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Original Article

bTUNED: transcutaneous tibial nerve stimulation for neurogenic lower urinary tract dysfunction

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Objective

To present the protocol for a randomized controlled trial (RCT) evaluating the efficacy and safety of transcutaneous tibial nerve stimulation (TTNS) for refractory neurogenic lower urinary tract dysfunction (NLUTD).

Study Design and Results

bTUNED (bladder and TranscUtaneous tibial Nerve stimulation for nEurogenic lower urinary tract Dysfunction) is an international multicentre, sham-controlled, double-blind RCT investigating the efficacy and safety of TTNS. The primary outcome is success of TTNS, defined as improvements in key bladder diary variables at study end compared to baseline values. The focus of the treatment is defined by the Self-Assessment Goal Achievement (SAGA) questionnaire. Secondary outcomes are the effect of TTNS on urodynamic, neurophysiological, and bowel function outcome measures, as well as the safety of TTNS.

Conclusions

A total of 240 patients with refractory NLUTD will be included and randomized 1:1 into the verum or sham TTNS group from March 2020 until August 2026. TTNS will be performed twice a week for 30 min during 6 weeks. The patients will attend baseline assessments, 12 treatment visits and follow-up assessments at the study end.

Keywords

tibial nerve stimulation, transcutaneous tibial nerve stimulation, neuro-urology, neuromodulation, neurogenic lower urinary tract dysfunction, neurogenic detrusor overactivity, clinical trial protocol

Introduction

Neurogenic lower urinary tract dysfunction (NLUTD) is characterized by storage (e.g., increased frequency, urgency, urgency incontinence) or voiding (e.g., hesitancy, weak stream, intermittency) symptoms or a combination of both [1]. NLUTD often severely impairs quality of life and, if left untreated, is a risk factor for damage to the upper and lower urinary tract [2–4]. Management of patients with refractory NLUTD is a challenge since oral antimuscarinics, the 'gold standard' first-line therapy, often fail and more invasive treatments such as onabotulinumtoxinA injections into the detrusor, sacral neuromodulation, bladder augmentation, and urinary diversion must be considered.

Neuromodulation therapies, including tibial nerve stimulation (TNS), may be alternative non-invasive treatment options [5–10]. Randomized controlled trials (RCTs) have shown that TNS is an effective and safe treatment for idiopathic overactive bladder (OAB) [11–13], but its mechanism of

action and its value in neurological patients remains unclear. Preliminary evidence for a central neuromodulatory effect after TNS treatment was reported by Finazzi Agrò et al. [14] in 24 patients with OAB non-responding to conventional treatments. After 12 TNS treatment sessions of 30 min, the active TNS group (16 patients) showed increased amplitudes of long latency somatosensory evoked potential components, which were not observed in the sham control group. A pilot RCT in spinal cord injury patients provided initial evidence that transcutaneous TNS (TTNS) could achieve bladder neuromodulation according to neuro-urological outcome measures [15]. In a recent systematic review [5], our group summarized the evidence that TNS is a promising treatment option for NLUTD, however, more reliable data from well-designed RCTs are urgently needed to reach definitive conclusions and establish recommendations. In contrast to the percutaneous approach, TTNS is less common, but more attractive considering the lower costs, non-invasiveness and possibility for home application [8,16,17]. In a pilot RCT by our group, verum and sham TTNS in a subsensory approach proved feasible and safe [18]. However, the clinical findings of this pilot study also raised doubts as to whether the subsensory threshold provided a sufficient stimulation dosage. Based on the pilot results, methodological adjustments have been incorporated into the current protocol to ensure that patients receive an adequate amount of stimulation current.

The primary outcome of the present study was to evaluate the success of TTNS for treating refractory NLUTD (assessed by key bladder diary variables) as compared to sham stimulation. Secondary outcomes were the effects of TTNS on objective and subjective clinical variables and safety of TTNS.

