RESEARCH PROTOCOL

(November 2019)

'The Experience Sampling Method (ESM):
a real-time Patient-Reported Outcome Measure for symptom assessment in patients with overactive bladder syndrome.'

PROTOCOL TITLE 'The Experience Sampling Method (ESM): a real-time Patient-Reported Outcome Measure for symptom assessment in patients with overactive bladder syndrome.''

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

3IQ	**3 Incontinence Questions**
ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
DSMB	**Data Safety Monitoring Board**
ePRO	**electronic Patient-reported Outcome Measure**
ESM	**Experience Sampling Method**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
HADS	**Hospital Anxiety and Depression Scale**
HRQL	**Health-related Quality of Life**
IB	**Investigator's Brochure**
IBS	**Irritable Bowel Syndrome**
IC	**Informed Consent**
ICC	**Intraclass Correlation Coefficient**
ICI-RS	**International Consultation on Incontinence-Research Society**
ICIQ-FLUTS	**International Consultation on Incontinence Modular Questionnaire for female lower urinary tract symptoms**
ICIQ-MLUTS	**International Consultation on Incontinence Modular Questionnaire for male lower urinary tract symptoms**
ICS	**International Continence Society**
IIEF-5	**International Index of Erectile Function 5**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
IPSS	**International Prostate Symptom Score**
LUTS	**Lower Urinary Tract Symptoms**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
MUMC+	**Maastricht University Medical Centre +**
NRS	**Numeric Rating Scale**
NVOG	**Nederlandse Vereniging Obstetrie & Gynaecologie**
OAB	**Overactive bladder syndrome**
OAB-q	**Overactive Bladder Questionnaire**
PRO(M)	**Patient-Reported Outcome (Measure)**
(S)AE	**(Serious) Adverse Event**
SF-36	**Short Form Health Survey 36 (questionnaires)**
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.
SR-BD	**Sensation-related bladder diary**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
VPSS	**Visual Prostate Symptom Score**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)**

SUMMARY

Rationale: The overactive bladder syndrome is diagnosed clinically by using the ICS criteria of ≥8 micturitions and at least 1 urgency episode per 24 hours. To determine whether patients fit the criteria, micturition diaries ('sensation-related bladder diaries') and other symptom questionnaires with considerable limitations are used. This makes it difficult to get a good impression of the fluctuation of complaints during the day / week. These limitations are overcome using the Experience Sampling Method (ESM). This is an electronic questioning method which is characterized by repeated and random, momentary assessments in the subject's current environment and state. This study follows other successful ESM studies done within the Gastroenterology and Psychiatry Department.[1-4] The aim of this study is to evaluate if the ESM is more accurate in the assessment of urological complaints in OAB compared to the current assessment with the use of the sensations-related bladder diaries (SR-BDs) and retrospective questionnaires. Furthermore the aim is to assess the reliability and validity of this OAB-specific electronic patient-reported outcome measure (ePRO), based on the Experience Sampling Method-principle, for symptom assessment and assessment of triggers for symptoms in OAB.

Objective: To evaluate the accuracy of the ESM to assess urological complaints in OAB compared to SR-BDs and retrospective questionnaires. To assess content validity, reliability and the accuracy to validate the developed ePRO in OAB patients.

Study design: The ESM study is a multi-centre, prospective, cross-sectional study.

Study population: 66 OAB patients will be recruited at the outpatient Pelvic Care Centre at Maastricht UMC+, the outpatient clinic Urology at Zuyderland Heerlen/Sittard and the outpatient clinic Urology at University Hospital Antwerp. 66 healthy volunteers will be recruited as well.

Methods: In a period of 7 days, participants will fill out an electronic ESM assessment at 10 random moments during the day. Moreover, they will fill out a sensation-related bladder diary (SR-BD) during the last three consecutive days of filling out the ESM and several symptom questionnaires at the end of the study period.

Main study endpoints: The main study outcome comprehends the psychometric properties of the PROM for symptom assessment of OAB symptoms. Secondary outcomes are increase in ESM score for OAB symptoms and environmental and psychosocial factors (*e.g.* as measured by the PROM) from one time point (t-1) to the next (t).

