



STUDY PROTOCOL

# Transcutaneous tibial nerve stimulation for the treatment of bladder storage symptoms in people with multiple sclerosis: Protocol of a single-arm feasibility study [version 1; peer review: 2 approved]

Hawra B. Al Dandan <sup>1,2</sup>, Rose Galvin <sup>1,3,4</sup>, Katie Robinson <sup>1,3,4</sup>,  
Dorren McClurg<sup>5</sup>, Susan Coote <sup>1,3</sup>

<sup>1</sup>School of Allied Health, Faculty of Education and Health Sciences, Clinical therapies, University of Limerick, Limerick, County Limerick, Ireland

<sup>2</sup>College of Applied Medical Sciences, Physiotherapy, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia

<sup>3</sup>Health Research Institute, University of Limerick, Limerick, County Limerick, Ireland

<sup>4</sup>Aging Research Centre, University of Limerick, Limerick, County Limerick, Ireland

<sup>5</sup>Nursing, Midwifery and Allied Health Professions Research Unit, Glasgow Caledonian University, Glasgow, UK

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## Abstract

**Background:** Neurogenic lower urinary tract dysfunction (NLUTD) is common among people with multiple sclerosis (MS) with a pooled prevalence of 68.41% using self-report measures and 63.95% using urodynamic studies. Transcutaneous tibial nerve stimulation (TTNS) is a non-invasive option to manage bladder storage symptoms; however, the potential efficacy of TTNS among people with MS is based on a small number of studies with the absence of high-quality evidence relating to efficacy, and lack of clarity of the optimal electrical stimulation parameters and frequency, duration and number of treatment sessions. This study aims to assess whether TTNS is feasible and acceptable as a treatment for bladder storage symptoms in people with MS.

**Methods:** We will use a single-arm experimental study to explore the feasibility and acceptability of TTNS in the treatment of bladder storage symptoms in MS. The CONSORT extension for pilot and feasibility studies will be followed to standardise the conduct and reporting of the study. The recruitment plan is twofold: 1) Open recruitment for people with MS through MS Ireland's communication channels; 2) recruitment from a convenience sample of people with MS who have previously participated in a qualitative interview study of urinary symptoms. We will assess recruitment/retention rates, the urinary symptoms changes and the effect on quality of life pre and post intervention using ICIQ-OAB, 3-day bladder diary, King's Health Questionnaire and collect self-reported data on adherence and


## Open Peer Review

Reviewer Status  

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1. **David Božidar Vodušek**, University Medical Centre Ljubljana, Ljubljana, Slovenia

2. **Noor Almousa**, King Fahad Medical City, Riyadh, Saudi Arabia

**Ahmed Al-Badr** , Women Specialized Hospital, King Fahad Medical City, Riyadh, Saudi Arabia

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adverse events. Acceptability of using TTNS will be evaluated at the end of intervention. This study has been reviewed and approved by the Education and Health Science's Faculty Research Ethics Committee, University of Limerick [2020\_06\_07\_EHS].

**Conclusion:** It is anticipated that assessing the feasibility and acceptability of TTNS for storage bladder symptoms in MS will inform the development of a definitive randomised trial.

**Trial registration:** ClinicalTrials.gov [NCT04528784](https://clinicaltrials.gov/ct2/show/study/NCT04528784) 27/08/2020

### Keywords

Multiple sclerosis, Neurogenic bladder, urinary symptoms, feasibility study, Tibial nerve stimulation.

**Corresponding author:** Hawra B. Al Dandan ([dan77\\_sa@hotmail.com](mailto:dan77_sa@hotmail.com))

**Author roles:** **Al Dandan HB:** Conceptualization, Data Curation, Formal Analysis, Writing – Original Draft Preparation, Writing – Review & Editing; **Galvin R:** Conceptualization, Formal Analysis, Funding Acquisition, Writing – Review & Editing; **Robinson K:** Formal Analysis, Supervision, Writing – Review & Editing; **McClurg D:** Conceptualization, Formal Analysis, Supervision, Writing – Review & Editing; **Coote S:** Conceptualization, Data Curation, Investigation, Methodology, Writing – Review & Editing

