Evaluation of the additional effect of continuous ultrasound bladder monitoring in urotherapy for children with functional daytime urinary incontinence. The SENS-U trial

Randomized controlled multi-center trial

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PROTOCOL TITLE : The SENS-U trial

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)
ADHD	Attention deficit disorder
AE	Adverse Event
DUI	Daytime urinary incontinence
DSQOL	Disease specific Quality of life
EQ-5D-Y	Validated questionnaire used for cost-effectiveness analyses
FVC	Frequency voiding chart
GDPR	General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)
IC	Informed Consent
ICCS	International Children's Continence Society
LUTD	Lower urinary tract dysfunction
METC	Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)
PIN-Q	Pediatric Incontinence Questionnaire
PROMS	Patient related outcome measurements
PVR	Post void residual
QOL	Quality of life
RCT	Randomized controlled trial
SPC	Summary of Product Characteristics; in Dutch: officiële productinformatie IB1-tekst
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
UTI	Urinary tract infection

UAVG	Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: Urotherapy is the first treatment of choice for functional daytime urinary incontinence (DUI) in children. Alarm therapy can be a part of urotherapy as it provides the child adequate feedback on wetting accidents. Current alarm systems notify either at a set interval or give a notification when wetting has already occurred to prompt the child to go to the toilet. These alarms do not teach the child the interpretation of the bladder sensation preceding wetting accidents. A new wearable bladder sensor, the SENS-U, recently became available. This is a small, wireless ultrasonic sensor, which continuously monitors bladder filling. The SENS-U is able to provide an alarm at the exact moment voiding is warranted. It facilitates the child to learn the sensation of bladder filling preceding voiding in an easier way, increasing the learning curve throughout treatment.

Objective: To study the (cost-)effectiveness of the SENS-U in urotherapy.

Study design: Multicenter randomized controlled trial with five participating centers.

Study population: Children between 6-16 years with functional DUI referred for urotherapy.

Intervention: Subjects are randomized to urotherapy with or without 3 weeks use of SENS-U/SHAM device for 3 consecutive months. The cost-effectiveness of addition of the SENS-U or SHAM is the intervention to be studied. Urotherapy is care as usual.

Main study parameters/endpoints: Main study outcome is number of wetting accidents per week after 3 months of training. Principal comparison is SENS-U compared to SHAM. Other outcomes are; main outcome compared between SHAM and control group, and SENS-U and control group, cost-effectiveness, long term outcome as number of wetting accidents at T6 = months, subjective experiences, adherence, frequency voiding chart (FVC) parameters, post-void residuals (PVR), uroflowmetry curves and quality of life (QOL) measured at the start (T0), at 3 months (T3) and during follow-up at 6 months after start (T6).

Nature and extent of the burden and risks associated with participation, benefit and group relatedness. Urotherapy is care as usual which includes standard procedures like a voiding diary, frequency voiding chart (FVC) and uroflowmetry and residual measurement (PVR) and regular contact moments with the health care provider. This is not an extra burden for subjects. To monitor incontinence-related QOL and adherence, questionnaires are used at T0, T3 and T6. The SENS-U or SHAM are alarm devices without additional risks which might give discomfort or redness of the skin while wearing it. The SENS-U and SHAM device

automatically register whether they are worn or not to measure adherence. The amount of questionnaires is limited and no intimate questions are asked.
All subjects might benefit from treatment with reduction in wetting accidents after treatment. The extent of reduction in wetting accidents or time to achieve response might be beneficial for those wearing an alarm device.

1. INTRODUCTION AND RATIONALE

Lower urinary tract dysfunction (LUTD; functional incontinence) is a common condition with a prevalence of 10-20% in 7 year-old children. [1-3] It is associated with an impaired Qol, lower self-esteem, and social stigmatization. [4, 5] Children rate “wetting their pants in class” repeatedly in the top 5 of most stressful life events [6].

According to the International Children’s Continence Society (ICCS) urotherapy is the first treatment of choice for functional incontinence. Urotherapy uses non-pharmacological, non-surgical methods and focuses on behavioral interventions, largely based on cognitive-behavioral psychotherapy. The main aim of urotherapy is to achieve the normalization of the micturition and bowel pattern and to prevent further functional disturbances by repeated training. If normalization is not possible, the aim should be the reduction of lower urinary tract symptoms (LUTS) and bowel dysfunction.[7]

Studies on the effectiveness of urotherapy report success rates between 40% and 70%, a meta-analytic evaluation of incontinence interventions reported a success rate of urotherapy of approximately 54% within one year of treatment (complete dry in 44% and a maximum of one wet episode a week in 10%). The spontaneous recovery rate in children is 15% per year [1, 8, 9].

Urotherapy combines education, instructions and demystification, behavioral modification, lifestyle advice regarding fluid intake, registration of voiding frequencies, voiding volumes and incontinence episodes, added with support/encouragement to children and their parents [10].

In essence the children learn during therapy, how to void, when to void, and how often they have to void. In this way children learn how to respond adequately to bladder filling and voiding signals which will enable them to change their voiding behavior. Tools like voiding diaries, frequency voiding charts (FVC), uroflowmetry, and alarm treatment are often used. They are intended to gain insight into the frequency of micturition, micturition volumes and wetting accidents. The voiding diary is used as a feedback tool that makes the child aware of his or her voiding behaviour. An alarm system gives feedback on wetting accidents. Current alarm systems notify either at a set interval or give a notification when wetting has already

occurred. These systems do not teach the child the interpretation of the bladder sensation that precedes wetting accidents.