Study Design

bTUNED (bladder and TranscUtaneous tibial Nerve stimulation for nEurogenic lower urinary tract Dysfunction) is a multicentre, randomized, sham-controlled, double-blind clinical trial investigating the efficacy and safety of 12 TTNS sessions during a 6-week intervention period in the treatment of adults with refractory NLUTD. The patients will attend baseline assessments, 12 treatment visits and follow-up assessments at the study end (Fig. 1) in one of the participating centres: Balgrist University Hospital, University of Zürich, Switzerland; Cantonal Hospital Aarau, Switzerland; Lausanne University Hospital, Switzerland; Cantonal Hospital St. Gallen, Switzerland; Azienda Ospedaliera-Universitaria Careggi, Florence, Italy; or Tor Vergata University and Unit of Urology, Tor Vergata University Hospital, Rome, Italy. A total of 240 patients will be included from March 2020 until August 2026.

This protocol follows the recommendations of the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement [19] (Fig. 2) and will be conducted in compliance with the current version of the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guidelines and ISO EN 14155, as well as all national legal and regulatory requirements. The study has been approved by the local ethics committees and registered at ClinicalTrials.gov (NCT04315142). The final study will be reported according to the Consolidate Standards of Reporting Trials (CONSORT) statement [20].

Randomization

bTUNED participants are randomly allocated in a 1:1 ratio into the verum or sham TTNS stimulation group. Computer-generated permuted block randomization lists for each participating study centre are used. To ensure a balanced distribution of prognostically relevant parameters, participants are stratified for cause of NLUTD (Parkinson's disease vs other neurological disorders [e.g., spinal cord injury, multiple sclerosis, or others]) and study centre.

Allocation Concealment

The randomization table is part of the study database (Research Electronic Data Capture, REDCap [21,22]), password secured, and only accessible to investigators responsible for randomization and verum/sham TTNS application (operator) but not involved in the clinical management and assessment of clinical outcomes. Thus, patients and care providers are blinded. To conceal the treatment allocation, a sophisticated four-electrode protocol (Fig. 3) will be used, in which the setups as well as the application procedure and treatment duration are identical between verum and sham TTNS.

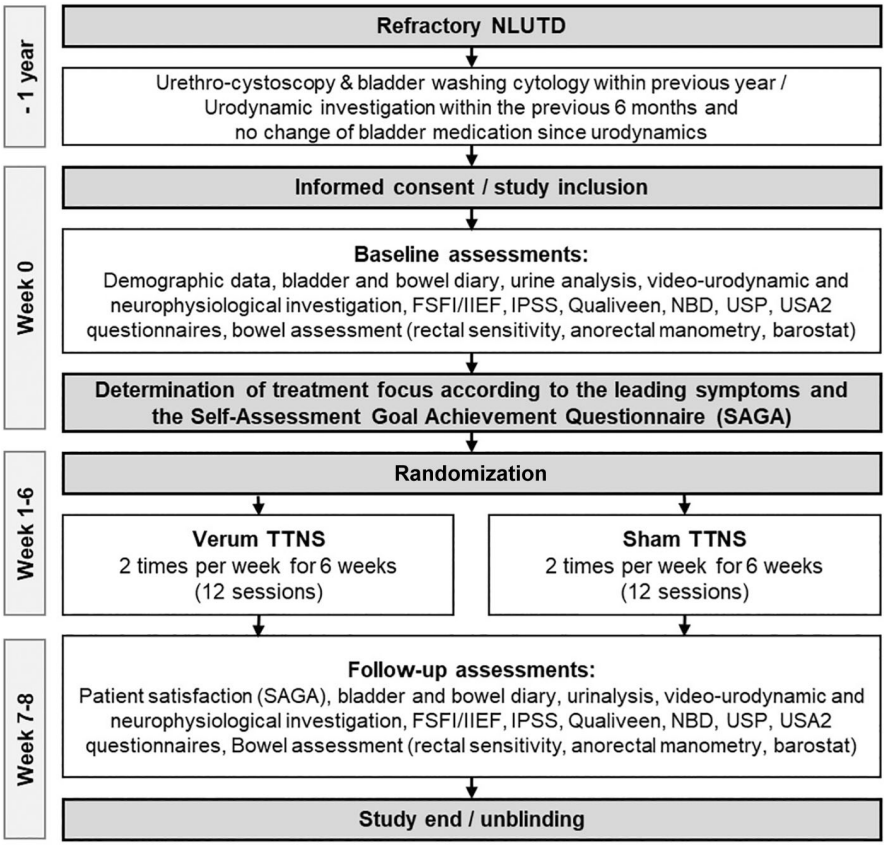
Outcomes

The primary outcome is the success of TTNS. Treatment will be categorized as success if one of the response criteria is achieved and no failure criteria are met. Response and failure criteria are displayed in Table 1.