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## Background

Neurogenic lower urinary tract dysfunction is defined by the International Continence Society (ICS) as “lower urinary tract symptoms (LUTSs) in the presence of a relevant neurological disease” (Gajewski *et al.*, 2018). Storage symptoms associated with LUTS include frequency, urgency, nocturia, and/or incontinence; voiding symptoms resulting in hesitancy, slow stream, intermittency, dysuria, straining, terminal dribble, need to immediately re-void, splitting or spraying whereas post micturition symptoms include incomplete bladder emptying and/or post micturition dribble (Gajewski *et al.*, 2018). The range and severity of neurogenic bladder symptoms depend on the location of the neurologic lesions (Li *et al.*, 2016; Peter & Peter, 2012), with more pronounced symptoms in people with MS associated with lesions at the pontine micturition centre (PMC) leading to storage symptoms and or the supra sacral lesions resulting in both storage and voiding symptoms accompanied with an increased post-void residual (Haylen *et al.*, 2010; McCombe *et al.*, 2009; Panicker *et al.*, 2015).

We recently undertook a systematic review and meta-analysis which demonstrated that LUTSs are prevalent in people with MS with a pooled prevalence of 68.41% using self-report measures and 63.95% using urodynamic studies. When considering types of LUTSs, urinary frequency was the predominant symptom followed by urgency with a pooled prevalence estimate of 73.45% and 63.87% respectively using self-report measures. Detrusor overactivity was found to be the most prevalent urodynamic symptom, with a pooled prevalence estimate of 42.9% followed by detrusor sphincter dyssynergia at 35.44% (Al Dandan *et al.*, 2020). The high prevalence of urinary symptoms among people with MS is concerning as several studies have highlighted the negative consequences of urinary symptoms for quality of life (Browne *et al.*, 2015; Finlayson *et al.*, 2006; Nortvedt *et al.*, 2001; Vitkova *et al.*, 2014). Studies have shown that urinary incontinence is considered as one of the worst morbidities associated with MS (Fowler *et al.*, 2009; Nakipoglu *et al.*, 2009). Urinary symptoms including loss of urine that results in fear of leaking in public is considered as a barrier to engaging in physical activities among people with MS (Kayses *et al.*, 2011). Furthermore, an increased risk of mortality and an aggravation of MS symptoms following an episode of urinary tract infection (UTIs) has been reported (Abrams *et al.*, 2017). Timely diagnosis and proper management are of utmost importance in maintaining good quality of life among people with MS and urinary symptoms.

Current therapeutic interventions for storage symptoms include pharmacologic therapy, behavioural interventions, pelvic floor muscle training (PFMT), and/ or neuromodulation. Pharmacologic interventions such as the use of anticholinergic medication are considered a first-line treatment for neurogenic bladder population (Chapple *et al.*, 2008; Tornic & Panicker, 2018). Anticholinergic short-term efficacy has been reported in previous studies, however, limited long-term efficacy due to side effects and lack of tolerance was reported (de Seze *et al.*, 2011; Fowler *et al.*, 2009; Li *et al.*, 2016; Panicker *et al.*, 2015; Stöhrer *et al.*, 2009; Tornic & Panicker, 2018; Valles-Antuna *et al.*, 2017). The reported side effects include; gastrointestinal

tract disorders, central nervous system particularly worsening in cognition and deterioration in memory, dry mouth, impact on complete bladder emptying and increase cost.

A systematic review identified very few high quality studies of non-pharmacological interventions such as behavioural interventions including management of fluid intake, bladder retraining and scheduled voiding among a neurogenic population including people with MS (Panicker *et al.*, 2015). Combined pelvic floor muscle training (PFMT) therapy with electromyography (EMG) biofeedback and intravaginal neuromuscular electrical stimulation (NMES) reduced urinary symptoms including number of leaks and pad test among 30 females with MS when compared to PFMT alone or PFMT and EMG biofeedback (McClurg *et al.*, 2006). A recent systematic review showed that PFMT alone or in conjunction with other interventions among people with MS is also considered to be effective and classified as a first-line treatment approach (Tornic & Panicker, 2018). Of concern, across numerous studies with non-neurological populations adherence to PFMT has been shown to be the main factor influencing the improvement of urinary symptoms (Bø *et al.*, 2005; Prasad *et al.*, 2019; Sacomori *et al.*, 2019). One study showed some barriers to adherence among postpartum women included forgetfulness, lack of time, and chores related to childcare (Sacomori *et al.*, 2019). On the other hand, another study showed that using simple reminder methods could improve the adherence rate of PFMT and consequently improve urinary symptoms (Prasad *et al.*, 2019). Further studies are needed to assess adherence to PFMT among people with MS and urinary symptoms and the influence of adherence on urinary symptoms in MS.

