Reducing anticholinergic bladder medication use in spinal cord injury with home neuromodulation

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STUDY PROTOCOL

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Reducing anticholinergic bladder medication use in spinal cord injury with home neuromodulation

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GENERAL INFORMATION

Name and address of the sponsor of the study:

UTHealth KL2 award
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Mission Connect [019-108]
[redacted]

Name and address of the person authorized to sign the protocol and amendments:

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Name and address of study monitor:

No plan for study monitor

Name, title, address and telephone number(s) of the medical expert for the trial

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Name and addresses of the clinical laboratories and/or other institutions involved in the trial

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STUDY PROTOCOL

** please note, this protocol is the next step in studying home TTNS (**HSC-MS-17-0423**.) Since feasibility has been established, we are looking to study efficacy with this proposed randomized sham-control trial.**

1. BACKGROUND AND RATIONALE

There are over 1 million people living with spinal cord injury (SCI) with devastating functional impairments including paralysis and bowel/bladder dysfunction.[1] Nearly every person with SCI develops neurogenic bladder.[2] The gold-standard treatment of neurogenic bladder involves the use of anticholinergic bladder medications, which suffers from non-compliance and adverse medication effects.[3] Improving bowel and bladder function is the number one priority that people living with SCI wish to achieve.[4] Treatments such as bladder neuromodulation with tibial nerve stimulation (TNS), have been shown to improve bladder function in SCI without adverse effects.[5 6] Percutaneous TNS (PTNS) is performed using a needle inserted into the skin to direct the electric current, provided by trained healthcare workers in the clinic setting under physician supervision. This requires frequent visits in a population with known accessibility challenges. Transcutaneous TNS (TTNS) accomplishes the same goal, but uses non-invasive surface electrodes. However, this modality has only been performed in the clinic setting. There is currently a gap in our knowledge about the safety and feasibility of TTNS at home for bladder neuromodulation in SCI. The proposed research is innovative, in our opinion, because it represents a substantive departure from the status quo by using TTNS at home to replace anticholinergic medications and provide a dignified treatment that can improve quality of life.

Electric stimulation is routinely being used in neurorehabilitation. The PI has published reviews on the current state of rehabilitation in SCI, describing the use of FES and NMES in SCI for motor/sensory recovery, decreasing spasticity, and improving neuropathic pain.[7-9] Patients are routinely prescribed electric stimulation units for home use to help with motor recovery and strengthening. We propose the development of a protocol that uses the same equipment in a novel way to affect bladder function. We have tested this in 2 pilot trials and published the results of the first. [10]

1. General Introduction

The management of NLUTD in SCI includes: maintaining continence via timed voiding, catheterization (intermittent or indwelling), use of OAB medications, chemodenervation, and/or surgery. While these approaches have dramatically improved morbidity and mortality related to the upper urinary tracts, they are also associated with significant functional impairment[11], challenges to community re-entry[12-14], expense[14 15], adverse effects [11 14], and ultimately QOL [11] (see **Table 1**).

We propose a **non-invasive, readily-available,** and **inexpensive** approach that can be **used at home** (and reduces reliance on the health care system) to improve bladder-related health and function, while overcoming existing barriers: ***TTNS (transcutaneous tibial nerve stimulation)***, the transcutaneous adaptation of PTNS (percutaneous TNS). PTNS has demonstrated equal efficacy to newer OAB medications in a randomized control trial of 100 SCI subjects, while boasting fewer adverse events. [6] Although a large study of this nature has not been performed with TTNS in SCI, in the population of people with NLUTD due to Multiple Sclerosis (MS), TTNS has been shown to improve urinary urgency in more than 80% of the subjects, reduce urinary frequency, and had a positive impact on QOL measures. [16]

Table 1. Limitations of current treatment approaches to NLUTD

		Pharmacologic		
Limitation	**Bladder Management**	**OAB medications**	**Chemo-denervation**	**Neuromodulation (NM)**
Side Effects	Functional limitations vary by bladder management method (i.e., incontinence between caths, supply management, hand function, etc.)	Sedation, dry mouth, constipation, etc. Increased risk of dementia Interaction with other medications	Urinary tract infectio Change in bladder management may be necessary	Surgical complications with sacral NM
Non-Compliance		Higher doses required in SCI	Requires urologic procedure every 3-6 months	PTNS> 55% non-compliance
Access/ Expense		Newer medications with decreased side effects are often not covered by insurance or are too expensive	Largely unavailable, very expensive, involves invasive procedure.	Both PTNS and sacral NM largely unavailable and very expensive

The Stamobil + is an electric stimulation unit used for the rehabilitation of those with paralysis. It is currently used at TIRR Memorial Hermann on nearly every patient with paralysis for the purposes of motor and sensory recovery. We have used the proposed TTNS protocol for research purposes (HSC-MS-15-0806, HSC-MS-17-0423). Based on the pilot safety data, we believe we should test the efficacy of the protocol for home use in a randomized control trial. The proposed protocol is using the device in a new way, to stimulate the nerves of the legs which is known to effect the bladder in a process described as “neuromodulation.”

Electric stimulation is currently being used in neurorehabilitation. The candidate has published reviews on the current state of rehabilitation in SCI, describing the use of FES and NMES in acute SCI for motor/sensory recovery, decreasing spasticity, and improving neuropathic pain.[9, 10] Patients are routinely prescribed electric stimulation units for home use to help with motor recovery

and strengthening. We propose the development of a protocol that uses the same equipment in a novel way to effect bladder function.