Secondary outcomes were selected to further evaluate the effect of TTNS intervention such as the Self-Assessed Goal Achievement (SAGA) questionnaire – a patient-reported outcome measure focusing on individual treatment goals – and furthermore changes in bladder diary parameters, urodynamic parameters, questionnaire scores and neurophysiology parameters. Table 2 provides a summary of the secondary outcome measures.

Generally, the outcome assessments are performed before (baseline) and after the TTNS intervention period (study end). Moreover, during the intervention period, patients will

Fig. 1 Trial flowchart: patients with neurogenic lower urinary tract dysfunction (NLUTD) meeting the inclusion criteria will be considered as study participants. After signing the informed consent form study participants will undergo all study related assessments and are allocated to one of the two symptom groups according to the Self-Assessment Goal Achievement questionnaire. The randomization is followed by the 6-weeks verum/sham transcutaneous tibial nerve stimulation (TTNS) treatment period. Thereafter, the study end assessments and the unblinding will take place. FSFI, Female Sexual Function Index; IIEF, International Index of Erectile Function; NBD, neurogenic bowel dysfunction; USA2, Urinary Symptom Assessment; USP, Urinary Symptom Profile.



complete the International Prostate Symptom Score (IPSS) [23], Qualiveen-30 (assesses the specific impact of urinary problems on quality of life) [24], Female Sexual Function Index (FSFI) [25] or International Index of Erectile Function [26], and Urinary Symptom Profile (USP) [27] questionnaires once a week. In case of withdrawal, all study completion assessments should be carried out, if possible. Safety outcomes of TTNS will be assessed as the number and intensity/severity (mild/moderate/severe) of adverse events (AE) and serious adverse events (SAE).

Eligibility Criteria

Patients aged 18 years and older with clinically refractory NLUTD will be recruited in this study. Refractory NLUTD is defined as neurogenic OAB [28] refractory to antimuscarinics (pharmacotherapy for at least 4 weeks with at least two different antimuscarinics), and/or neurogenic voiding dysfunction refractory to alpha-blocker therapy for at least 4 weeks. The primary treatment focus (voiding or storage symptoms) is defined using the SAGA questionnaire [29] in a joint decision by the patient and the investigator. In this way, even in patients with a combination of symptoms, a clear treatment goal with predefined success criteria, is defined.

Patients who fulfil the eligibility criteria become candidates to participate in the study. Detailed inclusion and exclusion criteria are displayed in Table 3.

Patients will not undergo any study-specific procedures, tests, or evaluations until written informed consent is obtained.

Methods

As an initial study-specific screening assessment, transcutaneous tibial nerve stimulation will be performed on both legs. If at least one leg is showing a motor response (i.e., flexion or fanning of the big toe) the patient is considered eligible for TTNS. In addition, the leg with better motor response (i.e., clearer response at lower current as compared

Fig. 2 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) timetable with designated study instruments.

STUDY SCHEDULE									
	Screening	**Baseline**	**Intervention**						**Follow-up**
TIMEPOINT (Weeks)	***-26 to 0***	***0***	***1***	***2***	***3***	***4***	***5***	***6***	***7 to 8***
ENROLMENT:									
Eligibility screen	X								
Informed consent	X								
Urethro-cystoscopy & bladder washing cytology	X								
Randomization		X							
INTERVENTION:									
verum / sham TTNS			Twice a week						
ASSESSMENTS:									
Medical history		X							X
General physical & neuro-urological examination		X							X
Video-urodynamics	X	(X)*							X
Self-assessment goal achievement (SAGA)		X							X
Questionnaire on intervention allocation				X					X
Uroflowmetry		X		X			X		X
Urinalysis		X		X			X		X
Bladder diary		X	X	X	X	X	X	X	X
Bowel diary		X							X
International Prostate Symptom Score (IPSS)		X	X	X	X	X	X	X	X
Qualiveen		X	X	X	X	X	X	X	X
Urinary Symptom Profile (USP)		X	X	X	X	X	X	X	X
Female Sexual Function Index (FSFI)		X	X	X	X	X	X	X	X
International Index of Erectile Dysfunction (IIEF)		X	X	X	X	X	X	X	X
ISCoS Neurogenic Bowel Score (NBD)		X	X	X	X	X	X	X	X
Urinary Symptom Assessment (USA2)		X							X
Neurophysiological exams		X							X
Rectal sensitivity, anorectal manometry & barostat motor function		X							X
Adverse events		X	X	X	X	X	X	X	X