The European Association of Urology (EAU), American Urology Association (AUA), and UK National Institute for Care and Clinical Excellence (NICE) recommend combined therapeutic interventions of PFMT and behavioural intervention for non-neurogenic OAB symptoms (Nambiar & Lucas, 2014) with no clear recommendations for neurogenic bladder symptoms. Intra-detrusor Onabotulinum toxin A (BoNT-A) injection is the most effective therapeutic intervention that classified as a second-line intervention for neurogenic bladder according to EAU guidelines (Nambiar & Lucas, 2014; Tornic & Panicker, 2018). Despite the reported efficacy of this intervention among neurogenic population and particularly people with MS in improving subjective urinary symptoms and urodynamic parameters (Cruz *et al.*, 2011; Denys *et al.*, 2017; Fowler *et al.*, 2009; Kalsi *et al.*, 2007; McCombe *et al.*, 2009; Woodwar, 2004), several adverse events and limitations have been reported including; generalised muscle weakness, the need for repeated injections, increased risk of urinary tract infections (UTIs), increased risk of post-void residual (PVR) due to decline in bladder contractility resulting in the need of clean intermittent catheterization (CIC) afterwards, and rare but severe side effects were also reported such as respiratory problems (Fowler *et al.*, 2009; Groen *et al.*, 2016; Kalsi *et al.*, 2007; Panicker & Fowler, 2015; Stöhrer *et al.*, 2009; Tornic & Panicker, 2018). Although the literature reported the required dosage for BoNT-A injection is 100 unit (Mehnert *et al.*, 2010), the needed dosage for each treatment session is still debatable (Sahai *et al.*, 2010).

Neuromodulation is another available intervention for neurogenic storage symptoms among people with MS. This intervention may include non-invasive, semi-invasive or an invasive surgical procedure. Non-invasive neuromodulation techniques include electrical stimulation of peripheral nerves such as pudendal nerve, dorsal genital nerves, and/ or tibial nerve. Although some studies showed a significant improvement of urinary symptoms using pudendal nerve or dorsal genital nerves among non-neurogenic OAB population, there is a need for further large high quality studies (Jaqua & Powell, 2017; Janssen *et al.*, 2017), with a lack of clear efficacy among neurogenic bladder populations.

Tibial nerve stimulation proximal to medial malleolus using adhesive cutaneous electrodes is another form of non-invasive neuromodulation for bladder storage management called transcutaneous tibial nerve stimulation (TTNS). Percutaneous Tibial Nerve Stimulation (PTNS) is a semi-invasive neuromodulation in which needle electrode is used to stimulate the tibial nerve fibres. Therefore, TTNS could be an alternative intervention among people with MS. Recent reviews have shown that tibial nerve stimulation may be effective in managing storage symptoms in people with non-neurogenic and neurogenic bladder with future high quality studies needed among people with MS (Aharony *et al.*, 2017; Panicker *et al.*, 2015; Schneider *et al.*, 2015; Tornic & Panicker, 2018). The tibial nerve is a mixed nerve containing sensory and motor fibres of L4-S3, and it originates from the same segments of the spinal cord as the innervation to the bladder, pelvic floor, and rectum. The exact mechanism through which tibial nerve neuromodulation potentially treats bladder storage related symptoms is not yet fully understood (Arya & Weissbart, 2017; Gaziev *et al.*, 2013; Jousain & Denys, 2015; Valles-Antuna *et al.*, 2017). However, it is believed that stimulation of the tibial nerve with low-frequency pulses at tolerable intensity can produce inhibition of the spinothalamic neurons within the spinal cord, reduce firing input to the pontine micturition centres (PMC), which in turn inhibits the information facilitated by those nerves to the bladder (Chancellor & Chartier-Kastler, 2000; Choudhary *et al.*, 2016; de Groat, 1997; Devane *et al.*, 2015; Zecca *et al.*, 2016). Neuro-modulation may also have supra-spinal effects which has been investigated in human studies by studying somatosensory evoked potentials before and after Percutaneous tibial nerve stimulation (PTNS) and sacral neuromodulation (SNM). The results showed alterations in somatosensory evoked potential (Finazzi-Agrò *et al.*, 2009; Valles-Antuna *et al.*, 2017). This means that stimulation at the tibial nerve, results in modifications of synaptic efficiency through the somatosensory pathway providing information on the function of somatosensory cortical structures at the spino-thalamic level. Although people with MS might have scattered lesions at spinal cord level, some studies showed some promising evidence from tibial nerve stimulation intervention for bladder control in MS. Further studies are needed to determine the correlation between spinal cord lesions and tibial nerve stimulation intervention among people with MS and bladder storage symptoms.

