Clinical Efficacy of Transcutaneous Tibial Nerve Stimulation (TTNS) Versus Sham Therapy (Part I) and TTNS Versus Percutaneous Tibial Nerve Stimulation (PTNS) (Part Ii) on the Short Term in Children With the Idiopathic Overactive Bladder Syndrome: Protocol for Part I of the Two-fold Randomized Controlled TaPas Trial

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Study protocol

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Abstract

Background: Transcutaneous tibial nerve stimulation (TTNS) and percutaneous tibial nerve stimulation (PTNS) are effective and safe therapies for the overactive bladder (OAB) syndrome in adults. However, few randomized sham-controlled trials have been conducted in a paediatric population. Both therapies have never been compared to our knowledge..

Aim: The aim of the complete study is twofold: 1) To assess the efficacy of TTNS therapy on bladder symptoms after 12 weeks of treatment in a paediatric population with idiopathic overactive bladder syndrome (iOAB) and/or nocturnal enuresis (part I). 2) To assess the effect of TTNS compared to PTNS (part II). In this article, we aim to present the protocol of the first part of the TaPaS trial (TTNS, PTNS, Sham therapy).

Methods: Part I of the TaPaS trial is set up as a single-centre randomized-controlled trial. Children, aged from 5 to 12 years with iOAB and/or nocturnal enuresis, are assigned to two groups by computer-generated randomization: TTNS therapy (intervention) and sham therapy (controls). The primary outcome is the percentage difference in average voided volume (AVV) between baseline and after 12 weeks of treatment. Secondary endpoints are the percentage difference in supervoids volumes, number of urinary incontinence episodes/24 hours and in voiding frequency, the difference in parent reported outcomes between baseline and after 12 weeks of treatment and the duration of clinical response.

Discussion: We hypothesize that TTNS is a non-inferior treatment for iOAB in children compared to PTNS therapy. Since literature is inconclusive about the efficacy of TTNS in a paediatric population, a sham controlled RCT on TTNS will be conducted (part I). A protocol for a prospective randomized sham-controlled trial has been developed. Enrolment has started in November 2018. Study completion of part I is expected by August 2021.

Trial Registration: ClinicalTrials.gov NCT 04256876. Retrospectively registered on February 5, 2020. URL: https://clinicaltrials.gov/ct2/show/NCT04256876

Administrative Information

Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

Title {1}	Clinical efficacy of Transcutaneous tibial nerve stimulation (TTNS) versus Sham therapy (Part I) and TTNS versus Percutaneous tibial nerve stimulation (PTNS) (Part II) on the short term in children with the idiopathic overactive bladder syndrome (TaPaS): Protocol for Part I of a two-fold randomized controlled trial.
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Role of sponsor {5c}	- Support in the preparation of a correct and complete submission package for the Ethics Committee and Competent Authority. - Performing on-site and remote monitoring according ICH-GCP for all clinical trials. - Providing a no-fault insurance.

Introduction

Background and rationale {6a}

The reported prevalence of daytime lower urinary tract dysfunctions (LUTD) in children ranges widely from 1–20%.(1) Among these, the overactive bladder syndrome (OAB) as a storage dysfunction and dysfunctional voiding as an emptying dysfunction are the two main entities. Failure to achieve continence (normally reached by the age of three to four), urgency, frequency, hesitancy and frequent urinary tract infections (UTI's) are reported complaints. Nocturnal enuresis without daytime LUTD is considered as a separate entity and has an estimated prevalence of 5–10% at the age of seven.(1)

In the management of both OAB and nocturnal enuresis the objective is to increase the bladder capacity if reduced for the age. Conservative therapy like lifestyle advices and behavioural modifications, including bladder re-education and bowel management is the first step in a multimodal approach (urotherapy). In case conservative therapy fails, anticholinergic drugs are the mainstay of medical treatment. As an alternative, in case one is reluctant to pharmacotherapy or in case pharmacotherapy has failed, peripheral neuromodulation can be offered.