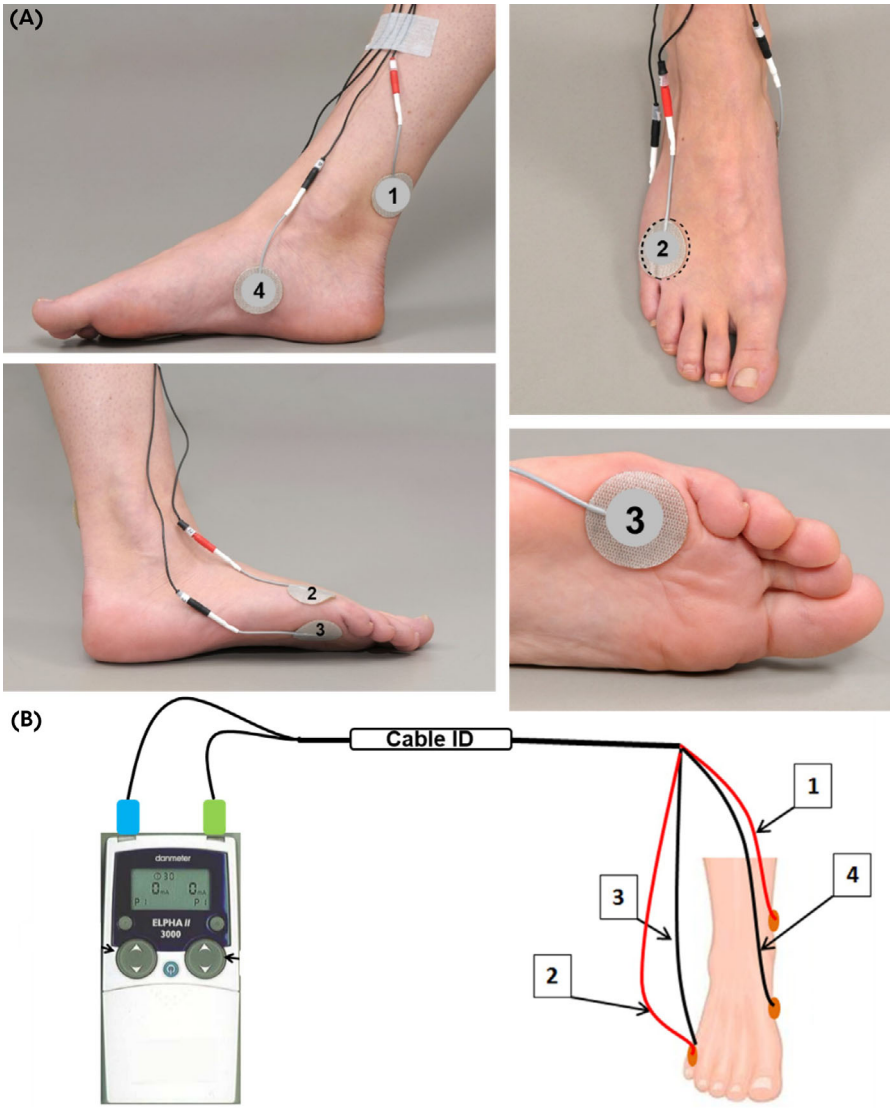
to the contralateral leg) will be selected for the study-specific intervention throughout the entire study.

Intervention

The ELPHA II 3000 (CE 0543 Certification, FH Service, Odense, Denmark), a low-voltage transcutaneous electrical nerve stimulation device (Fig. 3) with pre-programmed settings (current frequency: 20 Hz; pulse width: 200 μs; resistance: 500–4000 Ω) will be used. The current amplitude can be manually set between 0 and 100 mA for two channels separately.