A new wearable bladder sensor recently became available, the SENS-U. This is a small, wireless ultrasonic sensor, which continuously monitors bladder filling and alarms the child when it is time to void. The SENS-U may increase children's awareness of the sensation of a full bladder. It can be personalized by adjusting the percentage of bladder filling at which it sends an alarm, based on the children's own bladder capacity and FVC [11-13]. This teaches children which bladder sensation corresponds to a nearly full bladder and when it is time to void.

In current urotherapy, the bladder sensation that corresponds to a full bladder is explained by the urotherapist. Biofeedback on bladder filling with the SENS-U enables children to directly feel what the urotherapist means, thereby inducing less trial-and-error and reducing the number of failing experiences. This may increase the effectiveness of urotherapy.

Proof-of-concept of the SENS-U, its safety and feasibility have already been established [11-13]. In a pilot study of 15 patients between 6-16 years, children responded positively to the notification, resulting in a median level of response equal to 100%[13]. Clinical data with small number of patients show promising results with a complete response (100% dry) after only 1 week of training in 33-50%. However no large clinical randomized trials exist to evaluate its true additional effect in urotherapy. A meta-analysis (submitted for publication) done by our study group revealed an overall low amount of high quality studies on the effect of alarm interventions in urotherapy. After a thorough search only one RCT was found comparing urotherapy with or without an alarm watch and one RCT comparing alarm pants to a placebo[14, 15].

The aim of this study is to investigate whether the SENS-U improves the cost-effectiveness of urotherapy. We hypothesize a steeper individual learning curve and more cost-effective training period if the SENS-U is added to urotherapy.

2. OBJECTIVES

Primary Objective:

To assess the effectiveness of the SENS-U as part of urotherapy on the number of wetting accidents per week in children between 6 and 16 years with functional daytime urinary incontinence. Most studies follow the ICCS guidelines and categorize wetting accidents in 'complete response', 'partial response' and 'no response'. Such categorization leads to loss of accuracy and variation. Therefore, we choose to utilize the number of wetting accidents per week for this trial. The main time point of interest is directly after 3 months of training/ urotherapy. The number of wetting accidents per week of the SENS-U is compared to that of the SHAM device.

Secondary objective(s):

- Magnitude of the placebo-effect contribution (SHAM versus control group)
- Subjective improvement of LUTS according to child and parents.
- Number of wetting accidents per week during follow-up, 6 months after start of training in all groups.
- Change in frequency voiding chart parameters (average, minimum, maximum voided volumes corrected for bladder capacity for age (EBC) before treatment (T0), after urotherapy (T3) and during follow-up 6 months after start (T6)
- Change in disease specific Quality of Life (DSQOL) compared from baseline (T0) to the outcomes directly after urotherapy at three months (T3) and during follow-up 6 months after start (T6).
- Cost-effectiveness analysis (SENS-U versus control)

Other objectives

Adherence of treatment and adherence to wearing a SENS-U/SHAM device.
Experiences in user friendliness/(dis)comfort of the use of a SENS-U/SHAM device.
Occurrence of urinary tract infections during the 6 months study period of subjects.
Presence of constipation according to the Rome IV criteria during the training period.
Uroflowmetry curves and postvoid residual volumes outcomes.
Subgroup effect of treatment in different age-groups, center, gender, socio-economic background and psychiatric co-morbidity.

3. STUDY DESIGN

A multicentre, randomized controlled trial with three arms.
Eligible patients are randomized in a 1:1:1 fashion to either group 1 (urotherapy = control group) or group 2 (urotherapy + SHAM) or group 3 (urotherapy + SENS-U device). The SENS-U or SHAM will be worn for 3 consecutive weeks during the 3 months of urotherapy treatment. Outcomes parameters are measured at baseline, after the end of 3-weeks training with or without SENS-U/SHAM, after 3 months and at 6 months after start of the training. See also flow chart in paragraph 5. Total study duration is 4 years. Individual study duration for subjects is 6 months.

Participating centers are the Wilhelmina Children's Hospital in Utrecht, the Radboudumc Amalia Children's Hospital in Nijmegen, the Isala Clinic in Zwolle, TOP voor kinderen in Arnhem and Ziekenhuis Gelderse Vallei in Ede. The first two are academic referral centers, the others peripheral centers.
First, second and third line centres are participating in this study with the intention to select not only therapy-resistant children referred to 3rd line centres but also children seeking medical attention for functional daytime urinary incontinence at the start of their condition.

A randomized controlled trial (RCT) including an arm with a SHAM device is believed to be the appropriate study design to have true equipoise regarding the effect of the SENS-U. With the RCT design we can investigate whether the found effects can be truly attributed to the SENS-U. Furthermore, adding the urotherapy only arm allows for comparison of the costs between care-as-usual and the SENS-U.

4. STUDY POPULATION

All children between 6-16 years with functional daytime urinary incontinence – as part of LUTD- seen at the outpatient department of the participating centers, in which urotherapy/bladder training is offered as the treatment of choice, are eligible. These include children of all gender, ethnic and socio-economic backgrounds.

Functional DUI is defined according to the ICCS as daytime urinary incontinence in a child of at least 5 years if age with a minimum of one episode a month and a minimum duration of 3 months without congenital urological anomalies or neurological conditions[10]. LUTD is a broad term that encompasses subsets of dysfunction of the lower urinary tract with different manifestations. The heterogeneity of symptoms (e.g. daytime urinary incontinence, enuresis, urinary tract infections, straining, hesitation) is at times overlapping and at other times unique to the subtypes of LUTD.