Different types of peripheral neuromodulation have been widely practiced in the paediatric population like transcutaneous electrical nerve stimulation (TENS) – on the sacrum or over the posterior tibial nerve (TTNS) and percutaneous tibial nerve stimulation (PTNS).(2, 3)

PTNS is the standard alternative treatment for OAB in our department. It is proven to be effective and safe in children with iOAB.(4) However, the time-consuming weekly in-office visits and the percutaneous approach make therapy child-unfriendly. The transcutaneous technique by contrast is non-invasive and can be easily applied at home. It would benefit the patient and the parents if TTNS would form an equal alternative to PTNS therapy.

Ramírez-García et al. conducted a prospective efficacy study on TTNS compared to PTNS therapy as treatments for adults with OAB. The authors could demonstrate the non-inferiority of TTNS in comparison to PTNS in decreasing daytime voiding frequency.(5) However, the non-inferiority of the transcutaneous technique over the percutaneous technique in a paediatric population hasn't been proven so far.

In the TaPaS trial - acronym for Transcutaneous tibial nerve stimulation, Percutaneous and Sham therapy- we will evaluate both the superiority of TTNS over sham therapy (Part I) and the non-inferiority of TTNS compared to PTNS in children with idiopathic OAB (iOAB) (Part II).

To our knowledge, only two sham-controlled RCT's have been published on the efficacy of TTNS in children with OAB. In the first study published by Boudaoud et al. 20 children with OAB were randomized into a TTNS and a sham group. The clinical results remained the same between both groups, underlining the potential placebo effect of any type of management in this population.(6) In the second study by Patidar et al. a significant benefit of TTNS over sham therapy in a study population of 40 children with OAB was seen.(7) Since the results of both trials are contradictive, we decided to set up a new similar RCT. TENS therapy is completely safe and does not cause any adverse effects. (3)

Objectives {7}

The objective of part I of the TaPaS trial is to evaluate the efficacy of TTNS therapy by means of a sham-controlled RCT.

Trial Design {8}

A prospective, single-centre randomized controlled double-blinded trial is set up, comparing TTNS versus sham therapy. Participants are allocated on a 1:1 ratio to either the intervention arm, either the control arm according to a computer-generated list of random numbers. Superiority of TTNS over sham will be assessed. The treatment protocol was approved by the Ethical Board of the Ghent University Hospital (B670201837682) on the 6th of November, 2018. Recruitment has started in in November 2018 and is still pending. Study completion of part I will be expected by August 2021.

Methods: Participants, Interventions And Outcomes

Study setting {9}

The recruitment of participants is carried out by paediatric urologists and paediatric nephrologists from the Department of Urology and at the Department of Pediatrics at the academic hospital of the Ghent University (East-Flanders, Belgium). Children attending a paediatric specialist (PS) for urgency incontinence or bedwetting are eligible for inclusion. The inclusion criteria are listed below.

At the initial visit, the child with lower urinary tract symptoms (LUTS) is subjected to a complete diagnostic work-up according to the standard of care.(8) Besides a baseline history-taking assessment, a few additional evaluations are performed : urine sample analysis, a bladder and kidneys ultrasound (US) and an uroflowmetry with an US guided post-void residual (PVR) measurement. A three days daytime bladder diary and a 7 nights night-time bladder diary are distributed. Based on the completed bladder diaries and the baseline work-up, children are diagnosed at the second visit and subsequently screened for eligibility.

Eligibility criteria {10}

Patients who meet the following criteria are eligible for inclusion:

- Diurnal urgency urinary incontinence and/or nocturnal enuresis (primary or secondary).
- Aged from 5 to 12 years old.
- Being treatment–naïve or only having been treated with urotherapy (See intervention description 11a for a detailed definition of urotherapy).
- Having a parent or guardian who is able to complete bladder diaries reliably.

Exclusion criteria are the following:

- Patients already treated with non-conservative therapies: i.e. anticholinergic drugs, transcutaneous electrical nerve stimulation (TENS), PTNS or intradetrusor botulinum toxin injections.
- Patients with a neurogenic bladder dysfunction.
- Patients with dysfunctional voiding, diagnosed by the presence of a staccato-shaped curve on uroflowmetry at the moment of screening.
- Patients with nocturnal polyuria, registered on a 7 days night-time bladder diary. Nocturnal polyuria is defined by the International Children's Continence Society (ICSS) as a nocturnal urine production exceeding 130% of the expected bladder capacity for age.(9)
- Patients with behaviour disorders like attention-deficit hyperactivity disorder.
- Patients having a mental disability, unable to comprehend urotherapy.