Before starting any stimulation, the patient is asked to lie in a comfortable supine position in a room separated from other patients. A pillow is put in place on the lower part of the leg to restrict the patient's view of their foot. The first electrode is placed 4–5 cm (two fingers) proximal and 4–5 cm posterior to the medial malleolus. The second electrode is

Fig. 3 Transcutaneous tibial nerve stimulation (TTNS). (**A**) Different views of the foot illustrating electrode placement. The medial electrodes are placed 4–5 cm proximal and posterior to the medial malleolus, as well as in the middle of the medial longitudinal arch of the foot. Lateral view of the foot, showing the electrode placement on the dorsal bone and plantar fat pad of the 5th metatarsophalangeal joint. (**B**) Schematic of the TTNS intervention, showing the device, cables and electrode placements. Electrodes are placed in a standardized order [1–4].



placed on the dorsal forefoot at the 5th metatarsal (over the bone) and the third electrode on the plantar forefoot on the fat pad of the 5th metatarsal. The fourth electrode is placed in the middle of the medial longitudinal arch of the foot. The electrodes are connected to the stimulator according to a prespecified scheme and labels on the cables. To keep patients blind, the same protocol is used for all patients regardless of the group allocation, namely, standardized instructions covering the full range of possible sensory-motor responses (all patients are informed that independent of verum and sham TTNS, tingling or other sensations may occur in different regions of their foot) and a four-electrode protocol for all patients.

During the preparation period of few minutes, stepwise current adjustment is performed to assess sensory and motor thresholds, while the operator is carefully observing the foot looking out for any movements, such as flexion or fanning of the big toe or other motor responses. In case of unclear motor response, the electrodes may have to be repositioned. After motor threshold assessment the stimulation current is reduced by 0.5–1.0 mA to a sub-motor level [18]. The stimulator records the total amount of current emitted and will automatically switch off after 30 min. The intervention is performed twice a week for 30 min during a treatment period of 6 weeks. The standardized intervention will be applied by designated and trained personnel to ensure that the treatment

Table 1 Primary outcomes and outcome measures.

Response criteria	Failure criteria
• In patients with neurogenic OAB: ○ ≥50% reduction in incontinence rate per 24 h and/or ○ ≥50% reduction in micturition/catheterization frequency per 24 h • In patients with neurogenic voiding dysfunction: ○ Reduction of PVR below 25% of bladder capacity if bladder capacity ≥100 mL, or below 50% of bladder capacity if bladder capacity <100 mL • In patients with combined neurogenic OAB and neurogenic voiding dysfunction: ○ The response criteria of leading symptom/dysfunction will be chosen	• $pDet_{max}$ ≥40 cmH_2O (conventional cystometry but not ice water test) and/or • Increase of PVR by ≥150 mL

Success of transcutaneous tibial nerve stimulation. Treatment will be categorized as success if one of the response criteria is achieved and no failure criteria are met at the study end point. OAB, overactive bladder; $pDet_{max}$, maximum storage detrusor pressure; PVR, postvoid residual urine volume.

is administered correctly, and that blinding is maintained. For the sham treatment, a cable with a 1000 Ω resistance interposed allows the device to display and adjust the current amplitude, without delivering electrical stimulation to the patient. Full details of the verum and sham TTNS protocol will be disclosed at the conclusion of the study in order to minimize the risk of patient unblinding and thereby ensure the validity and reliability of the study results.

Sample Size Determination

A study of independent cases and controls is planned, with one control patient per case. Prior data [5] indicate that the (spontaneous) success rate among controls is 0.15. If the incremental success rate for experimental patients is at least 0.16 resulting in a success rate of 0.31, we will need to study 120 experimental patients and 120 control patients to be able to reject the null hypothesis that the failure rates for experimental and control patients are equal with probability (power) of 80%. The type I error probability associated with this test of this null hypothesis is 5%. Patients who withdraw or drop out will be replaced.