4.1 Inclusion criteria

- Age ≥ 6 years and < 16 years
- Presenting with functional daytime urinary incontinence according to previous definition (≥ one episode a month , ≥ 3 months)
- Diagnosed with overactive bladder, dysfunctional voiding or underactive bladder with or without recurrent urinary tract infections according ICCS criteria/classification
- Eligible for urotherapy/bladder training as the treatment of choice by the clinician
- No current urinary tract infection (UTI) at the start of the study

4.2 Exclusion criteria

- History of congenital urogenital anomalies except for successfully treated mild infravesical obstruction (meatal stenosis, mild urethral valves) < 3 months before inclusion
- History of neurological underlying disease as the cause of LUTD
- Botox treatment for LUTD < 3 months before inclusion
- Untreated or treated but persisting functional constipation according to Rome IV criteria at the start of the study < 3 months before inclusion.
- Recurrent culture proven UTI (< 6 weeks before start of the study or not under control by prophylactic antibiotics)
- Previous urotherapy/bladder training within 6 months of start of the study
- Adipositas preventing accurate measurement by the SENS-U as defined as a BMI > 95th percentile according to age/gender.

- Skin problems in the suprapubic area that are incompatible with the SENS-U adhesive
- Developmental and intellectual disabilities or severe behavioural and social problems that are incompatible with protocolled urotherapy treatment based on the history and opinion of the clinician/urotherapist.

4.3 Sample size calculation

The sample size calculation is based on detecting a difference between the intervention (SENS-U) group and the placebo (SHAM) group at the 3 month endpoint on the primary outcome number of wetting accidents per week.

The number of wetting accidents per week is a 'count' variable. Therefore, the sample size calculation is based on a generalized linear model with negative binomial distribution as presented in Cundill & Alexander (2015) and the skewsamp package in R. [16, 17]

We power to detect a difference of 3 wetting accidents between the intervention and placebo group, which is deemed relevant.[18, 19] Power is set at 0.80 with a two-sided alpha of 0.05. The available study data shows that the mean number of wetting accidents in the intervention and placebo group combined is 6.422 at T=3 months. The dispersion of the negative binomial distribution is also estimated based on available study data, with a generalized linear model with negative binomial distribution with the number of wetting accidents at T=3 months as dependent variable and group as independent variable (dispersion = 1.034). This results in a sample size of 81 children per group.

However, this calculation does not take into account that there are multiple measurement moments and is therefore an overestimation of the necessary sample size. Based on Vickers (2003) we performed a correction for multiple measures.[20]
The correlation between the post measures is based on available study data (Spearman r = .491). With Vicker's formula for two post measures this results in a 25% sample size reduction. This is however based on normally distributed data so we use a conservative reduction of 20%. This results in a sample size of 65 children per group.

With currently 10% lost to follow-up we need 73 children per group, 219 children in total. With five centers, this would mean that each center includes approximately 44 children. In case of failure to meet the required number of participants according to the power calculation by one of the centers, the other participating centers will try to compensate with inclusion of extra patients.

5. TREATMENT OF SUBJECTS

All eligible subjects as described in paragraph 4 are asked for participation after informed consent the subject is randomized in three arms:

- Urotherapy/bladder training (control group)
- Urotherapy/bladder training + SHAM
- Urotherapy/bladder training + SENS-U

After inclusion all subjects receive an appointment at the outpatient department with the urotherapist for intake at the start of the study. Those randomized to the SENS-U, SHAM will receive the device in one of the first appointments. A health care provider will instruct the subjects and parents how to wear and use the alarm device. The SENS-U or SHAM is used for 21 consecutive days in a total of 3 months training period.

Urotherapy/bladder training itself is care as usual and partly standardized in each center (education, demystification, instructions). However the guidance by the urotherapist differs in mode (live contact, telephone) and interval (weekly, biweekly, monthly) between centers according to local protocol used in each center.

At the start of urotherapy (T0), after 3 months (T3) and during follow-up 6 months (T6) after start of training several data are collected and subjects are asked to fill out two questionnaires; Disease specific Qol questionnaire (Pediatric Incontinence Quality of Life (PINQ) and general Qol questionnaires (EQ-5D-5L).
Another contact moment is planned 6 months after start of the training to re-evaluate the status and collect previous mentioned questionnaires. If continence is not achieved (or not sufficiently) after the initial 3 months training period, alternative treatments are discussed as

part of standard care by the professional. This is the end of the study period for participating subjects.

See also flow diagram.

5.1 Definition of Urotherapy/bladder training

The urotherapy/bladder training given in this study is care as usual. However, as urotherapy/bladder training encompasses multiple aspects the next paragraph is added for clarification purposes.

Urotherapy/bladder training is defined according to the ICCS as an umbrella term for all non-surgical, non-pharmacological interventions for LUTD in children and adolescents focusing on behavioral interventions tailored towards specific diagnosis of the condition of functional incontinence. The aim of urotherapy is to achieve the normalization of the micturition and bowel pattern and to prevent further functional disturbances by repeated training.