Who will take informed consent? {26a}

If a child is eligible for inclusion, the child and parent(s) or guardian are verbally informed about the study by their PS and a written informed consent adapted to minors is distributed. If both parties are willing to participate, the informed consent is signed and an appointment for a first visit at the paediatric physiotherapist is made. A research assistant, also being a medical doctor can function as an authorized surrogate to take informed consent.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

There are no additional informed consents needed since no biological specimens are taken.

Interventions

Explanation for the choice of comparators {6b}

The results of the two only RCT's that have been conducted to compare TTNS and sham-therapy in children are conflicting. (6, 7) Therefore we chose to set up a new sham-controlled RCT.

Intervention description {11a}.

Intervention group:

Active neuromodulation treatment is delivered by the Transcutaneous Electrical Nerve Stimulation (TENS) device from BioMedical Life Systems; the Impulse 3000 T®. The physiotherapist places a round self-adhesive surface electrode (Ø3.2 cm) on the tibia, two cm cranial from the medial malleolus (the negative electrode). The positive electrode is placed halfway the medial foot arch on the conduct of the posterior tibial nerve (see Fig. 1). Stimulation parameters are set on a fixed pulse width of 200 μS and a pulse frequency of 20 Hz. In literature, no consensus is reached on the ideal stimulation settings of TTNS. (10) Most studies report a pulse width of 200 μs.(3) We decided to choose the same frequency (20 Hz) as the previous study by Patidar et al. since significant results in this active treatment arm were seen.(7)

During the therapy session, parents are instructed by the physiotherapist how to apply the surface electrodes themselves. By increasing the pulse intensity by turning the wheel, the TENS-device will be switched on. The pulse intensity (in volt) is increased till a comfortable, painless sensation is felt. While increasing the pulse intensity, no motor responses may occur. During the following 30 minutes, in-office stimulation is given.

At the end of the session, the same device is given to the parents in order to apply ambulant therapy (AT). Parents are instructed to apply the TENS-device on the ankle of their child 1 hour daily during the next twelve weeks (two times six weeks with 1 visit at the physiotherapist in between), without changing the fixed settings. The TENS device must always be placed on the same ankle. If habituation to the electrical impulse occurs, the pulse intensity should be set around the perception threshold. The intensity may be increased from 1–20 volt, but stimulation may never be considered as painful. To conceal the allocation of treatment (effective treatment versus sham) for parents and child, they are told they cannot determine by sensation to which study group they belong.

Sham group:

The same TENS-device, electrode positioning, pulse frequency (20 Hz) and pulse width (200μs) as in the intervention group are applied for the sham group. Unlike the intervention arm, the pulse intensity button is set on position number ‘1’, which is the test button on which no electric current is delivered. To parent and child it is told that it is normal that no sensation is felt.

The same stimulation protocol as for the intervention group (1 hour daily during 2 periods of 6 weeks) needs to be followed at home after the first visit. When switching the TENS-device on, they may not exceed number 1. This way, no current is supplied.

Urotherapy:

Besides neuromodulation, every participant in the trial will receive standard Urotherapy. Urotherapy can be defined as a bladder re-education or rehabilitation program aiming for the correction of filling and voiding

difficulties.(11) It encompasses the following components (9):

- Education on normal lower urinary tract (LUT) functioning and on how the LUT function of the child differs from normal.
- Lifestyle advices: Counselling on drinking and voiding habits, diet, reduction of caffeine intake, proper stool management, etc.
- Behavioural modifications: Sustaining regular voiding habits and adequate toilet positioning, avoiding holding manoeuvres, etc.
- Regular follow-up and encouragement strategies: Specific for this trial a follow-up visit at the physiotherapist will be foreseen after 6 (the second visit) and 12 weeks (the third visit) of AT.
- Registration of symptoms, drinking, voiding and stool habits through diaries.

Specific for this trial, a one day bladder diary must be completed consistently weekly as part of the urotherapy. Additionally, 3 times weekly the participant must try to hold up urine for 5 minutes if the urge to urinate comes up. Gradually the duration of delayed urinating should be trained to be increased. The so called ‘supervoids’ are part of urotherapy.