2. Rationale and justification for the Study

We have selected a neuromodulation technique, TTNS, which we have used safely with evidence of efficacy.

Pilot Data: The ***leading theory*** for the ***mechanism of bladder neuromodulation*** by TNS is that stimulation of the tibial nerve sensory afferents block the visceral bladder afferents at the level of the spinal cord.[17] This leads to a disruption of the bladder reflex arc, thereby decreasing motor efferent activity and subsequent pathologic reflex bladder contractions. This reflex arc is intact in people with thoracic level 9 (T9) injury and above (rostral). This hypothesis has been tested in a pilot trial of TTNS in acute SCI.[10]

Pilot Trial I, Safety and Bladder Capacity: TTNS in acute SCI was performed in a randomized sham-control trial of TTNS for 30 minutes x 10 days using a commercially/readily available neuromuscular electric stimulation (NMES) device. In this trial, there were no safety events, compliance was 100%, and hospital staff noted ease of use. Decrease in bladder capacity and detrusor-sphincter dyssynergia (DSD) events were both mitigated in the TTNS group (**Fig. 1**). Also, evidence of the proposed mechanism was seen with significantly increased volumes to sensation in the TTNS group compared to the controls post-trial. These findings suggest that TTNS has the potential to ***mitigate the development of morbid neurogenic bladder*** in acute SCI. We also provided evidence of altering the nervous system response to bladder filling in a cohort of these subjects, suggesting the ability of reducing AD.[18] We then investigated home use of TTNS as the next phase of study.

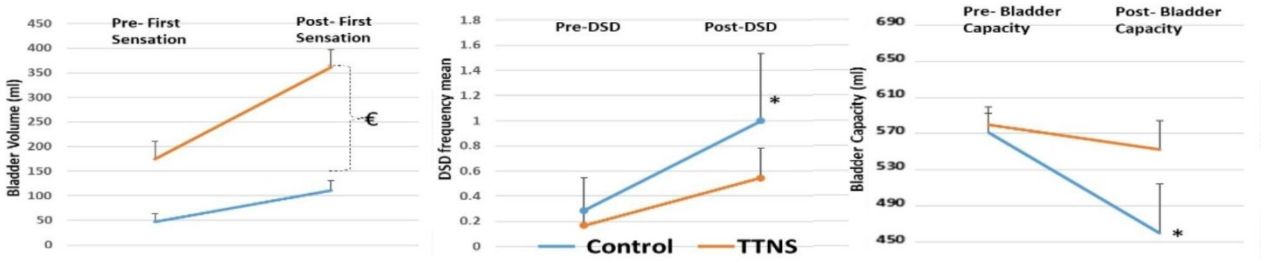

Fig. 1: Bladder sensation, detrusor-sphincter dyssynergia (DSD) frequency and bladder capacity changes in control and TTNS group over time. € between group difference p=0.01; *change from baseline p<0.02;

Pilot Trial II, Effect on Voiding Program and QOL: TTNS in the home setting was tested in a single-arm pre-post pilot trial in subjects with chronic SCI performing intermittent catheterization (IC) with complaints of incontinence. There was 100% (16/16) completion of trial, no complications, TTNS was found to be easy to use, 86% (12/14) reduced their OAB medication dosage and anticholinergic side effects, and QOL scores improved (**Fig. 2**). This pilot trial suggests TTNS is feasible and safe to be performed at home. A randomized sham-control trial is needed to determine if TTNS can be used at home to manage NGB symptoms, as proposed in this study.

