**Home Neuromodulation of the Neurogenic Bladder in Chronic Spinal Cord Injury with Transcutaneous Tibial Nerve Stimulation**

**NCT03458871**

**Version Date: 08/31/2018**





IRB NUMBER: HSC-MS-17-0423
IRB APPROVAL DATE: 08/31/2018

**STUDY PROTOCOL**

**PROTOCOL NUMBER:**
HSC-MS-17-0423

**PROTOCOL TITLE:**
Home Neuromodulation of the Neurogenic Bladder in Chronic Spinal Cord Injury with Transcutaneous Tibial Nerve Stimulation

**VERSION:** 1
**DATE:** 4/28/2017

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## GENERAL INFORMATION

**Name and address of the sponsor of the study:**
NA

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## 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.[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.

We are currently using the proposed TTNS protocol for research purposes (HSC-MS-15-0806) at TIRR for acute SCI during their inpatient rehabilitation admission (Table 1). Based on the preliminary safety data, we believe we can develop this protocol for home use (Table 2).

Table 1. Preliminary data demographics of subjects inpatient TTNS protocol

| Subject # | Group | Gender | Age | Etiology SCI | Days from injury to protocol start | Neurologic Level | ASIA injury severity |
|---|---|---|---|---|---|---|---|
| 1 | Exp | M | 27 | Motorcycle | 22 | T4 | B |
| 2 | Exp | F | 24 | MVA | 18 | T1 | A |
| 3 | Exp | F | 48 | MVA | 23 | C4 | A |
| 4 | Exp | F | 27 | MVA | 12 | C5 | B |
| 5 | ? | M | 29 | MVA | 38 | T3 | A |
| 6 | ? | M | 28 | Motorcycle | 11 | C6 | C |
| 7 | ? | M | 45 | Motorcycle | 18 | C6 | A |
| 8 | ? | M | 47 | MVA | 11 | T6 | C |
| 9 | ? | F | 55 | Fall | 12 | C4 | C |
| 10 | ? | F | 36 | MVA | 6 | T4 | A |
| 11 | ? | M | 48 | Motorcycle | 7 | T3 | A |
| 12 | / | M | 61 | MVA | 14 | C1 | B |

Exp= experimental group; ?= blinded to group allocation; MVA= motor vehicle accident; ASIA= American Spinal Cord Injury Association





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Table 2. Adverse events monitored in subjects recruited.

| Subject # | NPS change mean (range) | DVT/PE | UTI | Resp Infection | Cellulitis | Skin Irritation | Other Infection | Pressure Injury | Unexpected Discharge |
|---|---|---|---|---|---|---|---|---|---|
| 1 | -0.1 (0-1) | N | N | N | N | N | N | N | N |
| 2 | 0 | N | N | N | N | N | N | N | N |
| 3 | 0 | N | Y* | N | N | N | N | N | N |
| 4 | 0 | N | Y^ | N | N | N | N | N | N |
| 5 | -0.5 (-5-0) | N | N | N | N | N | N | N | N |
| 6 | 0.5 (0-5) | N | N | N | N | N | N | N | N |
| 7 | 0 | Y # | N | N | N | N | N | Y% | N |
| 8 | 0 | N | N | N | N | N | N | N | N |
| 9 | ? | N | Y* | N | N | N | N | N | N |
| 10 | ? | N | Y$ | N | N | N | N | N | N |
| 11 | ? | N | Y$ | N | N | N | N | N | N |
| 12 | ? | N | Y$ | N | N | N | N | Y$ | N |

* UTI 6 days after completion of protocol, unrelated
^ UTI 7 days after completion of protocol, unrelated
# PE discovered due to complaints of shortness of breath, unrelated to protocol.
% Sacral skin injury 7 days after completion of protocol, unrelated
$ prior to subject recruitment
?- have not completed study, blinded to stimulation pain scores

There have been 12 subjects recruited to the inpatient TTNS protocol with a variety of cervical and thoracic injuries, with subsequent complete and incomplete paraplegia and tetraplegia. Consecutive inpatients were screened and approached for the study. To date (7/12/2017), 11/12 patients that consented to the study completed the TTNS protocol and 1 (subject 12) has ongoing stimulation. There were no reported complaints about the TTNS. There were no adverse events directly related to the TTNS protocol, including worsening pain (numeric pain scale (NPS)), skin irritation, and bladder complaints (urinary tract infections, leaking, incontinence, etc).