In the sixth week, a 7 days night-time bladder diary must be completed. After the second visit at the physiotherapist the participant must continue the stimulation and urotherapy (plus completion of the diaries and supervoids) for another 6 weeks.

After the third visit, an observation period of 6 weeks is inserted during which no stimulation is given. Urotherapy however should be continued.

Study schedule

For a structured overview of the study schedule, see Fig. 2. After enrolment, the participant is referred to the physiotherapist for a first visit. Urotherapy and a first neuromodulation session are given. After home-therapy for six weeks, a second evaluation visit at the physiotherapist is planned. Together with the parent and participant, the progression in symptoms is evaluated by review of the completed diaries. After the second six-week period of home-therapy a third follow-up visit at the physiotherapist is planned. Final outcomes are then collected and delivered to the research assistant. At this point (at 12 weeks), the degree of clinical response to the treatment will be assessed. ‘No response’ is defined as less than 50% increase in the average voided volume (AVV) compared to baseline, registered in the bladder diary. ‘Partial response’ is predefined as 50–99% increase in the AVV and ‘Complete response’ as a 100% increase in AVV. (9)

To evaluate the duration of clinical response, a third period of 6 weeks without any treatment (the observation period) is inserted. During this ‘wash-out’ period, the same set of bladder diaries must be completed.

The study is closed at the end of the last follow-up visit at 18 weeks at the treating PS. The PS will be briefed beforehand to which treatment arm the participant was allocated. The same assessment as during baseline will be repeated and the parent and participant will be unblinded during this follow-up visit.

For post-trial care, see item 30.

Criteria for discontinuing or modifying allocated interventions {11b}

In case a dermal allergic reaction from the self-adhesive electrodes as an expected adverse event would occur, hypoallergenic electrodes will be provided to the participant, free of charge. On the participant' request the therapy can be discontinued at any time in the course of the study. No reason for this request should be given. In case symptoms would improve or worsen during therapy, no modifications to the stimulation protocol are allowed.

Strategies to improve adherence to interventions {11c}

At the first study visit, extensive counselling of the importance of therapy compliance is given to the parents. Adherence to therapy will be stimulated by the required completion of bladder diaries and the active encouragement of the participant and parent by the physiotherapist during the 6-weekly follow-up visits. During the follow-up visits, the potential progression of symptoms will be actively evaluated by going through the completed diaries, together with the participant.

To check the adherence to the treatment protocol by the participant, registration of the performance and duration of daily TENS-application in a diary will be requested.

Relevant concomitant care permitted or prohibited during the trial {11d}

During the trial, the following bladder medication may not be taken: Anticholinergic drugs and a β3 receptor agonist (i.e. mirabegron). Medication to stimulate bowel movement and treat constipation (such as laxative) are permitted. Another form of neuromodulation like sacral TENS is prohibited.

Provisions for post-trial care {30}

The study is closed at 18 weeks. Participants who had received partial or complete clinical success at 12 weeks (independently from the allocated group) can either choose to stop any further treatment or receive further therapy along the standard of care (i.e. bed-wetting alarm if enuresis is still present, pharmacotherapy or percutaneous tibial nerve stimulation (PTNS)).

If participants belonged to the sham group and did not perceived clinical success, voluntary enrolment in part II of the TaPaS trial is possible, wherein TTNS will be compared to PTNS therapy. No financial support for post-trial care will be provided.

Outcomes {12}

All outcomes will be assessed after 12 weeks of treatment and will be compared to baseline measures.

Primary outcomes:

The average voided volume (AVV)

The percentage change in average voided volume per void compared to baseline, registered on the daytime bladder diary.

We consider AVV as the most relevant variable to measure efficacy since it directly reflects the functional bladder capacity. Increasing the functional bladder capacity is the key of OAB and/or nocturnal enuresis (in the absence of nocturnal polyuria) treatment. An increased bladder capacity should ultimately lead to a decrease in micturition frequency and in urinary incontinence episodes.

Secondary outcomes:

The mean volume of supervoids

The percentage change in the mean volume of three 'supervoids' between week 12 and week 1, registered on the bladder diary. See section 'Interventions' for the definition of supervoids. Same as for the primary outcome, this outcome reflects the change in bladder capacity.