Burden, risks and benefits: The burden that is associated with participation in this study comprises completing the PROM questionnaire several times a day, which interrupts daily life due to its random character. Furthermore, the burden is limited to completing a SR-BD and other symptom questionnaires. Most importantly, participating does not bring along

important health related risks. However, awareness could trigger symptoms and therefore be considered as a burden. Nevertheless, for the patients it could be beneficial too to know what triggers complaints, to cope better with their disease.

INTRODUCTION AND RATIONALE

The overactive bladder syndrome (OAB) is defined by the International Continence Society (ICS) as a symptom complex of urgency, usually with frequency and nocturia (awakening at night to void), with (OAB wet) or without (OAB dry) urinary urgency incontinence. Urgency is the complaint of a sudden compelling desire to pass urine, which is difficult to defer[5]. OAB is clinically diagnosed using the ICS criteria of ≥8 micturitions and at least 1 urgency episode per 24 hours.

It is estimated that approximately 16-17% of the adult population of the Western world is affected by OAB [6,7]. The incidence of OAB, both wet and dry increases by age [8-10], and because of the worldwide ageing of the population, the number of adults affected by urinary urgency incontinence (UUI) would increase [11]. The health care costs of OAB are high [12], and work productivity can be significantly impacted as well [13]. In addition, OAB can be associated with comorbidity and increased mortality[14,15]. Furthermore, OAB with and without incontinence has been associated with significantly lower quality of life scores compared to matched controls without voiding complaints[8]. It is of particular interest that OAB does not only affect the patients, but also has an impact on family members [10].

There is a strong association between OAB and psychiatric comorbidities such as depression, anxiety and stress [15-19]. This association is most likely bidirectional.[16,18,19]

The current methods of diagnosis rely on voiding diaries (the sensation-related bladder diary) and retrospective questionnaires.

Retrospective, self-reported outcomes have important limitations. Firstly, there is a high risk for recall bias, in which retrospective information consists of a reconstruction of a few specific moments rather than a reliable reflection of symptoms over a predefined period of time[20-22]. Furthermore, it is well described that memory retrieval is influenced by the individual's environment and mental state at the time of recall, known as ecological bias.[20,21] In conclusion, patient experiences about symptoms in the past can be significantly distorted when retrospectively reported. Furthermore, lack of patient compliance is an important disturbing factor in recalled assessments. Studies that employed paper diaries in a population of patients with chronic somatic pain to measure symptoms resulted in very low patient compliance: only 11% actual compliance, but up to 80% fake compliance was determined, the latter presumably resulting from filling in diaries after the proscribed time window.[23]

The Experience Sampling Method (ESM), also referred to as Ecological Momentary Assessment (EMA), may overcome these limitations. ESM is an electronic questioning method characterized by random, repeated assessments in the subject's current state and environment, for several consecutive days. A digital device sends out an auditory beep at

random moments during the day, to which subjects have to respond by completing several assessments at the device. The assessments are identical between the moments [20,21,24]. Hereby, ESM offers the opportunity to reduce the risk for recall bias and to capture symptom variability over time with taking into account contextual, social and psychological factors, which might have an impact on symptom reporting.

ESM has already been used in different patient populations with different disorders, such as; irritable bowel syndrome (IBS) [1], depression [25,26], Parkinson's Disease [27] and mental illness in a broad sense.[28]