Please note, the above subjects have all been acutely injured and are at higher risk for morbidity compared to chronic SCI subjects. Half of the UTIs occurred before subject recruitment, and half of the UTIs occurred about 1 week after completion of the stimulation protocol. None occurred during the TTNS protocol. Based on our inpatient experience with this TTNS protocol, the high compliance, lack of adverse events, and feasibility, we believe this protocol can be translated to the outpatient setting and performed by the subjects themselves and/or their caregivers.



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UTHealth The University of Texas Health Science Center at Houston

## 1.1. General Introduction

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 are currently using the proposed TTNS protocol for research purposes (HSC-MS-15-0806) at TIRR for acute SCI during their inpatient rehabilitation admission. Based on the preliminary safety data, we believe we can develop this protocol for home use. 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."

The status quo as it pertains to the management of neurogenic bladder in SCI is anticholinergic medications to inhibit bladder activity, increase bladder capacity, and decrease detrusor pressures.[4] However, management of neurogenic bladder requires further improvement, with an estimated 50% developing serious urologic complications.[2] Ongoing research regarding the neuromodulation of chronic neurogenic bladder is promising, demonstrating equal efficacy to current management without non-compliance and adverse medication side effects, with improved quality of life.[5-8] Although neuro-modulation techniques are currently used for chronic neurogenic bladder, its use is limited to frequent clinic visits, imposing a barrier to a population known to have challenges accessing medical care. The proposed research is innovative, in our opinion, because it represents a substantive departure from the status quo by using transcutaneous tibial nerve stimulation in the home setting to improve bladder function. Rehabilitation horizons for neurogenic bladder management which have previously been unattainable through current efforts including the prevention of detrusor sphincter dyssynergia and related autonomic dysreflexia, maintenance of bladder capacity and compliance, and reduction in oral medication use with improved quality of life are also likely to become attainable.

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.




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## 1.2. Rationale and justification for the Study

We have selected a neuromodulation technique, TTNS, that has been used safely in chronic SCI with good results for improving quality of life and bladder parameters and have developed a protocol for home use.
Specific Aim 1: **Determine the safety, feasibility, and compliance of a daily home TTNS protocol in chronic SCI provided by self or caregiver for 4 weeks.**
Hypothesis 1.1: TTNS at home is safe and feasible with high compliance.
Hypothesis 1.2: TTNS protocol will demonstrate overall satisfaction as a neurogenic bladder treatment option based on survey questionnaire.

Specific Aim 2. **Determine the efficacy of a 4 week TTNS protocol.**
Hypothesis 2.1: Incontinence quality of life scores and frequency of incontinence will improve with TTNS compared to their baseline.
Hypothesis 2.2: Frequency of catheterization and volumes voided will improve with TTNS compared to baseline measurements.
Hypothesis 2.3: Anticholinergic-related side effects will improve with TTNS after discontinuation of bladder medications

### a. Rationale for the Study Purpose

Neuromodulation techniques have been safely used for improving neurogenic bladder in chronic SCI for many years. However, bladder neuromodulation is only being performed in the clinic setting requiring frequent visits, limiting its use in a population known to have high healthcare costs and barriers to accessing medical care. Based on our experience, we believe we can develop a home-based protocol.

Gaps in the knowledge which we intend to fill are:
1) Safety, feasibility, and compliance of a home TTNS protocol in chronic SCI.
2) Efficacy of a 4-week TTNS protocol in SCI based on the Incontinence Quality of Life (I-QOL), which will provide effect size to power future studies.