Number of urgency incontinence episodes during daytime and night-time

The percentage change of urinary incontinence episodes compared to baseline registered on a daytime bladder diary (the average of 3 days) and night-time bladder diary (the average of 7 nights).

For parents and participant this is the most relevant clinical outcome since it affects daily activities mostly.

Mean voiding frequency during daytime

The percentage change in diurnal voiding frequency registered on the daytime bladder diary.

Parents reported satisfaction of urinary symptoms: Parents are asked to rate the following question: 'How would you feel as a parent or guardian if your child's bladder symptoms were to remain as they are on this moment?" A score on a Likert-scale from 1 (extremely dissatisfied) to 7 (extremely satisfied) at baseline and after 12 weeks of treatment must be given.

The parent or guardian is the most trustworthy source to obtain a subjective assessment. Therefore a parent reported instead of patient reported outcome is obtained.

Duration of effect

The duration of persistent partial or complete response during the observation period, expressed in weeks. Same as during the treatment period, one diurnal bladder diary must be completed weekly. It tells us more about the maintenance of clinical effect that is either received by active stimulation plus urotherapy or by urotherapy alone and a potential placebo effect.

Participant timeline {13}

For an overview see Table 1.

Sample size {14}

The trial has a parallel superiority design. Based on the previous study by Patidar et al.(7), a mean difference of 20% in the primary outcome (i.e. percentage difference in MVV between baseline and after 12 weeks) between TTNS and sham can be expected, with an estimated standard deviation of 20. A sample size of 24 participants (12 in each treatment arm) is then required to achieve a power of 80% for two-sided testing at a 5% significance level.

Recruitment {15}

To reach an adequate sample size, recruitment of participants is performed by different paediatric specialists from both the Urology and paediatric Nephrology Department during the consultations. We chose to include patients who haven't been treated yet with non-conservative therapies, among others to increase the number of potential participants. Additionally, treatment-naïve patients are easier to convince to participate in a sham-controlled trial than patients who have been unsuccessfully treated and want the guarantee of an effective treatment.

Assignment Of Interventions: Allocation

Sequence generation {16a}

The randomization sequence list was computer-generated by the research assistant using the online platform 'Sealed envelope' (Available at: sealedenveloppe.com). Randomization is generated with a parallel 1:1 allocation of two treatment groups A and B, using random block sizes of 4. No stratification of participant characteristics was implemented.

Independently from the randomization sequence list, the physiotherapist defined randomly group A and B (TTNS or sham).

Subsequently, the randomization sequence list was exempted for use to the physiotherapist.

Concealment mechanism {16b}

The allocation sequence is not concealed for the physiotherapist, who assigns and implements the interventions. From the moment a participant is sent for a first visit to the physiotherapist, she allocates a

number to the participant in order of appearance. The sequentially numbered participants will receive the treatment as indicated in the order of the randomization sequence list.

The research assistant however, who analyzes all the data is neither aware of the participant number, nor of the identification of group A and B.

Implementation {16c}

Participants will be enrolled by the PS or the research assistant. Afterwards, the allocation sequence is generated by coincidence. The participant schedules an appointment with the physiotherapist according to his or hers own preference in time and the availability of the physiotherapist. This sequence will determine the sequentially numbered list who is developed by the physiotherapist. Assignment of participants to interventions is also performed by the latter.

Assignment Of Interventions: Blinding

Who will be blinded {17a}

The treatment is blinded for the patient, the parent, the treating PS and the research assistant. The physiotherapist is the only unblinded party.

Procedure for unblinding if needed {17b}

In case the participant and parent want to discontinue with the trial, the allocated intervention will be revealed. In no other circumstances unblinding is allowed. The treating PS will be unblinded before the last follow-up visit at 18 weeks. The research assistant will be unblinded after all data have been entered into the database.

Data Collection And Management

Plans for assessment and collection of outcomes {18a}

Bladder diaries and the parents reported satisfaction of urinary symptoms questionnaire are distributed at the beginning of treatment on paper. The demographic data from each participant will be derived from the electronic medical record (EMR). All outcome data will be collected at the end of the 12 weeks treatment period and converted by the research assistant into a digital file. A standard frequency-volume chart with additional information of urinary incontinence episodes and urgency episodes will be used as bladder diary. (9) The parents' reported satisfaction of urinary symptoms score is a non-validated 7 points Likert scale.