Standard urotherapy encompasses the following five components;

1) Information and demystification; explanation about normal lower urinary tract function and, how the particular child deviates from normal.
2) Instruction in how to resolve LUTD ; i.e. behavioral modification with regular voiding habits, proper voiding posture, avoidance of holding maneuvers, regular bowel habits, etc.
3) Life-style advice; this encompasses balanced fluid intake and diet, regular bladder and bowel emptying patterns, etc.
4) Registration of symptoms and voiding habits, using bladder diaries or frequency-volume charts and mobile apps.
5) Support and encouragement via regular follow-up with the caregiver.

When the results of standard urotherapy are unsatisfactory, specific urotherapy is recommended added. Specific urotherapy is often multidisciplinary and it comprises specific interventions such as biofeedback by the use of a uroflow meter and/or physiotherapy, timed voiding/alarm treatment, cognitive bladder training program, and neuromodulation. The indications for elements of specific urotherapy are multifaceted depending on the

specific type of LUT dysfunction. [7] Medication for constipation or to suppress bladder overactivity and treatment for behavioral problems (e.g. ADHD) are added if indicated [1].

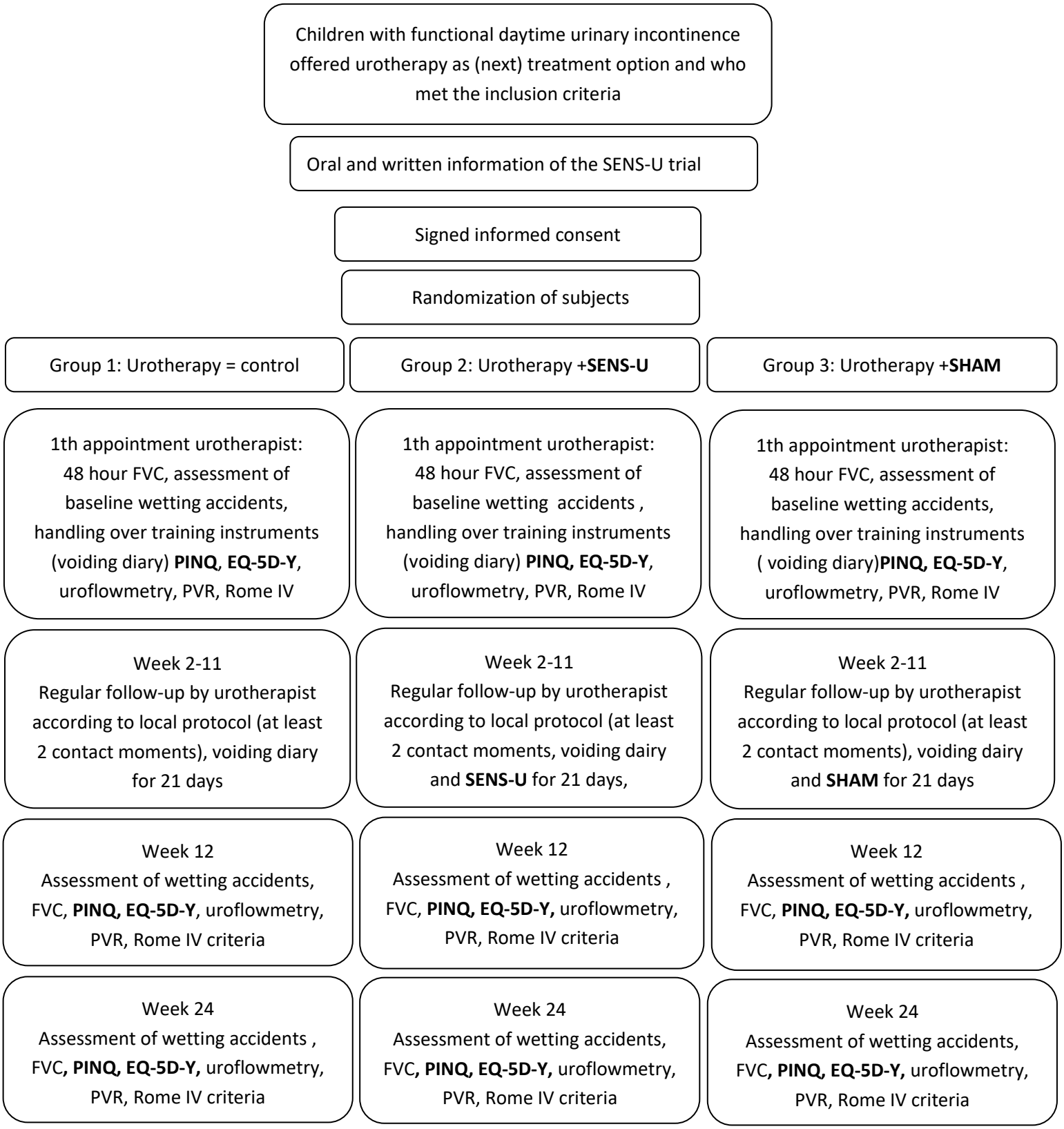
5.2 Technical support

The producer of the SENS-U, Novioscan BV. have expressed their official commitment to provide an in kind contribution of 36 SENS-U devices, concomitant adhesives, sonogel and maintenance for the study period to the participating centers. In case of technical failures devices will be replaced within 48 hours. Besides the in kind contribution, Novioscan BV. has no involvement in the initiation, progress and termination of the project or data analyzes afterwards.

Before the start of the study all involved health care professionals are instructed about the use of the SENS-U/ SHAM. The project leader will coordinate instructions and training on the research protocol for the SENS-U study. All devices -SENS-U and SHAM- used in this study are labeled and exclusively used for study purposes.