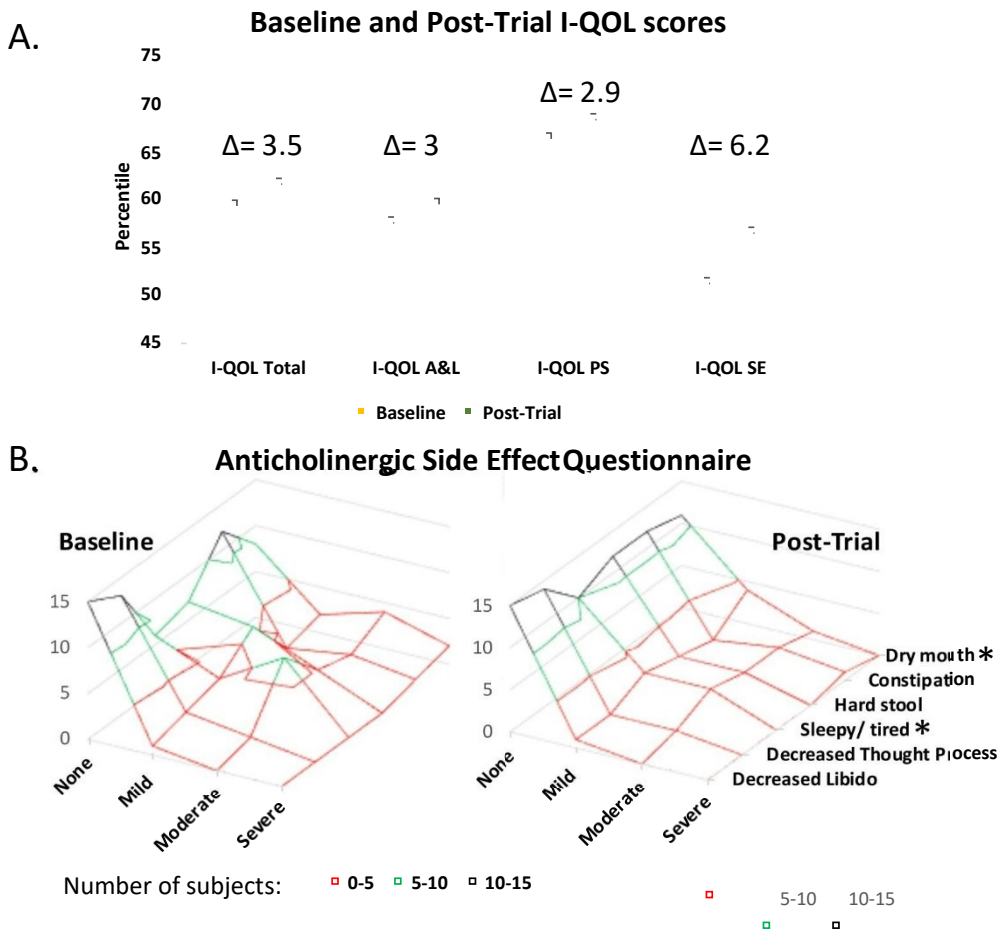

Fig 2. Incontinence QOL (I-QOL) and Anti-cholinergic Side Effect Questionnaire results. **A.** Baseline and Post-Trial Results of I-QOL total and subscores: A&L= avoidance and limitation; PS= psychosocial; SE= social embarrassment. Δ= change in scores from baseline to post-trial. **B.** Baseline and Post-Trial responses to anticholinergic side effects presented as color contours. Post-Trial, most subjects had none/mild side effects, with dry mouth and sleepy/tired symptoms significantly less post-trial, *p<0.03.

a. Rationale for the Study Purpose

The status quo for NB management in SCI is catheterization for safely emptying the bladder and anticholinergic medications once symptoms of DH or DSD occur.[3] This does not address the pathologic reflexes that lead to morbidity, including AD. Neuromodulation via TTNS may be able to address DH and DSD and alter the course of NB and prevent the morbidity arising from pathologic reflexes secondary to SCI. Pilot trial have tested the safety and feasibility of TTNS in acute SCI and have generated evidence of efficacy, including *mitigating the loss in bladder capacity* seen in chronic SCI. Preliminary data of TTNS performed at home provides evidence of high compliance, feasibility, and efficacy. Unlike the clinic-based treatment required for PTNS, compliance for the home-based treatment with TTNS is nearly double that of PTNS based on pilot data.[13]

b. Rationale for Doses Selected

Based on our pilot trials, tibial nerve stimulation protocols use submotor current intensity with a duration of 200 μs and frequency of 10Hz. [10] TTNS will be used 5 days weekly.

c. Rationale for Study Population

Participants: Participants will include SCI performing intermittent catheterization (IC) and using OAB medications, ages 18-75. Adults over 75 years old are excluded as age-related changes may influence bladder function.[19] Although NLUTD managed with an indwelling catheter could also benefit, the outcome measures in this study reflect areas of importance for those performing IC.

d. Rationale for Study Design

Based on our experience with TTNS, we believe this protocol can be used to help with neurogenic bladder management. Subjects who perform intermittent catheterization are being selected because they more likely to have incontinence than those with an indwelling catheter. If patients are interested, we will trial stimulation in clinic. We will exclude those who we cannot produce toe flexion with posterior tibial nerve stimulation.
After 2 weeks of home stimulation, those that are on bladder medicine will discontinue the medication. There is no other harm from rapid discontinuation of bladder medication, except for possible incontinence. The outcome measures are measure of bladder medication doses and surveys. The Incontinence Quality of Life (I-QOL) survey reflects the quality of life related to incontinence. [20] The Neurogenic Bladder Symptom Score (NBSS) measures and scores symptoms related to NGB. [21] Both will be conducted at baseline and at 3-months post-discharge. The medication + TTNS adherence survey and Medication + TTNS % survey. Adherence scales will measure adherence to medication and transcutaneous tibial nerve stimulation. Will be conducted at baseline, then every 4 weeks. The Connor-Davidson Resilience Scale (CD-RISC-25) will measure resilience. Conducted at baseline, week 6 and at the end of trial. The PROMIS General Self-Efficacy (GSE) will measure self-efficacy. (There is no validated Spanish version. Therefore, a conclusion cannot be made.) Conducted at baseline, week 6 and at the end of trial.

2. HYPOTHESIS AND OBJECTIVES

1. Hypothesis

Specific Aim 1. In a randomized sham-control trial (n=60), determine the *efficacy* of home TTNS in SCI.
Hypothesis 1.1: Those in the TTNS group will be able to reduce their OAB medication dosages while maintaining continence compared to controls over a period of 3 months.
Hypothesis 1.2: Symptoms of NGB measured by the Neurogenic Bladder Symptom Score (NBSS) and a voiding diary (VD) will be reduced in the TTNS group compared to controls.

Specific Aim 2. Determine the impact on *quality of life* using TTNS at home.
Hypothesis 2.1: Incontinence-related QOL (I-QOL) will be increased in the TTNS group compared to the controls and from baseline.
Hypothesis 2.2: Anticholinergic side effects will be decreased in the TTNS group at 3-months compared to the controls and from baseline.