Plans to promote participant retention and complete follow-up {18b}

The short duration of the clinical trial (i.e. 18 weeks) should be the most important incentive to complete the whole trajectory. By inserting a follow-up visit in the middle of the study period, participants are promoted to continue the treatment protocol. Participants who discontinue treatment are no longer candidates to be included in part II of the TaPaS trial.

Data management {19}

Data is entered manually in on online firewall protected data registry on the password-encrypted server of the Ghent University. Subsequently, data will be stored in a central IBM SPSS database which is also protected by the institutional firewall. Only the Principal investigator (PI) and trial coordinator have access to both data registries.

Confidentiality {27}

The participants' data are pseudo-anonymized by assigning an unique code to every participant at the moment of inclusion to ensure confidentiality. Data will be stored during and after the trial in an online protected data registry and IBM SPPS database, both only accessible by the trial coordinator (i.e. the research assistant) and the PI. (Cf. 27).

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

No laboratory examinations are performed, nor biological specimens are to be collected.

Statistical Methods

Statistical methods for primary and secondary outcomes {20a}

Statistical analyses will be performed using SPSS version 25.0. Descriptive statistics of demographic characteristics will be presented by median and interquartile ranges (IQR) for continuous variables and frequencies and percentages for categorical variables. An intention-to-treat analysis will be performed.

Intra-arm analyses (between baseline and final outcomes) will be assessed by the Wilcoxon Signed Rank-test. Since the small sample size, a non-parametric test will be chosen.

Inter-arm analyses (Sham versus TTNS therapy outcomes) will be assessed using the Mann-Whitney U-test.

Interim analyses {21b}

No interim-analysis will be carried out.

Methods for additional analyses (e.g. subgroup analyses) {20b}

No subgroup analyses will be carried out.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

The non-adherence to the treatment protocol by the participant can be detected by controlling the diaries that report the daily duration of application of TENS-therapy. We are counting therefore on the participant's reliability and honesty. In case non-adherence is noticed, besides the a priori intention-to-treat analysis, an additional per-protocol analysis will be carried out.

A missing value analysis will be performed. If data are missing (completely) at random, a multiple imputation model will be used, followed by a sensitivity analysis.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

Participant data may be available upon request (lynn.ghijselings@ugent.be) after completion of the trial.

Oversight And Monitoring

Composition of the coordinating centre and trial steering committee {5d}

The Ghent University Hospital as an ERN eUROGEN accredited centre is the coordinating centre. The trial steering committee is composed as follows:

- The PI: Prof. Dr. Anne-Françoise Spinoit.

- The trial coordinator: Dr. Lynn Ghijselings – i.e. the research assistant.

- The physiotherapist: Ms. Catherine Renson.

- Co-investigators: Dr. Lynn Ghijselings, Ms. Catherine Renson.

- Institutional data analysts.

- Data management team: HIRUZ (Ghent University Hospital's 'Health, Innovation and Research' department) Data Management Unit (DMU).

Composition of the data monitoring committee, its role and reporting structure {21a}

The trial is monitored by the HIRUZ Clinical Trial Unit. They perform on-site and remote monitoring according to the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use – Good Clinical Practice (ICH-GCP) guidelines. The Clinical Trial Unit is part of the institution (i.e. Ghent University Hospital) and has no competing interests. More details can be found on the webpage: http://hiruz.be/service/ctu/.

Adverse event reporting and harms {22}

During each follow-up visit, the physiotherapist will query the participant for adverse events. In case adverse events occur during ambulant therapy, participants are asked to contact the physiotherapist. This information will be briefed to the PI, who will include all the details (time of occurrence, severity and attribution of the event – related or non-related to the therapy) in the case report form (CRF).

Adverse events will be treated along the standard of care.

Frequency and plans for auditing trial conduct {23}

There are no trial audits planned.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

In case important changes will be needed to be undertaken, an amendment on the original protocol will be communicated to the Institutional Review Board (IRB) and the co-investigators.