Data Collection and Management

For data management, monitoring, reports and coding, an internet-based, secure database – REDCap – will be used, which fulfils the Good Clinical Practice requirements [21,22]. All investigators participating in the clinical assessments are responsible for complete and correct data entry in electronic case report forms (eCRFs). eCRFs have to be kept up to date to reflect the latest trial status of a patient, whereby corrections of recorded data will be automatically documented (with date, time, and name of executing person) in the database. To ensure confidentiality, access to the database is limited to a minimal number of people, and further restricted by role-specific access and personalized logins. Electronically stored study data are pseudonymized (all patient identification data are replaced by a 4-digit code). Personal data will only be kept in the internal patient database of the respective hospitals.

Analysis Plan

Descriptive statistics will be presented for all data, continuous variables will generally be reported as medians and quartiles, categorical variables as numbers and percentages. *T*-tests will be used to test differences in mean values between groups and chi-squared tests to compare dichotomous variables. For all outcome assessments (primary and secondary outcomes), multivariable analyses will be performed to adjust for patient characteristics at baseline, using the outcome of interest as a dependent variable and an indicator variable for type of exposure, along with indicator variables for the unequally distributed patient characteristics between groups, as independent variables. Linear models will be fitted in case of an interval outcome and logistic regression models in case of a dichotomous outcome. Repeated measures will be analysed using longitudinal techniques, namely, mixed-effects regression models. Techniques such as time-to-event (survival) analysis and structural equation modelling will be considered in cases where they could help to appropriately model time trends. The planned adjustment set for the primary outcome will place an emphasis on variables known or hypothesized to be strong prognostic predictors [30] of the success of TTNS: symptom/dysfunction group, age, gender, cause of NLUTD, and study centre. Additionally, baseline status of key bladder diary parameters that will be used to classify outcome success/failure is also an important consideration for the planned subgroup analyses.

Subgroup analyses are specified *a priori* and will be carried out on the major symptom/dysfunction groups (neurogenic OAB and neurogenic voiding dysfunction) and underlying neurological disorders (Parkinson's disease, spinal cord injury, multiple sclerosis, or others) and effect modification by

Table 2 Secondary outcomes and outcome measures: secondary clinical outcome measures are assessed based on standardized protocols, questionnaires and urodynamic, neurophysiological and bowel function parameters.

Secondary outcomes and outcome measures	Assessment periods
1. Changes in key bladder diary variables: a. Mean voided/catheterised volume (mL) b. Number of used pads per 24 h c. Number of night-time voids d. Mean pain score (visual analogue scale)	Baseline; once per week during the TTNS intervention period; study end
2. Changes in urodynamic variables: a. Cystometric capacity (mL) b. Compliance (mL/cmH_2O) c. Detrusor overactivity, if yes: i. Bladder volume (mL) at first detrusor overactivity ii. Maximum detrusor pressure amplitude (cmH_2O) iii. Detrusor leak point pressure (cmH_2O) d. Maximum storage detrusor pressure (cmH_2O) e. Maximum voiding detrusor pressure (cmH_2O) f. Detrusor pressure at maximum flow rate (cmH_2O) g. Maximum flow rate (mL/s) h. Voided volume (mL) i. Post-void residual urine volume (mL) j. Pelvic floor EMG activity (normal/detrusor sphincter dyssynergia/non-relaxing pelvic floor) k. Videography (vesico-uretero-renal reflux: yes/no; grade of vesico-uretero-renal reflux)	Baseline; study end
3. Goal attainment scaling assessed by a SAGA questionnaire	Baseline; study end
4. Changes in Qualiveen questionnaire score & IPSS	Baseline; once per week during the TTNS intervention period; study end
5. Variability of University of South Australia USA2 for treatment follow-up	Baseline; study end
6. Changes in urinary symptoms as assessed by the USP questionnaire	Baseline; once per week during the TTNS intervention period; study end
7. Changes in FSFI/IIEF	Baseline; once per week during the TTNS intervention period; study end
8. Changes in ISCoS version of NBD	Baseline; once per week during the TTNS intervention period; study end
9. Changes in bowel function parameters: a. Rectal sensitivity outcome measures i. Initial sensation (mL) ii. Urge to defecate (mL) iii. Maximum tolerated volume (mL) b. Anorectal manometry and Barostat motor function outcome measures i. Basal internal anal sphincter pressure (mmHg) ii. Squeeze external anal sphincter pressure (mmHg) iii. Relaxation internal anal sphincter pressure during defecation (%, mmHg) iv. Intraabdominal pressure during defecation (mmHg) v. Defecatory disorder (Rao's Classification I–IV) vi. Rectal capacity (mL) vii. Rectal compliance c. Bowel diary parameters i. Number of defaecations per 24 h ii. Number of urgency episodes per 24 h iii. Quantity of stool per defaecation iv. Feeling of incomplete evacuation per 24 h v. Number of accidental bowel leakage per 24 h and quantity per leakage vi. Stool consistency score vii. Pain related to defaecation (score) viii. Medications for bowel	Baseline; study end
10. Changes in neurophysiology measurements of EPs as well as nerve conduction measurements and their relation to clinical outcomes	Baseline; study end