2. Primary Objectives

OBJECTIVE: to advance the science and care around bladder function and management among people with spinal cord injury/disease (SCI/D) and NLUTD with TTNS (and if so, we anticipate translating this research to other populations with NLUTD). Specifically, we seek to demonstrate that TTNS will improve NLUTD in SCI/D by:

1. intervening acutely with neuromodulation of the neurogenic bladder via TTNS to maintain bladder capacity by reducing pathologic reflexes, DH and DSD;

2. altering pathologic autonomic nervous system (ANS) responses and reducing autonomic dysreflexia (AD).

3. improving the quality of life (QOL) of those living with SCI/D by providing a feasible, non-pharmacologic, and dignified intervention for NLUTD that can be performed at home;

In this proposed study, we seek to provide evidence for overall objective #3 using home TTNS. We hypothesize that TTNS can be used in the home setting to maintain continence while reducing OAB medication dosages and improve quality of life.

Primary Objective 1: Evidence of TTNS efficacy with reduced OAB medication dosage
Primary Objective 2: Evidence of TTNS efficacy with reduced NGB symptoms as measured by the NBSS and the Voiding Diary

3. Secondary Objectives

Secondary Objective 1: I-QOL scores will be increased in the TTNS group compared to the controls

Secondary Objective 2: Anticholinergic side effects will be reduced in the TTNS group compared to the controls.

4. Potential Risks and Benefits:

a. End Points - Efficacy

Primary Objective 1: Evidence of TTNS efficacy with a greater proportion of bladder medication reduction in the TTNS group compared to the control group. Time to achieve this endpoint will be approximately 3 months after subject recruitment, anticipated 1 year to complete all subject recruitment.

Priamry Objective 2: Evidence of TTNS efficacy with reduced NGB symptoms as measured by the NBSS and the Voiding Diary. Time to achieve this endpoint will be approximately 3 months after subject recruitment, anticipated 1 year to complete all subject recruitment.

b. End Points- Quality of Life

Secondary Objective 1: Improved QOL in the TTNS group compared to the controls at the end of the 3-month trial, based on I-QOL scores. Time to achieve this endpoint will be approximately 3 months after subject recruitment, anticipated 1 year to complete all subject recruitment.

Secondary Objective 2: Decreased anticholinergic side effects in the TTNS group compared to the controls at the end of the 3-month trial, based on an anticholinergic side effect survey. Time to achieve this endpoint will be approximately 3 months after subject recruitment, anticipated 1 year to complete all subject recruitment.

c. End Points - Safety

Urinary Tract Infection (UTI) risk:
We expect the rates of morbidity to be the same between those who participate and those who do not. However, because UTI is directly related to the bladder, we will focus on the occurrence of UTI. Based on literature, the overall rate of UTI in SCI is about 2.5 episodes per patient per year. As a result, we expect to see 0.6 episodes per patient during the 3-month study period. Based on that, we construct the stopping rules to stop at 20% UTI rate using lower 90% exact Blyth-Still-Casella confidence bounds. If the number of patients with UTI exceed 3 in the first 5 patients, 4 in the first 10 patients, or 5 in the 14 patients, then patient accrual will be paused pending a review by a medical advisory board comprised of SCI experts.

Bladder medication discontinuation risk:

- Worsened incontinence

Electric Stimulation Risks:
Electric stimulation is commonly performed on the extremities of those with spinal cord injury at the study institution. There are few adverse reactions to electric stimulation. The common ones include:

- Pain with electric stimulation: in these cases, the intensity is reduced until it is comfortable.
- Skin irritation: it is common for redness to occur on the skin at the site of the surface electrode. This typically dissipates within an hour of removing the electrode. In some cases, the redness remains the next day. In these cases, they are likely sensitive to the adhesive used and a hypoallergenic skin electrode will be provided.

3. STUDY POPULATION

1. List the number of subjects to be enrolled.

60 subjects. Consecutive SCI clinic encounters meeting the inclusion/exclusion criteria will be asked to enroll. Children and pregnant women will be excluded.

2. Criteria for Recruitment

- Initial screening will be performed in the clinic with the subject and PI
- In those interested, they will be given an IRB-approved consent form to review and to sign.
- Those with tetraplegia will unlikely have the ability to sign and we will have a 3rd party attest to the consent.
- Patients will ideally decide to participate in clinic, but can always decide at a later date and return to clinic to trial the TTNS as part of the I/E criteria.
- Flyers will be posted and distributed in the outpatient clinic to increase study awareness.

3. Inclusion Criteria (table 1)

Inclusion criteria: 1) ages 18-75 years; 2) SCI performing IC; 3) up to 2 anticholinergic OAB medications; 4) stable OAB medications in the past 2 months; 5) SCI neurologic level above T10; 6) English and Spanish speaking. Subjects that satisfy initial screening and willing to participate in the trial will have electric stimulation placed to attempt toe flexion as a check of the tibial nerve integrity. Those who cannot achieve toe flexion will be excluded.