Dissemination Plans {31a}

In case the superiority of TTNS over sham therapy is proven, phase II of the TaPaS trial will be launched. Since showing the non-inferiority of TTNS compared to PTNS is the ultimate objective of the TaPaS trial, only results of part II will be communicated to a broader public. Trial results of part I will be submitted in the form of an original article for peer review in a not yet determined journal.

Discussion

We don't expect there to be major practical or operational difficulties in the implementation of the trial. The biggest issue lies within the limited control on the adherence to treatment. Since the treatment is mainly home-based, there is little control on how strictly participants will have applied the TENS device daily. The requirement to complete regular bladder diaries and register the applied home–therapy does not guarantee full trial compliance and so compliance bias cannot be avoided.

Trial Status

The treatment protocol version 2 was approved by the Ethical Board of the Ghent University Hospital on the 6th of November, 2018 (B670201837682). Recruitment has started in in November 2018 and is still pending. Study completion of part I will be expected by August 2021.

Abbreviations

AT	Ambulant therapy
CRF	Case Report Form
LUTS	Lower Urinary tract Symptoms
OAB	Overactive bladder syndrome
PI	Principal Investigator
PTNS	Percutaneous tibial nerve stimulation
PP	Paediatric physiotherapist
PS	Paediatric specialist
PVR	Post-void residual volume
TENS	Transcutaneous electrical nerve stimulation
TTNS	Transcutaneous tibial nerve stimulation
US	Ultrasound

Declarations

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Authors' contributions {31b}

AFS as the Principal Investigator conceived the idea of the study. The authors LG, CR, JVW and AFS contributed to the study design and the development of the protocol. The proposal for the Ethical Board Committee was led by LG. All authors contributed to the implementation of the protocol. LG and AFS wrote the manuscript. AFS and KE supervised the trial. All authors read and approved the final manuscript.

Funding {4}

The purchase of the TENS-devices was financially supported by the grant of the 'OptiLUTS' Chair, by Medtronic (Grant number: A1357636). However, the funder has no role in the design of the study, in the collection, analyses or interpretation of the data, nor in the writing of the manuscript or in the decision to publish the results.

Availability of data and materials {29}

The final dataset will be accessible for the physiotherapist and the data-analyst. Data and materials will be available on request. See title page for contact details.

Ethics approval and consent to participate {24}

The study protocol was approved by the Ethical Review Board of the Ghent University Hospital on the 6th of November, 2018 (Approval number: B670201837682). A written, informed consent to participate is and will be obtained from all participants.

Consent for publication {32}

A written informed consent for publication of figure 1 was obtained from the parents of the study patient. A model consent form in Dutch can be provided on request. See title page for contact details.

Competing interests {28}

The TENS-devices from BioMedical Life Systems were purchased with a discount from the company Charco, Ghent (BE). The employment of LG is financed from the OptiLUTS Chair by Medtronic (Grant number: A1357636). CR, JVW and AFS have no conflicts of interest to declare.

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Tables

Due to technical limitations, table 1 is only available as a download in the Supplemental Files section.

Figures

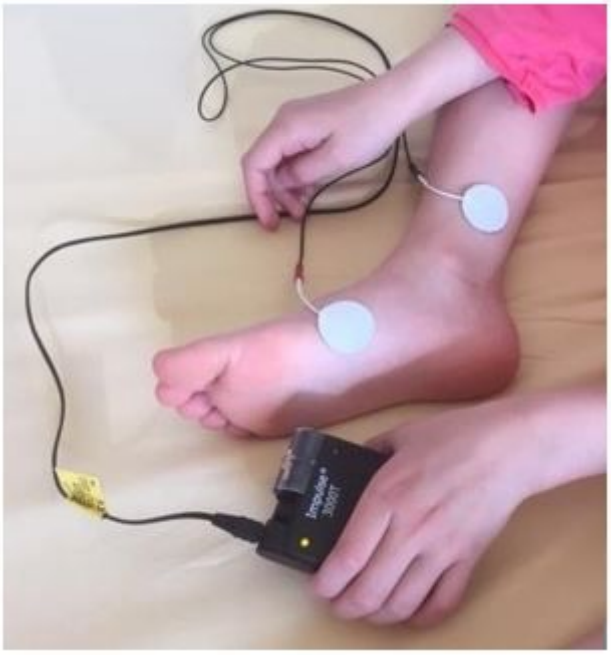

Figure 1

Application of the TENS –device.

