazarou G, Du C, Medamana J, Grigorescu B. Percutaneous tibial nerve stimulation associated with occipital headaches: a review of the adverse effects of percutaneous tibial nerve stimulation. *Obstet Gynecol Int J*. 2018;9(5). doi:10.15406/ogij.2018.09.00363