5.3 Flow chart

Flow chart showing recruitment of subjects, study arms and study procedures.
Study procedures (not care as usual) are presented bold .



6.0 INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)

The SENS-U is a CE notified medical device for monitoring the bladder of children with urinary incontinence and will be used accordingly in this study.

The SENS-U is a small (95 x 55 x 16 mm), wearable, battery-operated sensor which is positioned on the lower abdomen using a double-sided adhesive (combined with standard ultrasound gel). The sensor is based on a combination of four ultrasonic transducers, arranged with a field of view of 30°. The SENS-U transmits ultrasonic waves towards the bladder region and an internal algorithm automatically processes the received ultrasonic reflections of the bladder walls to estimate the bladder filling status. Based on the child's maximum voided volume and FVC, a personalized threshold is set by the medical professional using the SENS-U mobile application. As soon as the personalized threshold is reached (at 80% bladder filling), the SENS-U will provide a vibration alarm on the child's abdomen, allowing to the child to go to the toilet in time. For detailed description of the SENS-U/SHAM device, see attachment also the User Manual in the attachment.

6.2 Summary of findings from non-clinical studies

The proof-of-concept and feasibility of the SENS-U have been investigated **[11, 12]**. One article from 1998 investigated the proof-of concept of a similar device for bedwetting **[23]**. Bladder filling detection of this device was fairly accurate in a laboratory setting, but its use in real life situations was not investigated. We did not find any further publications of non-clinical studies about comparable devices. Clinical evaluation of the SENS-U in a large population of children has not been done yet.

6.3 Summary of findings from clinical studies of wearable alarm devices in general

Several studies suggest other forms of wearable alarm systems for functional DUI to be a sensible addition to urotherapy. Two randomized controlled trial (RCT) compared urotherapy with or without addition of alarm interventions**[14, 15]**. In the study by Hagstroem et al. urotherapy with (n=30) and without a timer watch (n=28) was compared.

Outcome was partial and complete response according to the ICCS criteria. Directly after the end of treatment, there was 60% response (30% complete, 30% partial) in the intervention group, and 18% response (all partial) in the control group. The OR was 6.9. Follow-up was not randomized and given only for the intervention group. At a median 9.5 weeks after the end of the intervention, there was 59% complete response (of which 38% timer-free) and 11% partial response. At a median 7 months after the intervention there was 67% complete response (of which 55% device free).

The other RCT by Halliday et al. studied the difference between a contingent (n=22) and non-contingent pants alarm (n=22). Outcome was continence, based on the number of wet episodes per week. Directly after treatment, 73% was dry in the intervention group compared to 59% in the placebo group. The OR was 1.85.

A systematic review and meta-analysis was performed by our study group (submitted for publication). A fixed model of both RCT's revealed a summary OR of 3.9 (95%: 1.4-11.3) for achieving continence in favor of the alarm therapy. The alarm condition performed better than the control condition on both complete continence (100% dry) or improvement (>50% decrease in incontinent episodes) as treatment outcome[21].

Several other observational studies report the outcomes of urotherapy with alarm tools added [24-26]. Boelens et al. gave a pants alarm to 4 children, of which 1 became dry (25%) directly after treatment [25]. Hagstroem et al. (2008) retrospectively investigated the outcome of 60 children receiving urotherapy with a timer watch. Directly after treatment, 70% had a complete response according to ICCS criteria [24]). Van Laecke et al. also retrospectively investigated outcomes of 15 children receiving urotherapy with a pants alarm. Directly after treatment, there was 47% complete response according to ICCS criteria. Six weeks after the end of training there was still 40% complete response [26]. Other studies have reported outcomes of clinical training programs were alarm devices were part of broader treatment protocol. They report similar outcomes with continence rates 43-68% in therapy refractory children [22, 27, 28].
A random meta analytic model of both RCT's and non-RCT's revealed an complete response rate (100% continence after treatment with an alarm) of 53% CI 42%-64%.

6.4 Summary of known and potential risks and benefits

The SENS-U is a CE notified medical device for monitoring the bladder of children with urinary incontinence and will be used accordingly in this study. The SHAM device is identical to the SENS-U with the exception that the software is adapted to facilitate this study. There are no additional risks.

7. METHODS

7.1 Primary objective

7.1.1 Main study parameter of primary objective

Main study outcome is number of wetting accidents per week after 3 months of training, with a comparison between the SENS-U and the SHAM-device.

7.1.2. Secondary objectives, study parameters of secondary objectives

- Number of per-post wetting accidents classified according to ICCS standards as **[10]**:
  - 1) complete response, 100% reduction of complaints
  - 2) partial response, 50-99% reduction
  - 3) no response, less than 50% reduction.
- Magnitude of the placebo-effect contribution (SHAM versus control)
- Subjective improvement of LUTS according to child and parents
- Number of wetting accidents per week during follow-up 6 months after baseline (T6)
- Change in FVC parameters (average, minimum, maximum voided volumes corrected for bladder capacity for age (EBC) between T0, T3,T6
- Change in DSQOL of life outcomes between T0, T3,T6
- Change in general QOl outcomes between T0,T3,T6.
- Cost-effectiveness of urotherapy (SENS-U versus control)

7.1.3. Other study objectives, study parameters of other objectives

- Adherence of treatment and adherence of wearing the SENS-U/SHAM
- Experiences of user friendliness/(dis)comfort of the SENS-U/SHAM device
- Occurrence of urinary tract infections during the 6 months study period of subjects
- Presence of constipation according to Rome IV criteria during the study period of subjects
- Uroflowmetry curves and PVR outcomes.
- Subgroup effect of treatment in different age-groups, center, gender, socio-economic background and psychiatric co-morbidity.