Our review of the literature revealed few studies investigating TTNS among neurogenic bladder (Amarenco *et al.*, 2003;

Monteiro *et al.*, 2014; Perissinotto *et al.*, 2015; Valles-Antuna *et al.*, 2017). Specific to people with MS, two experimental studies were identified (de Seze *et al.*, 2011; Seth *et al.*, 2018). In the uncontrolled experimental study by de Seze *et al.* (2011), the authors recruited 70 people with MS and OAB. All participants were asked to apply TTNS daily for 20 minutes for 12 weeks. This study found significant improvements in urinary related symptoms of urgency, frequency, and nocturia in 82.6% at the end of week 4, and 83.3% improvement at the end of week 12. Urodynamic studies showed significant improvement by increasing maximum cystometric capacity and reflex volume in about half of the participants (51.2%).

A second study was a randomised pilot study assessing the safety, acceptability and pilot efficacy of transcutaneous low-frequency TTNS using self-applicating ambulatory skin-adhering device stimulating the tibial nerve called geko™ at a frequency of 1 Hz. The study compared two different protocol of TTNS 30 min daily vs. 30 min weekly, for 12 weeks between 24 MS participants with OAB to 24 participants with idiopathic OAB. TTNS was shown to be safe, acceptable and significant improvements in urinary symptoms including OAB were reported for both groups (Seth *et al.*, 2015; Seth *et al.*, 2018). The electrical stimulation parameters for both groups were at 27 mA current, with 1 Hz current frequency and pulse width was between 70 and 560 µs and was consecutively increased depending upon the maximum tolerable sensory and best sensory-motor response.

The potential efficacy of TTNS among people with MS with urinary symptoms is based on a small number of studies with a large number of authors identifying the absence of high-quality evidence relating to the electrical stimulation parameters, frequency of treatment per week, and total number of sessions (Booth *et al.*, 2018; Burton *et al.*, 2012; Schneider *et al.*, 2015; Slovak *et al.*, 2015; Tudor *et al.*, 2020; Zecca *et al.*, 2016).

Randomised controlled trials are required to provide a robust evidence-base for using TTNS for neurogenic bladder storage related symptoms in MS. Therefore, there is a need to assess the feasibility of TTNS in storage symptoms among people with MS using, widely available and affordable device, the transcutaneous electrical nerve stimulation (TENS) unit to proceed with a definitive randomised trial.

### Specific objectives

The overarching aim of this study is to assess whether transcutaneous tibial nerve stimulation (TTNS) is feasible as a treatment for bladder storage symptoms in people with MS. In particular, the study will explore the feasibility and acceptability of TTNS application in people with MS by addressing the following specific objectives:

*The primary objectives are* to a) assess the recruitment and retention rates, b) investigate the completion rate and appropriateness of outcome measures by participants; c) assess safety by reporting the number of participants with adverse events; d) determine participants' adherence to the treatment protocol, and e) assess participant's satisfaction with TTNS application.

The secondary objectives are to a) evaluate the preliminary effectiveness of TTNS in managing bladder storage symptoms in MS; and to b) determine the effect of TTNS on quality of life in people with MS.

Addressing these objectives will establish a foundation for future definitive randomised trial to explore the efficacy of TTNS on bladder storage symptoms in MS.