### b. Rationale for Doses Selected

Based upon an extensive review of the literature on neuromodulation of neurogenic bladder and the clinical experience of the mentorship team, we believe a TTNS protocol over a 4 week period will improve continence. Tibial nerve stimulation protocols use submotor current intensity with a duration of 200 μs and frequency of 10Hz.[13,14] Increasing the treatment frequency dramatically shortens the time required for response while maintaining efficacy, varying from 6-12 sessions.[14]

### c. Rationale for Study Population

Participants will include consecutive SCI subjects at the SCI clinic who meet the I/E criteria (Table 1) and consent to the protocol.

### d. Rationale for Study Design

Based on our current inpatient experience, we believe this protocol can be performed safely at home by subjects and/or their caregivers if given detailed instructions. Subjects who perform intermittent catheterization are being selected because they more likely to have incontinence



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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 1 week 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 incontinence. We expect that incontinence will be reduced from this first week of TTNS.
The I-QOL questionnaire is administered at baseline, and at the end of 2 and 4 weeks to determine when best effects of TTNS are achieved.

## 2. HYPOTHESIS AND OBJECTIVES

### 2.1. Hypothesis

Specific Aim 1: **Determine the safety, feasibility, and compliance of a daily home TTNS protocol in chronic SCI provided by self or caregiver for 4 weeks.**
Hypothesis 1.1: TTNS at home is safe and feasible with high compliance.
Hypothesis 1.2: TTNS protocol will demonstrate overall satisfaction as a neurogenic bladder treatment option based on survey questionnaire.

Specific Aim 2. **Determine the efficacy of a 4 week TTNS protocol.**
Hypothesis 2.1: Incontinence quality of life scores and frequency of incontinence will improve with TTNS compared to their baseline.
Hypothesis 2.2: Frequency of catheterization and volumes voided will improve with TTNS compared to baseline measurements.
Hypothesis 2.3: Anticholinergic-related side effects will improve with TTNS after discontinuation of bladder medications

### 2.2. Primary Objectives

**Primary Objective 1:** Safety, feasibility, and compliance of TTNS at home.
**Primary Objective 2:** Overall satisfaction with TTNS based on survey.

### 2.3. Secondary Objectives

**Secondary Objective 1:** I-QOL scores will improve and incontinence episodes will reduce after TTNS compared to baseline.

**Secondary Objective 2:** The frequency of catheterization and the volumes voided will improve with TTNS compared to baseline based on bladder diary.

**Secondary Objective 3:** Anticholinergic side effects will be reduced based on survey after TTNS protocol.

### 2.4. Potential Risks and Benefits:

#### a. End Points - Efficacy

**Specific Aim 1:** No efficacy requirement for the safety and feasibility studied in specific aim 1.

**Specific Aim 2:** We expect improved I-QOL scores compared to baseline. As a pilot trial, we have not powered the study for this measure. Results from this study will provide effect size to power a larger study.

### b. 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 0.2 episodes per patient during the 4-week 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

### 3.1. List the number of subjects to be enrolled.

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

### 3.2. 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 critreria.

### 3.3. Inclusion Criteria (table 1)

**Table 1.** Inclusion/ Exclusion Criteria

| ***Inclusion*** | ***Exclusion*** | |
|---|---|---|
| 18-65 years old | Multiple medications for the bladder | Cancer in the tibial nerve path and/or bladder. |



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| | | |
|---|---|---|
| Neurologically stable SCI for ≥ 6 months | Other diagnoses to explain incontinence (ex: UTI, bladder stones, multiple sclerosis, etc.) | Inability to elicit toe/plantar flexion with electric stimulation during clinic visit. |
| Intermittent catheterization to empty bladder | 2+ pitting edema that does not resolve | Inability to understand directions |
| Stable bladder medications for ≥ 3 months | Known peripheral neuropathy or injury to the path of the tibial nerve | Non-English speaking |
| | Demand-type cardiac pacemaker or implanted defibrillator | |

### 3.4. Exclusion Criteria (table 1)

Patients on multiple bladder medications will be excluded for the rationale that they have a severely dysfunctional bladder that requires multiple bladder medications, likely having developed over many years. It is unlikely that TTNS alone can benefit this population and it would skew the results for efficacy.