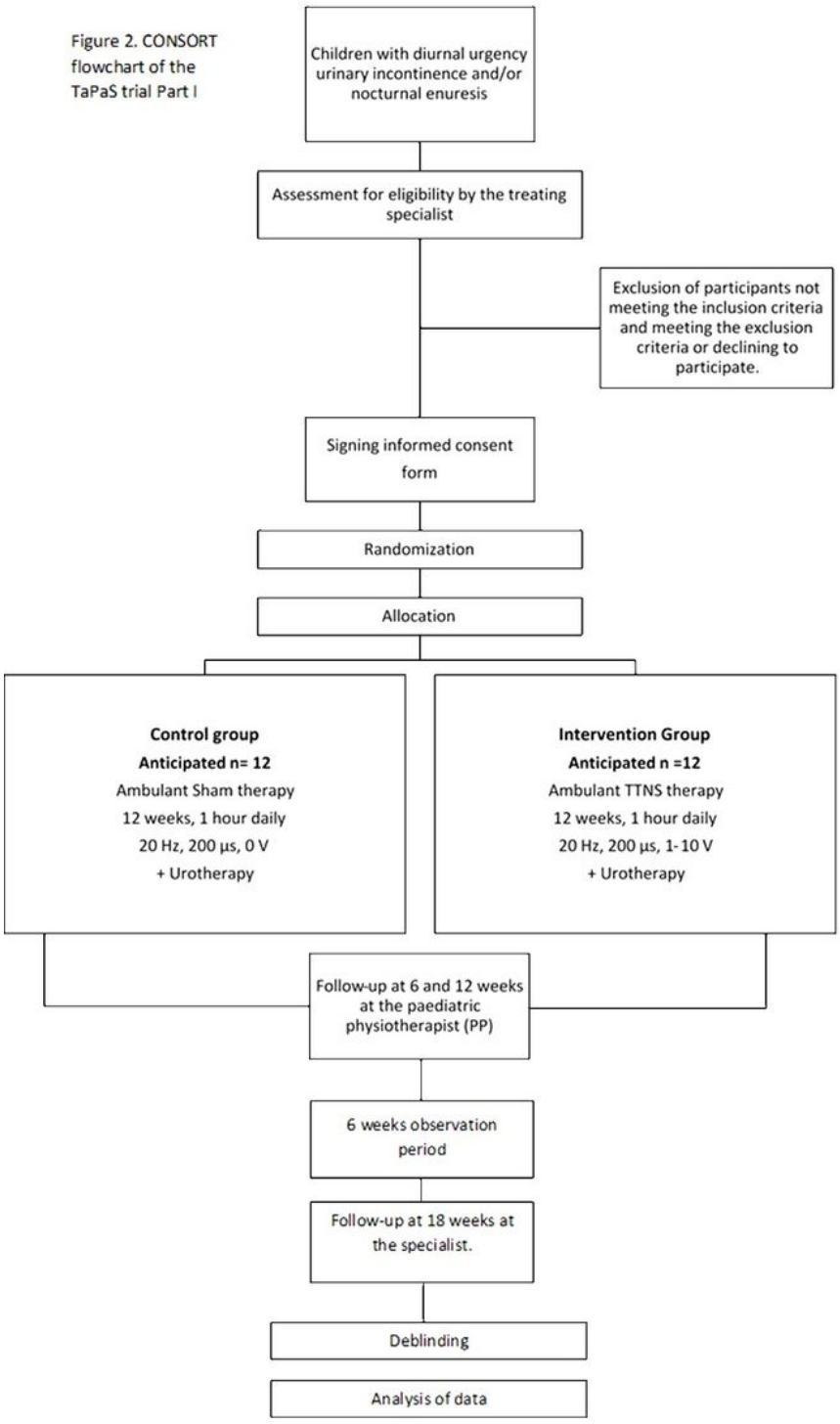

Figure 2

CONSORT flowchart of the TaPa$ trial Part I

Supplementary Files

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- Table1.pdf