## Methods

The CONSORT extension for pilot and feasibility studies will be followed to standardise the conduct and reporting of the study (Eldridge *et al.*, 2016). Ethical approval was obtained from the Faculty of Education and Health Sciences Research Ethics Committee at the University of Limerick [2020\_06\_07\_EHS]. This study was registered with ClinicalTrials.gov on 27<sup>th</sup> August 2020 (NCT04528784). The trial registration platform will be updated if any changes are made to the trial.

### Study design

A single-arm experimental study to assess the feasibility of TTNS in MS bladder storage symptoms.

### Setting

The intervention will be accessible to community dwelling people with MS in Ireland and self-administered by participants in their own homes.

### Participants

Inclusion criteria: People with a self-reported diagnosis with any type of MS who are ambulatory; aged  $\geq 18$  years old; who have at least one bladder storage related symptom such as urinary frequency, urinary urgency, nocturia, with or without incontinence; and who are willing to give written informed consent.

People with MS will be excluded if they have: indwelling urethral catheter; indwelling suprapubic catheter; urologic disease including bladder malignancy; diabetic mellitus; pregnant women or plan to be pregnant during the study time; recent pelvic related surgery <1 year; pacemaker or other metallic internal devices; urinary tract infections (UTIs) during recruitment phase.

### Participant identification and consent

The recruitment plan is twofold: 1) Open recruitment for people with MS through MS Ireland's communication channels for two months duration. This will employ the same procedures as that of our published protocol for a previous qualitative study (Al Dandan *et al.*, 2019). A co-investigator (HD) will send recruitment letters (Appendix A, extended data (Al-Dandan, 2020)), study information sheets, and screening forms (Appendix B, extended data (Al-Dandan, 2020)) to a gatekeeper at MS Ireland who will send the emails to all people with MS and who will place the study notifications on their social media channels. 2) In addition, our recruitment strategy will include a convenience sample of people with MS from an existing cohort of people with MS who have already

participated in a qualitative telephone interview study of urinary problems. The protocol for that study, including recruitment strategies, are described in detail elsewhere (Al Dandan *et al.*, 2019).

Interested and eligible participants will be invited to contact a member of the research team including the principal investigator (KR) or co-investigators (SC) or (HD) using the contact methods provided in the email. Once a participant contacts any member in the research team, a call will be arranged via MS Ireland's Zoom for Healthcare account with (HD) to review eligibility and provide details of the full procedure of the study including the protocol of the nerve stimulation intervention and the outcome measures and give prospective participants the opportunity to ask questions. Participants will be made aware that they have the full right to withdraw at any stage without any explanation. Those who elect to participate will be provided with the link via email to a survey hosted on Qualtrics Survey Software to read and sign the informed consent form, complete demographic data (Appendix C, extended data (Al-Dandan, 2020)) including the Patient Determined Disease Steps (PDDS) (Learmonth *et al.*, 2013), the International Consultation of Incontinence Questionnaire-Overactive bladder (ICIQ-OAB), King's Health Questionnaire, the 3-day bladder diary (Appendix D, extended data (Al-Dandan, 2020)), adverse events report diary (Appendix E, extended data (Al-Dandan, 2020)), and adherence to treatment protocol (Appendix F, extended data (Al-Dandan, 2020)). The 3-day bladder diary, ICIQ-OAB, and King's Health Questionnaire are to be filled twice during the study; at base line before commencing the intervention (week 0) and post commencing the intervention at the end of (week 6). Diaries including adverse events report diary and adherence to treatment protocol diary are to be filled throughout the study from (week 0) till the end of (week 6) to document any observation related to the application of the intervention. The Questionnaire for Acceptability (Appendix G, extended data (Al-Dandan, 2020)) is to be filled at the end of the intervention at the end of (week 6) to allow the researcher to determine the participant's satisfaction level with application of TTNS.

Once participants provide the signed consent form and complete the required outcome measures, a call will be arranged using MS Ireland Zoom Healthcare account to provide details in how to apply the nerve stimulation and allow an opportunity to ask questions. After the call, all participants will be emailed a short video showing the nerve stimulation application as a reminder in how to apply the TENS unit.