Adherence of treatment (urotherapy/bladder training) is measured as a proportion and given by; (number of failed contact moments/number of expected contact moments in 3

months training). The SHAM and SENS-U measure the number of days actually worn. Adherence of wearing the SENS-U/SHAM is measured as a proportion (number of days not worn/total number of days used in training).

7.2 Randomisation, blinding and treatment allocation

Permuted block randomization with block size 6 stratified for age groups (6-7 years, 8-10 years, 11-15 years) will be done within each participating center by a computer. The program used is CASTOR edc. Because some heterogeneity of bladder training/urotherapy within the participating centers exists (in mode and interval of guidance by the urotherapist), the randomization will be performed within each center to correct for small differences between centers. Subjects are blinded for SENS-U versus placebo (SHAM device) condition.

7.3 Study procedures

All subjects will receive urotherapy/bladder training which starts with previously mentioned explanation and instructions. These instructions are also handed out in paper.

At baseline uroflowmetry and ultrasound to measure post void residual (PVR) is performed at least twice. Several patient related outcome measurements (PROMS) are collected; a 48-hour FVC, questionnaires (Pediatric Incontinence Quality of Life (PINQ), EQ-5D-Y), and Rome IV criteria. Number and severity of wet days per week is assessed as baseline parameter.

After this urotherapy/bladder training is given for 12 consecutive weeks according to ICCS standards[7]. During this practice period, counselling is given at frequent follow-up appointments according to the local protocol in each center. Medication for constipation, to suppress bladder overactivity are added if indicated and prophylactic antibiotics to prevent urinary tract infections are continued if applicable. After three months of training, the urotherapist evaluates the outcome of training and number and severity of urinary incontinence per week is assessed again. Uroflowmetry and ultrasound for PVR, voiding diary/FVC parameters are collected again and outcomes are discussed with the child and its parents. Questionnaires (PINQ, EQ-5D-Y) are filled in and Rome IV criteria are determined.

If continence is not achieved (or not sufficiently) after 3 months alternative treatments are discussed as part of standard care by the professional. This is the end of the study period for participating subjects.
Another contact moment is planned 6 months after start of the treatment to re-evaluate the status, assess the number and severity of urinary incontinence and collection of previous mentioned PROMS.

Procedures part of urotherapy as care as usual are: assessment of urinary incontinence in number and severity, voiding diary, 48-hour frequency voiding chart, Rome IV criteria, uroflowmetry and postvoiding residual urine. In some centres (Radboudumc/UMCU) Qol questionnaires are part of standard care (PINQ), in others (Top voor kinderen, Isala and Gelderse Vallei) not.

Procedures extra as part of study: PINQ (Top voor kinderen, Isala, Gelderse Vallei), EQ-5D-Y, SHAM or SENS-U device, evaluation of user-friendliness of device.

7.3.1 Interventions for subjects randomized to urotherapy + SENS-U

Urotherapy/bladder training is given as mentioned previously and the same for all participating subjects. In addition to the urotherapy given, the SENS-U is added as an additional tool in the training. A health care provider will administer and install the SENS-U and explain parents and child how to apply and use the device. The SENS-U is used to provide biofeedback which teaches the child the feeling that corresponds with 80% bladder filling. The SENS-U is able to monitor the natural bladder filling during regular activity in children, as required for application in urotherapy. To establish a good learning effect but preventing any dependency of the child on the SENS-U, it will be worn for a total of 21 days in the overall 3 months of training. Subsequently, a questionnaire is used to assess user-friendliness of the device.

7.3.2 Interventions for subjects randomized to urotherapy + SHAM device

Urotherapy/bladder training is given as mentioned in previous paragraph and the same for all groups. In addition to the urotherapy given, the SHAM device is added. The feeling of a device on the children's belly could increase awareness of their bladder and might induce a placebo effect. Therefore, we included a placebo group, wearing a SHAM device that alerts independent of bladder filling at a set interval. The SHAM device resembles the traditional timer watch which is currently often used in urotherapy. Therefore it is not considered an extra burden for children to wear a SHAM device. The SHAM and accompanying instructions are identical to the SENS-U. The interval between alarms is randomly chosen between 2 to 3 hours to appear realistic. It will be worn for a total of 21 days in the overall 3 months of training. Subsequently, a questionnaire is used to assess user-friendliness of the device.

7.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

7.4.1. Specific criteria for withdrawal

- Skin problems that occur during the use of the SENS-U/SHAM device that are incompatible with continuation of the device. Urotherapy will be continued without the device.
- Severe behavioural and/or social problems that develop throughout the training and are incompatible with protocolled urotherapy.

7.5 Follow-up of subjects withdrawn from treatment/replacement of individual subjects

Subjects discontinuing the study receive regular follow-up and treatment otherwise for their LUTD. Statistical analysis will be according to intention to treat without replacement of individual subjects after withdrawal. In the initial power calculation a 33% drop out is calculated.

7.6 Premature termination of the study

No interim analysis is done as no significant risks or benefits are expected for one of the three different study groups.