Table 2. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
18-75 years old Traumatic and Non-traumatic SCI performing IC	Past history of genitourinary diagnoses or surgeries History of CNS disorders and/or peripheral neuropathy
Up to 2 anticholinergic OAB medications	Pregnancy
No changes in OAB medications	Lower motor neuron bladder
Neurologic level of injury above T10	Concern for tibial nerve pathway injury
English and Spanish speaking	Absence of toe flexion or AD with electric stimulation
	Bladder chemodenervation in past 6 months
	Potential for progressive SCI including neurodegenerative SCI, ALS, cancer myelopathy, Multiple sclerosis, transverse myelitis

SCI= spinal cord injury; IC= intermittent catheterization; OAB= overactive bladder; T10= thoracic level 10; CNS= central nervous system; AD= autonomic dysrelflexia

4. Exclusion Criteria (table 1)

Subjects meeting any of the exclusion criteria at baseline will be excluded from participation:

- - History of genitourinary diagnoses (i.e. prostate hypertrophy, overactive bladder, cancer, etc.)
- Potential for progressive SCI including neurodegenerative SCI, ALS, cancer myelopathy, Multiple sclerosis, transverse myelitis
- - History of central nervous system disorder (i.e. prior SCI, stroke, brain injury, Parkinson's disease, MS, etc.)
- - History of peripheral neuropathy
- - pre-SCI symptoms of peripheral neuropathy (numbness and/or tingling in feet, sharp/jabbing/burning pain in feet, sensitivity to touch, lack of coordination, muscle weakness, etc.)
- - Pregnancy
- - Known injury to the lumbosacral spinal cord or plexus, or pelvis with associated neuropathy
- - concern for tibial nerve pathway injury
- - absence of toe flexion or autonomic dysreflexia during electric stimulation test
- - bladder chemodenervation in prior 6 months

5. Withdrawal Criteria

Possible reasons for discontinuation of study intervention:

- Intolerable incontinence after discontinuation of bladder medications
- Intolerant to electric stimulation
- Non-compliance

To mitigate non-compliance, a stipend for effort in completing voiding diary will be provided at $10 per day (2 days per month). An additional $20 will be provided for logging bladder medication use and TTNS use/settings monthly. If both voiding diary and TTNS diary are reported, a $10 bonus will be provided, therefore $70 month 1, and $50 for each months 2 and 3. At most per subject= $170 for the 3-month trial per subject. Subjects will also receive reimbursement for travel for the urodynamic studies up to $200 per trip (two urodynamic studies = up to $400 per subject) and if medication reduction requires new prescriptions to cover co-payments when applicable up to $50 total per subject.

6. Subject Replacement

Subjects who drop out will be replaced by recruitment from the SCI clinic and asking for informed consent from those who meet the I/E criteria.

4. TRIAL SCHEDULE

Table 3. Study Timeline

	Year 1				Year 2			
Task	1	2	3	4	1	2	3	4
Obtain IRB approval								
Register study with www.clinicaltrials.gov								
Subject screening and recruitment (n=60, ~2-6/month)								
Baseline assessments								
Neurogenic Bladder Symptom Score (NBSS) (**SA 1.2**)								
Incontinence quality of life (I-QOL) (**SA 2.1**)								
Anticholinergic Side Effects (**SA 2.2**)								
Collection of Voiding Diary Weekly								
Overactive Bladder Medication dosage (**SA 1.1**)								
Cath frequency, volumes, and incontinence (**SA 1.2**)								
Compliance								
Evaluate the efficacy of TTNS at home (**SA 1**)								
Evaluate the impact of TTNS on quality of life (**SA 2**)								
Analyze **SA 1** & **SA 2**								
Present findings								
Development of manuscript(s)								

5. STUDY DESIGN

IRB NUMBER: HSC-MS-19-0518
IRB APPROVAL DATE: 10/20/2020

Anticipated number of patients to screen: 80

- Anticipated number of patients to enroll: 60
- Anticipated drop out or loss to follow-up: 6

Approximate time to complete study recruitment: 1 year
Expected duration of subject participation: 3-months. 3-months was selected as a fair assessment of efficacy. Clinically, medications are determined efficacious based on 1-month or less of use.

TTNS protocol: Same TTNS setting will be used as protocols HSC-MS-15-0806 and HSC-MS-17-0423. Electrodes 2 inch by 2 inch will be placed according to anatomic landmarks, with the negative electrode behind the internal malleolus and the positive electrode 10cm superior to the negative electrode, verified with rhythmic flexion of the toes secondary to stimulation of the flexor digitorum and hallicus brevis. The intensity level will be set to the amperage immediately under the threshold for motor contraction. If there is not contraction seen, patients will be excluded. In addition, if the patient perceives pain, the intensity will be lowered until comfortable. Stimulation frequency of 10 Hz and pulse width of 200ms in continuous mode will be used.[13, 14]

Sham protocol and rationale: Toe flexion will be attempted, as in the TTNS protocol. Then the stimulation will be reduced to 1 mA for 30 minutes. ***Rationale:*** In order to make this a convincing blind, the TTNS protocol must be simulated closely as subjects may interact and discuss. Rather than turning the device off, they will be instructed that the stimulation required is below motor threshold, at 1 mA. Based on the knowledge of the pilot trial requiring about 40mA for TTNS, and the amperage for needle-driven PTNS adjacent to the tibial nerve at 0.5 – 1mA, it is unrealistic that 1mA via surface electrodes is sufficient to activate the tibial nerve. Both TTNS and sham participants will be instructed to use the device for 30 minutes, 5 days per week.