The nerve stimulation unit will be posted to them by an MS Ireland's staff member. In this package, a stamped addressed envelope will also be provided to facilitate return of the nerve stimulation unit.

During the Zoom video call participants will be given an option for paper copy of diaries instead of downloadable documents via Qualtrics Survey Software. In this scenario, HD will inform the interested participants that the hard copies of the diaries will be posted with the TENS unit.



Participants will be called by HD on a weekly basis using MS Ireland Zoom Healthcare account to check adherence to treatment protocol, any reported adverse event, discuss any issues raised up by participants, and at the end of the study will remind them to complete the outcome measures. Responses from participants will be documented to be cross-checked against the self-reported diaries for adherence and adverse events. The study will be discontinued for individual participants if participants report an adverse reaction to the application or use of TTNS.

#### TTNS Intervention:

- **Type of equipment:** Stimulation of posterior tibial nerve will be delivered by Transcutaneous Electrical Nerve Stimulation (TENS) unit.
- **Application of TTNS:** based on the anatomical distribution and previous reports: the anode will be positioned between 5–10 cm above medial malleolus and posterior to the edge of the tibia and the cathode will be positioned distally on arch of the foot (Castel-Lacanal, 2015; McGuire *et al.*, 1983). The accurate location of electrode is considered by contractions of the appropriate muscles innervated by posterior tibial nerve; sensory response by tingling sensation of sole of the foot and / or motor response by flexion of big toe and fanning of the other toes.
- **Patient position:** participant will be advised to lie supine with extended legs or supported sitting with knee extension in order to allow the nerve roots to be free from any compression at knee joint.

Participants will be advised to ensure that their skin is clean skin under the electrode to minimize skin resistance. In cases where participants apply skin moisturiser, they will be advised to wipe the area with alcohol swap or with soap and water and ensure the area is completely dry prior to electrodes application.

- **Duration of Treatment:** A six weeks intervention period has been shown to be effective among a neurogenic population (Monteiro *et al.*, 2014) and preferable among participants who has been interviewed during phase II study (Al Dandan *et al.*, 2019)
- **Side of Lower leg:** based on physiology of the central nervous system control of the bladder we would use the left ankle for the application of TTNS because it has been shown that the right side of the brain is the predominant active area in micturition (de Groat, 1997; Sand & Sand, 2013).
- **Frequency:** 10 HZ. It has been shown that low frequency of 10HZ is effective in inhibiting sympathetic nervous system that might normalize bladder functions (Robertson *et al.*, 2006).
- **Intensity:** the intensity of stimulation will be at the sensory and motor threshold by tingling sensation on sole of the foot with flexion of big toe and /or fanning of other

toes. The stimulation should not be painful (Zecca *et al.*, 2014).

- **Pulse duration:** 200 microseconds, it is important to be long enough to allow action potentials to leave the hyperpolarization zone induced by anodic phase (Vargas Luna *et al.*, 2017). It is consistent with previous studies.
- **Stimulus duration:** 30 minutes
- **Frequency of treatment:** 3 times/ week for 6 weeks

#### Outcomes

**Primary outcome measures.** A) Feasibility will be assessed by the proportion of participants who: are recruited to the study, complete assigned outcome measures, complete the 6-week intervention, and are lost to follow up. Also, feasibility will be assessed by the overall level of adherence achieved over the study period of 6-weeks through the self-report diary (Anghel *et al.*, 2019). Adverse events will be measured using a self-report diary and will include (but will not be limited to) any device related skin redness at the site of stimulation, discomfort at the stimulation site that might persist post treatment session. B) Acceptability (satisfaction) of TTNS application will be assessed using a self-report questionnaire developed by the researchers containing 5-point Likert scales: 1= “strongly disagree”; 2= “disagree”; 3= “neutral”; 4= “agree”; 5= “strongly agree”.