8.SAFETY REPORTING

8.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

8.2 AEs, SAEs and SUSARs

8.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the experimental intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

Adverse events due to SENS/SHAM device include:

- Discomfort of the device while wearing it
- Inflammation/redness of the skin due to the SENS-U adhesive
- Feelings of social embarrassment (despite the fact that the SENS-U/SHAM only gives a discrete notification)

8.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;

- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The principal investigator will report all SAEs without undue delay after obtaining knowledge of the events.
The principal investigator will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the principal investigator has first knowledge of the serious adverse events.

8.3 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. SAEs are reported from the moment of signed informed consent till the last moment of follow up at 6 months.
According to the NFU risk classification, no serious additional risks are to be expected due to the SENS-U or SHAM device.

9.0 STATISTICAL ANALYSIS

9.1 Primary study parameter(s)

Main study outcome is number of wetting accidents per week after 3 months of training. A linear mixed model with negative binomial distribution with all study time-points (3 and 6 months) is used. The difference between the SENS-U and the SHAM group will be investigated within this model at the 3 month time-point. A correction for baseline, center,

age, cumulative dose of antimuscarinics (if applicable), and adherence/ drop-out will be performed. A random intercept and slope will be estimated if model fit allows for it.

9.2 Secondary study parameter(s)

A linear mixed model as mentioned for the primary outcome is used to compare outcomes in number of wetting accidents per week between the SENS-U and the control group to study cost-effectiveness and between the control group and the SHAM to study the magnitude of the placebo effect. Long-term effects are investigated by assessing the difference between groups at the 6 month time-point within these models.

Descriptive statistics are used to analyze subjective improvement according to child and parents. Change in FVC parameters (average, minimum, maximum voided volumes corrected for bladder capacity for age (EBC) before treatment (T=0), after treatment (T=3) and during follow-up (T=6)) are compared between the groups with two-way ANOVA. Frequency voiding chart parameters are expressed as numbers (mean ± standard deviation [SD] or median and range).

The data generated by the validated PIN-Q and EQ-5D-5L instruments are transformed and interpreted according to instructions given for each questionnaire [29-31]. A multivariate analysis is done to detect any difference in outcome between the three groups.

9.2.1 Cost-effectiveness analysis

The economic evaluation is embedded in the design of the clinical study and will be undertaken as a cost-effectiveness analysis (CEA) with the costs per wetting incident avoided (over a 3 months period) as outcome measure. Based on available (weak) evidence it is supposed that the addition of the SENS-U device results in a dominant strategy. If so no incremental cost-effectiveness ratio (ICER) can be inferred and cost and effects will be reported separately. Additionally, a cost-utility analysis (CUA) will be performed with the costs per quality adjusted life-year (QALY) as outcome. The CEA closely relates to the results concerning the primary clinical outcome measure, the CUA is performed to enable priority

setting during health care policy making across patient groups, interventions and health care settings. For the CUA also applies, if dominance occurs, no ICER can be inferred. Both analyses will be performed from a health care perspective (as base-case) and the time horizon is set at 6 months (to make inferences based on sustainability of effect). With this time horizon discounting of costs and effects is unnecessary. The choice for the health care perspective as base-case is motivated by the young target population that is not active in the labour process. However we acknowledge that parents might suffer productivity losses as well as time and travel expenses. We will infer these from clinic visits (with parents) and if relevant we report a societal perspective scenario.

In case of confounding (baseline differences, etc.) the net monetary benefit approach (NMB) will be applied incorporating the confounders in the regression model with NMB as dependent variable, or if dominance occurs the cost and effect outcome. Depending on the efficiency outcome results will be displayed graphically by means of cost-effectiveness planes and acceptability curves. The Dutch guideline for economic evaluations will be adhered to (ZIN, 2016).

2.2 COST ANALYSIS

Direct and indirect medical and (for the societal scenario) non-medical costs will be included. The direct and indirect medical costs include all costs of inpatient and outpatient hospital visits, diagnostic and therapeutic procedures, and consultations, to be collected digitally from hospital information systems and with clinical report forms. The costs of out-of-hospital care by general practitioner as well as the direct non-medical out-of-pocket expenses (over-the-counter medication) will be based on volume data gathered with repeated patient/parent questionnaires at baseline, and 3 and 6 months post randomisation (an adapted version of the iMCQ, ZIN 2016).

Unit costing will preferably be based on the existing national guideline for costing in health care research (ZIN, 2016). Otherwise, the unit costs especially those for hospital admissions will be assessed using hospital based absorption costing. Unit costs derived from different calendar years will be indexed to 2021 prices.

Cost is usually a parameter with a skewed distribution. If this occurs as well as possible heteroscedasticity cost analysis will be performed using a generalized linear model with a log ink function relating the conditional mean to independent variables using a gamma distribution specifying the relationship between the variance and the mean.

9.3 Other study parameters

Adherence to treatment and to the SENS-U/SHAM device is expressed as a proportion (number of non-adherent days/adherent days).
User friendliness and (dis)comfort of the SENS-U/SHAM are descriptive parameters as uroflowmetry curves with postvoid residual measurements, occurrence of urinary tract infections and Rome IV criteria and analyzed accordingly. These parameters are expressed as numbers (mean ± standard deviation[SD] or median and range).

Other demographics (gender, ethnicity, age socio-economic status measured by highest achieved educational level of the parents/care giver, co-morbidity like ADHD or associated conditions) are expressed as numbers and proportions (mean ± standard deviation[SD] or median and range). Chi-Squared or Fisher 'exact test is used to compare binary of nominal data, two-way ANOVA for normally distributed continuous data and a Mann-Whitney U test for non-normally distributed data.