Medication reduction protocol: Subjects will be using up to 2 anticholinergic OAB medications. Subjects generally use similar medications with a common approach- maximize one medication before adding a second medication. The PI will provide a weekly weaning schedule, individualized for each subject. No changes will occur during the first 2 weeks of TTNS. Starting week 3, the secondary OAB medication will be halved if possible, otherwise discontinued. Should the subject tolerate this, weaning will continue until one medication is discontinued, then the other. If the subject does not tolerate weaning, they will remain on the lowest, tolerable dose and we will attempt weaning the following week.

- Information gathered:
  - Clinical demographics, morbidity, and Neurologic Exam findings from interview with subjects, exam, and EMR review.
  - Bladder diary will include:
    - use of TTNS with amperage and presence of toe flexion, and pain score 0-10
    - log of catheterization, volumes
    - log of incontinence episodes
    - Description of other observed changes, including but not limited to: fatigue, vision changes, mental status, bowel program changes, and sexual function changes.
  - I-QOL at baseline initial visit and then at 3-month follow-up. Can be conducted over phone.

- NBSS at baseline and every 4 weeks (monthly) and at the 3-month follow-up. Can be conducted over phone.
- Anticholinergic survey at baseline and then at 3-month follow-up. Can be conducted over phone.
- TTNS satisfaction survey at 3-month follow-up. Can be conducted over the phone.
- Information will be tabulated on an Excel spreadsheet on my personal work desktop, password protected. Any paper data (bladder diary) will be de-identified and retained in a locked drawer in the locked office of the PI.
- General self-efficacy at baseline, week 6 and at the end of the trial. Can be conducted over the phone.
- CD-RISC at baseline, week 6 and at the end of the trial. Can be conducted over the phone.
- The medication and TTNS adherence survey at baseline then every 4 weeks. Can be conducted over the phone.
- The medication and TTNS % survey at baseline then every 4 weeks. Can be conducted over the phone.

1. Summary of Study Design

A randomized control trial of TTNS v sham-control in chronic SCI (n=60) performing intermittent catheterization on OAB medications will be performed to address the following Specific Aims:

In Specific Aim 1, we will assess the efficacy of TTNS based on reduced OAB medication use over 3 months while maintaining stable NGB symptoms based on NBSS score. A bladder diary will also capture important information such as frequency and volume of catheterization, incontinence episodes, and other related observations.

In Specific Aim 2, we will assess whether TTNS improves incontinence-related QOL based on I-QOL survey scores.

Schedule of events Home RCT													
Procedures	Baseline	Week 1	Week 2	Week 3	**Week 4**	Week 5	Week 6	Week 7	**Week 8**	Week 9	Week 10	Week 11	**End of Study/ week 12**
Review study procedures; Informed consent & privacy	x												
Eligibility criteria for study entry	x												
Demographics	x												
Medical / SCI history	x												
Urodynamic study	x												x
IQOL	x												x*
NBSS	x				x*				x*				x*
Anticholinergic Suvery	x												x*
Voiding diary data		x*	x*	x*	x*	x*	x*	x*	x*	x*	x*	x*	x*
TTNS Survey Satisfaction													x*
AE reporting and follow up		x*	x*	x*	x*	x*	x*	x*	x*	x*	x*	x*	x*
Qualitative Experience													
Medication Adherence	x				x				x				x
TTNS Adherence					x				x				x
Medication %	x				x				x				x
TTNS %					x				x				x
CD-RISC	x						x						x
Self-efficacy	x						x						x
* Will be completed over the phone													

6. METHODS AND ASSESSMENTS

a. Physical exam will be performed per usual care at TIRR, by the attending SCI physicians. Data will be retrieved from the electronic medical record and placed into the data spreadsheet. Missing data will be requested from the attending physician or directly from the patient.
b. Transcutaneous Tibial Nerve Stimulation (TTNS) will be placed by trained research assistants in the clinic to determine if the subject meets I/E criteria. Skin inspection will be performed before and after the trial stimulation session at the electrode sites. Blood pressure will also be monitored during this trial for an additional safety measure to ensure autonomic dysreflexia is not occurring.
c. The Bladder diary will be used to collect data use of TTNS with amperage and presence of toe flexion, pain score 0-10, as well as incontinence episodes and volumes. The research assistant (RA) will call weekly to capture the written data and monitor progress with the protocol.
d. The RA will also perform the survey outcome measures (NBSS, I-QOL,CD-RISC, GSE, Medication adherence surveys and anticholinergic side effect questionnaire) at baseline every 4 weeks, 6 weeks and at 3-months. Surveys can be conducted over the telephone.

2. Randomization and Blinding

Subjects will be randomized to either TTNS or sham control (1:1) using a block size of 4 and stratified based on complete/incomplete SCI to ensure the equal allocation of the most severely injured in the two groups. The PI will be blinded to randomization and treatment allocation, managed by the research assistant.

3. Contraception and Pregnancy Testing

Females of childbearing age will have to adhere to medically recommended contraception if sexually active with men, such as condoms and/or birth control pills.

4. Study Visits and Procedures

- *Screening Visits and Procedures*

Screening will be performed in the SCI clinic by the PI or co-I SCI attendings.

Those that meet the I/E criteria will be approached for the study by the PI or co-I attendings. They have until the study period is complete to decide whether they want to participate. However, they will have to return to clinic to have the TTNS trial performed and the directions for home use.

- *Study Visits and Procedures*

Subjects will have their first study visit after their normal clinic visit. Once consented, we will trial TTNS for a response of toe flexion. If they have a response, they will be included in the study. If no response or not tolerating electric stimulation, they will not be included in the study.