**Secondary outcome measures** include the followings:

- The storage symptoms will be assessed by ICIQ-OAB (Abrams *et al.*, 2018; Zappavigna & Carr, 2015). It has grade A for validity, reliability and responsiveness to change established with rigour on one data set. The total score ranges from 0 to 16 with higher values indicating increased symptom severity. Bother scales are not incorporated in the overall score (Abrams *et al.*, 2006).
- Severity of frequency, nocturia, and incontinence will be assessed by using a standard 3-day bladder diary (Jimenez-Cidre *et al.*, 2015; Nambiar & Lucas, 2014). Number of episodes of frequency, nocturia, and incontinence/ 72 hours will be calculated and compared from baseline with higher values indicating increased symptom severity.
- Severity and intensity of urgency will be assessed using Patient Perception of Intensity of Urgency Scale (PPIUS) (Notte *et al.*, 2012). Number of urgency episodes and severity of urgency/72 hours will be calculated and compared from baseline. The total score ranges from 0 to 4 with higher values indicating increased symptom severity.
- Quality of Life (QoL) will be evaluated by using King’s Health Questionnaire (Nambiar & Lucas, 2014; Okamura *et al.*, 2009; Pat Ray *et al.*, 2003). A change from baseline of 5 points or higher on most of the King’s Health Questionnaire domains represents a clinically meaningful improvement in health-related quality of life after treatment (Kelleher *et al.*, 2004).

### Sample size

This is a pilot study and a formal sample size is not computed. We anticipate that a total of 20 participants will be recruited to the pilot study within two months.

### Data management and confidentiality

The applications used in this study including Zoom Healthcare provided by MS Ireland which uses password protected calls with random meeting ID's and locked rooms after entry. It is accredited as a tele-health communication system. Also, Qualtrics Survey Software (account held by School of Allied Health, University of Limerick) are accepted to be used for research as a secured and confidential by the University of Limerick. Data will be handled confidentially and will be stored in accordance with Data Protection Policy at the University of Limerick and in line with the Health Research Regulations 2018 and General Data Protection Regulation (GDPR). All participants will be anonymised by given a unique identifying number and will be entered in a password-protected laptop. Data collected will be accessed only by the team of the study including; HD, KR, SC, RG and DM. All data collected during the study will be entered securely and confidentially in the same laptop by HD. The data will be stored for seven years then all electronic files will be deleted permanently. The full protocol and supplementary Materials are available in an open repository. There are no plans to make the participant dataset open access.

### Statistical methods

SPSS software (Version 26.0. Armonk, NY: IBM Corp) will be used for statistical analysis:

•*The primary outcomes* will be analysed using descriptive statistics (numbers, means, and percentage) with 95% confidence interval (CI). Medians and interquartile ranges will be reported where data are not normally distributed.

•*The secondary outcomes* for the scores of ICIQ-OAB and King's Health questionnaire at the baseline, and at the end of week 6 will be reported as mean scores with SD and changes in scores between baseline, and week 6 will be examined using T-tests to provide a quantitative indicator of the significance of the changes in the assessment measures following stimulation sessions. The non-parametric equivalent tests will be employed where data are non-parametric.

The incidence of nocturia, incontinence and urinary frequency and urgency will be reported across the two groups and differences will be quantified using a Chi-squared test.

The scale of Patient Perception of Intensity of Urgency Scale (PPIUS) will be assessed using descriptive statistics means and standard deviation (SD).

### Dissemination

The findings of the study will be shared with MS Ireland to be distributed to people with MS and healthcare professionals (HCPs). Also, the study will be submitted for publication to a peer reviewed journal.

### Study status

The study is yet to commence. It is due to commence in September 2020

### Conclusion

To the authors' knowledge, no feasibility studies have been conducted to evaluate the feasibility of TTNS application for managing storage bladder symptoms in MS. It is anticipated that assessing the feasibility for the application of TTNS among people with MS will contribute to proceed with a definitive randomised trial.

### Data availability

#### Underlying data

No underlying data is associated with this article.

#### Extended data

Open Science Framework: Transcutaneous tibial nerve stimulation for the treatment of bladder storage symptoms in people with multiple sclerosis: Protocol of a single-arm feasibility study.