The data are analysed using SPSS Statistics 25.0. Differences were considered statistically significant at $p<0.05$.

9.4 Handling of missing data

The linear mixed model will impute for data missing completely at random.

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

The study is conducted according to the principles of the Declaration of Helsinki (2013), see also www.wma.net and in accordance with the Medical Research involving human subjects act (WMO) and other guidelines, regulations and acts (AGV/WGBO).Also the study will be conducted according to the codes of conduct for minors (available on the CCMO site and accepted by the Board of the Dutch Society for Pediatric on May 21, 2001).

10.2 Recruitment and consent

Patients and their parents are asked to participate during the regular appointment at the outpatient clinic where information is given orally and in writing by the treating physician or nurse practitioner/urotherapist, including informed consent. Referring general practitioners, pediatricians, urotherapists - among other health care providers involved in treatment of LUTD in children - will be informed about the trial in journals, conferences and using online media including a study web site. Children and/or parents who are not yet under active treatment but still interested in the trial can contact the research team by email. One of the research members will contact the child/parent(s) and invite them to the outpatient department in one of the nearby participating centres.

Patients are asked for permission to be contacted within 14 days by telephone by a member of the research team. When given permission, being contacted and if agreed upon participation, patients receive an appointment at the outpatient clinic for an intake and start of bladder training/urotherapy after prove of signed informed consent (life or photocopy send digitally). Subjects and parents can sign the informed consent at home and bring it along at this first appointment or they can sign it at the appointment itself. A copy of the signed informed consent is given to the subjects.

10.3 Objection by minors or incapacitated subjects

The study will be conducted according to the codes of conduct for minors (available on the CCMO site and accepted by the Board of the Netherlands Association for Pediatric Medicine (NVK) on May 21, 2001.

https://www.ccmo.nl/onderzoekers/publicaties/publicaties/2001/06/01/gedragscode-verzet-bij-minderjarigen

10.4 Benefits and risks assessment, group relatedness

There are no known risks or adverse effects to ultrasound imaging, when the intensity is limited to the current Food and Drug Administration (FDA) regulations as is the case in this CE notified device. There are no additional serious risks expected for participants.
Potential burden for the individual subject is mainly time consummation (regular hospital visits/telephone contact with the health care provider) which is not different between the groups and part of standard care in urotherapy/bladder training. In addition discomfort or social embarrassment might be experienced by the subjects wearing the SENS-U of SHAM device (despite the fact that only a discrete notification is given).
Potential benefit for the individual subject is improvement of their complaints.
Whilst it remains unclear if addition of the SENS-U to bladder training/urotherapy remains (cost)-effective , in future other subjects might benefit from the outcomes of this study.

10.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents

Data from the study participants will be handled confidentially according ICH-GCP regulations. Confidentiality will be maintained at all times. The original signed informed consent forms will be kept in a binder in a locked closet in a locked room of all participating centers.

All study protocols, CASTOR data, statistical analyses and reports are stored in a secured Digital Research Environment (AnDREa) created and access is password protected and assigned to research members only.

After written consent, per center each subject will receive a unique identifier, after which members of the research team will extract all necessary clinical parameters from the electronic health records into an electronic Case Report Form (eCRF) of Castor EDC. Castor EDC is a browser-based, metadata-driven EDC software solution and workflow methodology for building and managing online databases. The eCRF contains data items as specified in this research protocol. Modification of the eCRF will be made only if deemed necessary and in accordance with an amendment to the research protocol. Access to the eCRF is password protected and specific roles are assigned (e.g. study coordinator, investigator, monitor, etc.).

The CASTOR database will be supplemented with the outcome of a validated questionnaires automatically sent via an email URL-link via Castor at set times.

When required, authorized personnel of the main study center (Radboudumc) can access this source data for intermediate analysis or regular back-ups. A manual (meta)data export in either Excel or SPSS will then be made to the DRE previously mentioned.

A subject identification code list will be used to link data to subjects by authorized members of the research team. The key to the code is stored in a file at a network drive only accessible to members of the research team of that center. Besides the research team, study monitors/auditors have access to the study data.

At the end of the study, all generated (meta)data will be stored as a proprietary format (.sav/.xlsx format) in DANS EASY. In order to reproduce the study findings and to help future users to understand and reuse the (meta)data, all changes made to the raw data, including analysis steps will be documented in an data management analysis plan. Thus the secure DRE will serve at the end of the study as a data package. The data package will be locally archived on the secured research network DANS EADSY for 15 years after the study has ended. More details, including the state of FAIRness, can be found in the data management plan: https://dmp.radboudumc.nl/plans/69677.

11.2 Monitoring and Quality Assurance

Monitoring will take place conform Good Clinical Practice (GCP 5.18.3). Further details concerning name of the monitor, frequency of monitoring etc. is described in the monitor plan.

11.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion. All substantial amendments will be notified to the METC and to the competent authority.

11.4. Annual progress report

The principal investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/serious adverse reactions, other problems, and amendments.

11.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.
Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

11.6 Public disclosure and publication policy

The results are shared with relevant fora and data will be presented at international conferences and published in peer reviewed medical journals

12. STRUCTURED RISK ANALYSIS

The SENS-U is a CE notified medical device for monitoring the bladder of children with clinical urinary incontinence and will be used accordingly in this study. Safety and feasibility have been proved. [11-13]The SHAM device is identical to the SENS-U with the exception that the software is adapted to facilitate this study. There are no additional risks.

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