Participants will have direction in clinic on the use of the Stamobil+, including written, oral, and smartphone images/video if they have access.

The electric stimulation protocol will use stimulation frequency of 10 Hz and pulse width of 200ms in continuous mode for 30 minutes daily, beginning as soon as possible. The goal is 5 days per week of TTNS use for 3-monhts.

Subjects will be called weekly to capture the information of the TTNS log and to monitor progress of protocol. They will also be reminded to change electrodes weekly. 3 days prior to the NBSS call, the RA will contact the subjects to remind them to begin recording in their voiding diary for 2 days.

- *Final Study Visit:*

Upon completion of the 3-month study period, final voiding diary information will be collected and the post-trial questionnaires will be conducted.

- *Post Study Follow up and Procedures*

The data will be statistically analysed in the post-study follow up. Subject participation is not required.

- *Discontinuation Visit and Procedures*

If withdrawal occurs, no evaluation will be required for the final study visit, regardless of the withdrawal reason. There are no safety risks in withdrawing from this study at any point. OAB medications can be resumed at the prior efficacious dose.

7. TRIAL MATERIALS

The electric stimulation device used for TTNS is the Stamobil +.

1. Trial Product (s)

The Stamobil + is a class II medical device that requires a prescription for use. It is a multifunction electrotherapy device currently used at TIRR Memorial Hermann for the purpose of motor and sensory recovery in people with paralysis. It has the ability to provide conventional neuromuscular electric stimulation (NMES), transcutaneous electric nerve stimulation (TENS) and Pulsed Galvanic Stimulation electrotherapy. The device has wide-ranging capability and programmability, with stimulation and wave parameters adjusted for the proposed study purpose. The FDA Approved indications are:

As an NMES device, indications are for the following conditions:
• Retarding or preventing disuse atrophy
• Maintaining or increasing range of motion
• Re-educating muscles
• Relaxation of muscle spasms
• Increasing local blood circulation
• Prevention of venous thrombosis of the calf muscles immediately after surgery

As a TENS device, indications are for the following conditions:
• Symptomatic relief and management of chronic, intractable pain
• Adjunctive treatment for post-surgical and post-trauma acute pain
• Relief of pain associated with arthritis

As a Pulsed Current device, indications are for the following conditions:
• Reduction of edema (under negative electrode)
• Reduction of muscle spasm
• Influencing local blood circulation (under negative electrode)
• Retardation or prevention of disuse atrophy
• Facilitation of voluntary motor function
• Maintenance of increase of range of motion

As a functional electrical stimulation (FES) device, the indications for the following condition:
• Stimulation of the leg and ankle muscles of partially paralyzed patients to provide flexion of the foot, thus improving the patient's gait

2. Storage and Drug Accountability

There are no special storage needs for the device. They will be stored in the locked office of the PI in a dry, dedicated place.

8. TREATMENT

1. Rationale for Selection of Dose

Neuromodulation of the bladder is currently available with percutaneous TNS in the clinic setting, for a variety of patient populations. Stimulation frequency of 10 Hz and pulse width of 200ms in continuous mode will be used.[13,14]

Neuromodulation of the bladder has been shown to be effective after 6-8 sessions, with sessions performed once weekly over 12 weeks or 3 times weekly. The 30 minute stimulation session is commonly used for bladder neuromodulation.[23, 24]

2. Study Drug Formulations

NA

3. Study Drug Administration

NA

4. Specific Restrictions / Requirements

NA

5. Blinding

NA

6. Concomitant therapy

Medications that may have an effect upon the bladder will be recorded. The medication classes include: 1) bladder medications, 2)anti-spasm medications, 3) anti-depressants/anxiolytics; 4) neuropathic pain medications.

9. SAFETY MEASUREMENTS

1. Definitions

An adverse event is any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure.

The FDA definition of unanticipated adverse device effect will be used, as followed: *An unanticipated adverse device effect* as defined by FDA regulations at 2CFR 812.3(s) – Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Skin irritation, inflammation, and electrode burn beneath the electrodes are potential adverse events directly related to the use of electric stimulation.

2. Collecting, Recording and Reporting of Adverse Events

The Investigator will be responsible for collecting and reporting adverse events during the UDS. The research assistant and the PI will collect adverse events related to the randomized control trial.

Grading of the severity of the adverse events will be made by the PI, using the Common Terminology Criteria for Adverse Events v4.0 developed by the National Cancer Institute. The relevant "Burn" category is included below.

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		Grade				
Adverse Event	Short Name	1	2	3	4	5
Burn	Burn	Minimal symptoms; intervention not indicated	Medical intervention; minimal debridement indicated	Moderate to major debridement or reconstruction indicated	Life-threatening consequences	Death
REMARK: Burn refers to all burns including radiation, chemical, etc.						

Reporting procedures for:

- Deaths and life-threatening events
- other SAEs
- Other adverse events

The PI will report problems according to the UTHSC-Houston IRB policy, specifically in the event which in the opinion of the PI is both unexpected and related and places subjects or others at risk of harm.

The PI will report the reportable events to CPHS via iRIS within 7 days, unless the report involves the death of a participant, in which case the report needs to be provided to CPHS within 24 hours.

3. Safety Monitoring Plan

The Data Safety Monitoring Plan (DSMP) for the research study includes periodic statistical analysis on rates of morbidity of study participants compared to controls by the PI and the statistician. Because of the rolling recruitment in the proposed protocol, we anticipate the number of recruited individuals will be sufficient for morbidity review quarterly.