Outcomes are assessed prior to intervention start and after 12 transcutaneous tibial nerve stimulation treatments at the study end. EMG, electromyographic; EP, evoked potential; FSFI, Female Sexual Function Index; IIEF, International Index of Erectile Function; ISCoS, International Spinal Cord Society; NBD, neurogenic bowel dysfunction; SAGA, Self-Assessment Goal Achievement; TTNS, transcutaneous tibial nerve stimulation; USA2, Urinary Symptom Assessment; USP, Urinary Symptom Profile.

female gender. Subgroup analyses for study centre might be performed, especially if there is an interaction between centre and treatment effect.

Interim analyses of the baseline assessments are planned only in the case that the independent study monitoring board advises to suspend or stop the trial. Main analyses will be

Table 3 bTUNED eligibility criteria.

Inclusion criteria	Exclusion criteria

• Female and male patients
• Age ≥18 years
• Informed consent
• Last urethro-cystoscopy and bladder washing cytology within 1 year before inclusion
• Last urodynamic investigation within 6 months before inclusion and no change of bladder medication since then
• Refractory LUTD due to a neurological disorder:
  ○ Neurogenic OAB (i.e., urgency frequency syndrome with or without urgency incontinence) refractory to antimuscarinics (pharmacotherapy for at least 4 weeks with at least two antimuscarinics)
  ○ Neurogenic voiding dysfunction (i.e., incomplete bladder emptying → incomplete/complete urinary retention) refractory to alpha-blocker (pharmacotherapy with an alpha-blocker for at least 4 weeks)
  ○ Combination of neurogenic OAB and neurogenic voiding dysfunction (i.e., urgency frequency syndrome with or without urgency incontinence and incomplete/complete urinary retention) refractory to antimuscarinics (pharmacotherapy for at least 4 weeks with at least two antimuscarinics) and alpha-blocker (pharmacotherapy with an alpha-blocker for at least 4 weeks)
• Motor response to TTNS stimulation in at least one leg
• Willing to not change or start any new medications or treatments for the LUTS during the entire study period (from screening until unblinding)
	• Contraindications to the investigational product
	• Known or suspected non-adherence, drug or alcohol abuse
	• Inability to follow the procedures of the study, e.g., due to language problems, psychological disorders, dementia
	• Participation in another study with investigational drug or product within the 30 days preceding and during the present study
	• Neuromodulation treatment for urological indication in the last 6 months or ongoing
	• Botulinum toxin injections into the detrusor and/or urethral sphincter in the last 6 months
	• Women who are pregnant or breastfeeding
	• Intention to become pregnant during the course of the study
	• Individuals especially in need of protection (according to Research with Human Subjects published by the Swiss Academy of Medical Sciences [www.samw.ch/en/News/News.html])
	• Enrolment of the investigator or any other dependent persons

The presence of haematuria and UTI are not principal exclusion criteria, but need to be appropriately evaluated and managed prior to baseline and any follow-up assessment. Urine will be routinely checked before urodynamic and neurophysiology investigation, at every fourth stimulation session, and at any time if appropriate. In case of UTI, the patient will receive a course of antibiotic therapy reflecting standard clinical care, and functional assessments will be rescheduled to after 3 days of absence of UTI-related symptoms. LUTD, lower urinary tract dysfunction; OAB, overactive bladder; TTNS, transcutaneous tibial nerve stimulation.

carried out according to the intention-to-treat principle at the end of the trial when all follow-up assessments have been performed.