<https://doi.org/10.17605/OSF.IO/Q2N9E> (Al-Dandan, 2020)

This project contains the following extended data:

- Appendices.docx (recruitment letter, screening form, demographic data sheet, 3- day bladder diary, adverse events report diary, adherence to treatment protocol and the questionnaire for acceptability of treatment)

#### Reporting guidelines

Open Science Framework: SPIRIT checklist for 'Transcutaneous tibial nerve stimulation for the treatment of bladder storage symptoms in people with multiple sclerosis: Protocol of a single-arm feasibility study' <https://doi.org/10.17605/OSF.IO/Q2N9E> (Al-Dandan, 2020)

Data are available under the terms of the [Creative Commons Zero "No rights reserved" data waiver](#) (CC0 1.0 Public domain dedication).

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## Open Peer Review

Current Peer Review Status:  

### Version 1

Reviewer Report 20 October 2020

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#### Noor Almousa

King Fahad Medical City, Riyadh, Saudi Arabia

#### Ahmed Al-Badr

Urogynecology and Pelvic Reconstructive Surgery Division, Department of Obstetrics and Gynecology, Women's Specialised Hospital, Women Specialized Hospital, King Fahad Medical City, Riyadh, Saudi Arabia

Multiple sclerosis is a progressive disease affecting patients between 20 and 40 years of age. It is characterized by multiple lesions and usually a progressive form of bladder dysfunction especially if the plaques are involving the frontal lobe of the cerebral cortex or the lateral columns of the spinal cord. Bladder dysfunction might be the earliest symptom leading to the diagnosis. Approximately 60% of patients with urinary symptoms show detrusor contractions. Whereas 30% of patients might have underactive or areflexic detrusor.

The use of percutaneous tibial nerve stimulation (PTNS) was found effective in reducing overactive bladder symptoms among idiopathic and neurogenic candidates. This treatment modality is non-invasive, ambulatory; easy to perform, with minimal adverse effects. PTNS remains a reasonable treatment option for these patients.

The research project is well structured, the ideas are clear and the writing is concise. You managed successfully to show the importance of your research.

I have a comment regarding the duration of intervention in your study design. The duration of treatment you mentioned is 3 times per week for 6 weeks although it is well known in some studies that a statistically significant improvement was noted on bladder symptoms after 12 weeks of weekly therapy (Peters *et al.*, 2010).<sup>1</sup>

The other point is; are you ruling out any urinary tract infection during the recruitment phase only? Or at the end of treatment as well while filling up the QoL questionnaires? Or weekly just before each PTNS session?

Regards,  
Noor Almousa

Ahmed Al-Badr

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**Is the rationale for, and objectives of, the study clearly described?**

Yes

**Is the study design appropriate for the research question?**

Yes

**Are sufficient details of the methods provided to allow replication by others?**

Yes

**Are the datasets clearly presented in a useable and accessible format?**

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Pelvic floor dysfunction, prevalence

**We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Reviewer Report 05 October 2020

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**David Božidar Vodušek**

Division of Neurology, University Medical Centre Ljubljana, Ljubljana, Slovenia

Neurogenic lower urinary tract dysfunction is common in MS patients with ensuing "storage" and "voiding" symptoms, resulting in risks for the general health outcome, much bother and poor quality of life.

Neuromodulation is an available intervention for neurogenic storage symptoms among people with MS, optimally using a non-invasive approach, such as electrical stimulation of the tibial nerve (TTNS). Although there is some clinical and theoretical basis to substantiate such therapy, there is a need for large high quality studies.

This "...Protocol of a single-arm feasibility study" describes a planned study to assess the feasibility of TTNS in storage symptoms among people with MS using a widely available and

affordable device (the transcutaneous electrical nerve stimulation (TENS) unit). Such a study is very helpful before proceeding with a definitive randomised trial.

This is an excellent, well defined proposal for a study of a clinically very relevant problem. Assessing the feasibility for the application of TTNS among people with MS will contribute to proceed with a definitive randomised trial, which is much needed.

I have only a comment on correct nomenclature: In "TTNS Intervention" there is the statement "...in order to allow the nerve roots to be free from any compression at knee joint". At the knee joint there are NERVES, and not NERVE ROOTS. (See anatomical texts).

**Is the rationale for, and objectives of, the study clearly described?**

Yes

**Is the study design appropriate for the research question?**

Yes

**Are sufficient details of the methods provided to allow replication by others?**

Yes

**Are the datasets clearly presented in a useable and accessible format?**

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Clinical Neurophysiology, Uroneurology, Peripheral neurology.

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

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