Patients with known etiologies of incontinence other than SCI will be excluded.

Those patients with severe lower leg edema will be excluded because in our current trial, we have found that the electric current does not elicit toe flexion in those with extensive leg edema.

For electric stimulation, we exclude those that have an implanted cardiac device, cancer at the stimulation site, and those that we cannot elicit toe flexion in clinic.

### 3.5. Withdrawal Criteria

Possible reasons for discontinuation of study intervention:

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

### 3.6. 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.



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## 4. TRIAL SCHEDULE

**Table 2. Timeline of protocol per subject** *Weeks in Study Protocol*

| Activities | 0 | W1 | W2 | W3 | W4 |
|---|---|---|---|---|---|
| ***Clinic Enrolment:*** | | | | | |
| Eligibility screen | X | | | | |
| Informed Consent | X | | | | |
| Incontinence Questionnaire (I-QOL) | X | | | | |
| Side effect questionnaire | X | | | | |
| TTNS demonstration | X | | | | |
| ***Home*** | | | | | |
| Bladder diary | | □----------□ | | | |
| I-QOL | | | X | | X |
| TTNS | | □----------□ | | | |
| Discontinue bladder medication | | | X | | |
| Side effect questionnaire/ TTNS survey | | | | | X |

## 5. STUDY DESIGN (Table 2)

Anticipated number of patients to screen: 40

- Anticipated number of patient to enrol: 20
- Anticipated drop out or loss to follow-up: 4

Approximate time to complete study recruitment: 1 year
Expected duration of subject participation: 4 weeks

TTNS protocol: (please refer to protocol HSC-MS-15-0806) 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, maximal tolerable intensity will be used. 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]

- Information gathered:
  - Clinical demographics, morbidity, and Neurologic Exam findings from interview with subjects, exam, and EMR review.



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- 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.
- 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.

### 5.1. Summary of Study Design

In Specific Aim 1, we will monitor for safety, feasibility, and compliance of a home TTNS program for bladder management. In Specific Aim 2, the efficacy of home TTNS will be compared to baseline Incontinence- Quality of Life questionnaire. A bladder diary will also capture important information such as frequency and volume of catheterization, incontinence episodes, and other related observations.



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## 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 daily 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.
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 will call weekly to capture the written data and monitor progress with the protocol.

### 6.2. Randomization and Blinding

a. Not Applicable.

### 6.3. Contraception and Pregnancy Testing

For females of childbearing age included in the trial, sexually active women with male partners will be excluded.

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



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## 6.4. Study Visits and Procedures

- *Screening Visits and Procedures*

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

Those that meet the I/E criteria will be approached for the study by the PI and 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. For sexually active women of child-bearing age, the home use will begin after the results of a pregnancy test are provided. The goal is daily use of TTNS for 4 weeks.

Subjects will be called weekly to capture the information from the bladder diary log and to monitor progress of protocol. They will also be reminded to change electrodes weekly.

- *Final Study Visit:*

Upon completion of the 4-week protocol, subjects will return with the stimulator and the bladder diary.

- *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.

## 7. TRIAL MATERIALS

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

### 7.1. 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 for the Empi Continuum 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

### 7.2. 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.



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## 8. TREATMENT

### 8.1. 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]

### 8.2. Study Drug Formulations

NA

### 8.3. Study Drug Administration

NA

### 8.4. Specific Restrictions / Requirements

NA

### 8.5. Blinding

NA

### 8.6. 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.





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## 9. SAFETY MEASUREMENTS

### 9.1. 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.

### 9.2. 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.

### 9.3. 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



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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 0.2 episodes per patient during the 4-week 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

### 10.1. 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.

### 10.2. Data Entry and Storage

Data will be entered on a spreadsheet file located on the TIRR Memorial Hermann password-protected desktop computer of the PI located in a locked office in TIRR Memorial Hermann. After data from reports generated from the UDS are entered into the spreadsheet, they will be filed in a study binder in a locked drawer in the office of the PI with HIPPA information removed.