Specifically, we will focus on the occurrence of UTI. We hypothesize that the rate of UTIs in TTNS group will be similar to the SCI population. Based on literature, the overall rate of UTI in SCI is about 2.5 episodes per patient per year. As a result, we expect to see 0.6 episodes per patient during the 3-month study period. Based on that, we construct the stopping rules to stop at 20% UTI rate using lower 90% exact Blyth-Still-Casella confidence bounds. If the number of patients with UTI exceed 3 in the first 5 patients, 4 in the first 10 patients, or 5 in the 14 patients, then patient accrual will be paused pending a review by a medical advisory board comprised of SCI experts.

10. DATA ANALYSIS

1. Data Quality Assurance

The PI will be solely responsible for the accuracy of the data. Single data entry will be performed with plans to check 10% of primary variables as a quality control. Single data entry error rates are slightly higher than 0.5% when performed by trained staff and the minimally improved error rate through double data entry is outweighed by substantial cost savings for single data entry.[25] Data anomalies will be reviewed by the PI and clarification and/or correction will be performed. Incomplete entries will be reviewed and corrected if information is available.

2. Data Entry and Storage

Data will be entered on a UTH google drive spreadsheet file, with permission to access controlled by the PI. Data collected by the RA from the voiding diary and survey outcome measures will be entered into the spreadsheet. Data will be coded by subject ID.

The RA will have the linking log of the patients to their subject ID in her password-protected desktop in the TIRR Memorial Hermann Research building.

5 years after manuscript publication, the paper reports will be placed into the shredder bins for destruction.

11. SAMPLE SIZE AND STATISTICAL METHODS

1. Determination of Sample Size

Sample size will be determined from **Aim 1.1**. Assuming that 40% of the subjects in the control group are able to reduce their bladder medications (placebo effect), the study would require a sample size of 21 for each group (i.e. a total sample size of 42), to achieve a power of 80% for detecting a difference in proportions of 43% between the two groups (83% in TTNS group –40% in control group) at a two sided p-value of 0.05. Accounting for 40% dropout, we will recruit 30 subjects in each arm for a total of 60 subjects. In **Aim 1.2**, the NBSS has demonstrated responsiveness to change after bladder chemodenervation with a mean difference of 11.8 (11),[22] which would require a sample size of 20. For **Aim 2.1**, a 7±17 point improvement in the I-QOL score was observed after 4 weeks of TTNS use in our pilot study. We expect the control group to have minimal improvement in I-QOL scores due to placebo effect, estimated as 3 points. With power of 80% and a more conservative standard deviation of 4 points, we need a sample size of 22 in total by two-sample two-sided t-test at a type I error rate of 0.05. The sample size determined by Aim 1.1 is sufficient for this aim.

2. Statistical and Analytical Plans

Patients will be randomized to control and TTNS at a 1:1 ratio by computer-generated sequences, with stratified allocation in blocks of 4 controlling for complete SCI, with the investigator blinded to the treatment allocation. Changes in outcomes listed in Aim 1 and 2 will be compared between groups by two-sample two-sided t-test or Wilcoxon rank-sum test. Descriptive statistics and mean plots will be provided for the longitudinal measurements. Multilevel mixed-effects regression models will be used for longitudinal analyses of treatment effects, controlling for confounding variables including age, sex, severity of SCI, compliance (number of sessions), and OAB medication dosages. Multiple testing will be adjusted by Bonferroni correction if necessary. Non-random missing data will be analyzed using the method in Ibrahim and Molenberghs.[23] Considering the unknown long-term effects of TTNS, we may not see significant treatment effect on some outcomes by conventional (frequentist) analyses. We plan a Bayesian analysis (with either skeptical or neutral priors) to estimate the probability (with 95% credible intervals) of treatment effect. Conventional analysis will be performed in SAS 9.4 (SAS Institute, Cary NC) and Bayesian analysis will be performed in R 3.5.0 using packages like R2WinBUGS.

12. ETHICAL CONSIDERATIONS

1. Informed Consent

The PI will obtain informed consent from subjects meeting I/E criteria after screening in their SCI clinic visit. Ideally they can decide that day, but can have until study completion to decide. Likely 1 year.
IRB-approved study participation material will be provided to the subjects.

2. IRB review

This protocol and the associated informed consent documents have been submitted to the IRB for review and approval, pending.

3. Confidentiality of Data and Patient Records

All patient records will remain confidential. Data with Protected health Information (PHI) will be de-identified and given a number assignment found on the Linking Log. The Linking Log is a separate file controlled by the RA on her password-protected desktop computer at TIRR Memorial Hermann.

13. PUBLICATIONS

We anticipate publication in a peer-reviewed journal within 2 years of beginning this study describing the effects of home TTNS in SCI.

14. RETENTION OF TRIAL DOCUMENTS

All records for all participants including CRFs and source documentation will be retained by the PI in a binder locked in his office, and on his desktop computer locked in his office. IRB and regulatory records will be placed in a binder along with the mentioned documents and will be retained by the PI in his office at TIRR Memorial Hermann, locked in a cabinet.

List of Attachments

Appendix 1 **Case Report Form**

Appendix 2 **Sample Voiding Diary Log**

Appendix 3 **Informed Consent Form**

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