Methods for Handling Missing Data

Multiple imputation will be used to appropriately account for missing data in the predictor variables (or item non-response) [31,32], and a pattern mixture model may be used to account for missing outcome variable data. Sensitivity analysis will be used to evaluate the robustness of the estimators to changes in the underlying assumptions regarding handling of early withdrawals and protocol violations, as well as to handling of missing data.

Quality Assurances and Safety Oversight

Monitoring during the entire clinical trial ensures the highest possible data quality and early detection of sources of error. A study monitoring board has been established to perform ongoing study surveillance and to perform interim analyses if appropriate. All data in context with the clinical trial, including patient records, examinations, and test results have to be accessible to the monitoring board. The monitor inspects eCRFs and informed consents of the patients. Through the above-mentioned sources, the correctness of data is verified. The site qualification and initiation visit(s) will ensure that the study site has the appropriate facilities and personnel, and that the personnel are able to conduct the study according to protocol.

Discussion

bTUNED is the first adequately powered, randomized, sham-controlled, double-blind trial assessing TTNS for the treatment of refractory NLUTD. This RCT will provide significant insights into the efficacy and safety of TTNS in patients with NLUTD and has the potential to relevantly improve the management of NLUTD in daily clinical practice. Moreover, as bTUNED is assessing neuro-urological outcomes in combination with changes in neurophysiological measurements it might help to elucidate the underlying mechanisms involved in the neuromodulation process.

In neurological patients, the effect of neuromodulation techniques is still less clear than in patients with idiopathic LUTD [5]. Gaspard et al. [33] compared the effect of TTNS with pelvic floor muscle exercises including biofeedback in patients with multiple sclerosis. The patients were randomly assigned to TTNS (n = 15) and pelvic floor muscle exercises (n = 16). Symptoms improved in both groups, but no relevant differences were detected between the two groups. However, there was no control group and urodynamic variables were not assessed. Monteiro et al. [34] investigated the effects of percutaneous TNS (PTNS) in patients with ischaemic stroke. The patients were randomized into a PTNS (n = 12) and control (n = 12) group. PTNS improved LUTS,

but the between-group differences were very limited, probably partially due to the low number of patients. In addition, there was a lack of blinding, and urodynamic data were not assessed. Perissinotto et al. [35] randomly allocated 23 patients with Parkinson's disease to a TTNS and sham group. Patients in the TTNS group (n = 8) experienced significant reduction in urgency and nocturia episodes, questionnaire scores and some urodynamic data improved. However, there was a high dropout rate with a low number of patients finishing the study (n = 13). Accordingly, TTNS is a promising treatment for NLUTD with potential neuromodulatory effects [14], but the evidence base is poor, and comes from small, mostly non-comparative studies with a high risk of bias and confounding so more reliable data are needed to draw definitive conclusions [5]. In a recent pilot RCT by Stampas et al. [36], safety and feasibility has been proven after 2 weeks of TTNS in acute spinal cord injury. The results of this promising trial are pointing towards differential effects on urodynamic variables after 10 sessions of 30-min TTNS compared to sham stimulation. These results suggest that specific neuromodulatory effects of TTNS might decisively alter the detrimental course of NLUTD that is frequently observed. Indeed, TTNS might prevent neurogenic detrusor overactivity in patients with acute spinal cord injury [37].

Although preliminary data are very promising, the overall evidence base for the efficacy of TTNS as a treatment in the population with NLUTD is poor. bTUNED is the first adequately powered, sham-controlled, double-blind RCT assessing TTNS for treating refractory NLUTD and has the potential to relevantly improve the management of NLUTD in daily clinical practice and to elucidate the underlying mechanisms involved in the neuromodulation process.

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Disclosure of Interests

None.

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Abbreviations: eCRF, electronic case report form; NLUTD, neurogenic lower urinary tract dysfunction; OAB, overactive bladder; PTNS, percutaneous tibial nerve stimulation; RCT, randomized controlled trial; SAGA, Self-Assessment Goal Achievement questionnaire; TNS, tibial nerve stimulation; TTNS, transcutaneous tibial nerve stimulation; USP, Urinary Symptom Profile.