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




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## 11. SAMPLE SIZE AND STATISTICAL METHODS

### 11.1. Determination of Sample Size

For SA 1, safety, feasibility, compliance, we use as a convenient sample size. The preliminary data with 12 subjects have shown high compliance, lack of adverse events, and feasibility. So we believe 14 is sufficient and we will enrol 20 patients to account for non-compliance in the outpatient setting. This study will help us to determine effect size for future studies.

### 11.2. Statistical and Analytical Plans

This pilot study will serve as an earlier-phase developmental function that will enhance the probability of success in a larger subsequent randomization intervention trial.

**In Aim 1,** for safety, we hypothesize that there will be no unusual adverse events. 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.[18] As a result, we expect to see .2 episodes per patient during the 4-week 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.

For feasibility and compliance, we will calculate descriptive statistics to determine the dropout rate and percent of adherence to the prescribed regimen as well as program satisfaction. If the dropout rate is less than 25%, and if subjects complete greater than 70% of daily TTNS use in the 4-week period, we will consider the study has high feasibility/adherence. If more than 80% of subjects report that they were satisfied with the program, then we will consider the study has high satisfaction.

**In Aim 2**, descriptive statistics will be provided for incontinence episodes, catheterization frequency, volumes voided, and anticholinergic-related side effects after the TTNS. The results along the time will be compared to baseline by paired t test, signed t test, or repeated measure methods when appropriate. Since this is an exploratory study and the efficacy of TTNS in this study will be further studied in future larger studies, Bonferroni correction will not be necessary. TTNS satisfaction will be based on the scores of a TTNS survey and descriptive analysis will be provided as well. We will also check the association between these changes from baseline, as well as bladder medication associations.

## 12. ETHICAL CONSIDERATIONS

### 12.1. 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.
Non-English speakers will be excluded.

### 12.2. IRB review

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

### 12.3. 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 in a separate folder found on the PI's desktop computer.

## 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** **Study Schedule and Study Design**

**Appendix 2** **Case Report Form**

**Appendix 3** **Sample Voiding Diary Log**

**Appendix 4** **Informed Consent Form**





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## REFERENCES:


1. Ackery A, Tator C, Krassioukov A. A global perspective on spinal cord injury epidemiology. Journal of Neurotrauma. October 2004, 21(10): 1355-1370.
2. Weld KJ, Dmochowski RR. Association of level of injury and bladder behavior in patients with post-traumatic spinal cord injury. Urology. 2000 Apr;55(4):490-4.
3. Stöhrer M, Blok B, Castro-Diaz D, Chartier-Kastler E, Del Popolo G, Kramer G, Pannek J, Radziszewski P, Wyndaele JJ. EAU guidelines on neurogenic lower urinary tract dysfunction. Eur Urol. 2009 Jul;56(1):81-8.
4. Anderson KD. Targeting recovery: priorities of the spinal cord-injured population. J Neurotrauma. 2004 Oct;21(10):1371-83.
5. Chaabane W, Guillotreau J, Castel-Lacanal E, Abu-Anz S, De Boissezon X, Malavaud B, Marque P, Sarramon JP, Rischmann P, Game X. Sacral neuromodulation for treating neurogenic bladder dysfunction: clinical and urodynamic study. Neurourol Urodyn. 2011 Apr;30(4):547-50.
6. Chen G, Liao L, Li Y. The possible role of percutaneous tibial nerve stimulation using adhesive skin surface electrodes in patients with neurogenic detrusor overactivity secondary to spinal cord injury. Int Urol Nephrol. 2015 Mar;47(3):451-5.







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