ESM has proven to be a viable and novel approach to assess symptoms, affective states and contextual factors at the level of the individual subject[27]. It provides precise, prospective information that may contribute to clinical practice[26] with several distinct advantages over traditionally used (retrospective) assessment of mental health related phenomena[28]. OAB shows fluctuating symptom patterns in which urological complaints might be influenced by daily life factors as well as psychological and psychiatric comorbidities. To our knowledge, there are no previous studies on the use of ESM in a urological patient population. In order to study the performance of ESM in a population as such there is a need for developing a patient-reported outcome measure suitable for real-time symptom assessment of urological symptoms, using the ESM principle. Patient-reported outcome measures (PROMs) are assessment methods completed by patients, and are meant to capture one or several aspects of a disease course or health status[29]. Focus group research in OAB patients was done for item selection and to evaluate the quality of the PROMs according to the ESM principle. The outcomes of the focus groups have been discussed in an expert meeting and a final questionnaire has been constructed, specifically for the ESM in the urological patient population. Now, this OAB-specific ESM tool should be tested to see if there is a difference between symptom scores on ESM and the currently used retrospective reports and SR-BDs. Furthermore content validity, reliability and the accuracy will be tested to validate the developed ePRO in OAB patients. Additionally, specific triggers for the onset of OAB complaints will be objectified, with use of the OAB specific ESM tool. It will be objectified if there is a direct link between OAB and psychiatric disorders as depression, anxiety and stress too.

Summarizing, electronic, repeated symptom assessments during daily activities should assure ecological validity and eliminate recall bias, lead to higher compliance rates, and capture symptom variability during the day. For these reasons it is expected that the Experience Sampling Method (ESM) may prove to be a more objective tool for evaluation and quantification of urgency and other urological complaints that will overcome the limitations of currently used retrospective symptom assessment methods in OAB.

1. OBJECTIVES

This project will be subdivided into three sections:

Part I. Comparison of the ESM vs. SR-BDs and other retrospective questionnaires in the assessment of urological complaints in OAB such as urgency.
Part II. Validation of new patient-reported outcome measure, based on the Experience Sampling Method, which will be used in the assessment of urological symptoms in patients with overactive bladder syndrome.

Part I – Comparison of assessment methods
Primary aim: To compare the ESM to SR-BDs and other retrospective questionnaires in the assessment of urological complaints in OAB.

Objectives:

1. To compare the ESM to SR-BDs and other retrospective questionnaires in the assessment of urological complaints in OAB.

   Hypothesis*:* The ESM is more accurate in the assessment of urological complaints in OAB compared to the current use of SR-BDs and other retrospective questionnaires (like the OAB-q). We hypothesize to find good correlations between ESM scores (i.e. the newly developed ePRO) and 'concurrent' instruments (i.e. conventional retrospective questionnaires), since we purport to measure the same constructs with both methods. However, ESM measures real-time symptoms whereas our conventional questionnaires measure retrospectively. Therefore, we do not expect to find perfect correlation coefficients, i.e. >0.8. Correlation coefficients between 0.4 and 0.8 are considered appropriate. Correlation coefficients lower than 0.4 reflect very weak or no correlation between the methods, which probably means that we are measuring some other construct with our new ePRO than is measured with the conventional method (current 'gold standard'). On the contrary, correlation coefficients higher than 0.8 reflect very strong correlations, meaning that we are more or less measuring exactly the same construct. In this case, there is no rational for replacing the conventional methods by the new (more intensive) method. For each correlation coefficient its significance will be checked as well.
   Furthermore it is expected that the mean urgency scores from the ESM will be significantly lower when compared to the urgency scores from the SR-BDs and retrospective questionnaires.

Additionally it is expected that in the SR-BDs the daily peak of urgency scores is reported rather than the average level of urgency over the day.

Part II - Validation

Primary aim: To validate and test the reliability of electronic patient-reported outcome (ePRO) for the evaluation of the complex symptoms and their potential triggers in OAB patients in day-to-day life with the use of the Experience Sampling Method.

Objectives:

1. To assess content validity of the developed ePRO.

   Hypothesis: We consider content validity of the ePRO adequate since items were carefully selected based on evidence from qualitative studies. Furthermore, item relevance was judged by a multidisciplinary panel of experts in the fields of urology, gastro-enterology, psychiatry and gynaecology as well as by OAB patients.

2. To assess concurrent validity of the developed ePRO.

   Hypothesis: We hypothesize to find good correlations between ESM scores (*i.e.* the newly developed ePRO) and 'concurrent' instruments (*i.e.* conventional retrospective questionnaires), since we purport to measure the same constructs with both methods. However, ESM measures real-time symptoms whereas our conventional questionnaires measure retrospectively. Therefore, we do not expect to find perfect correlation coefficients, *i.e.* >0.8. Correlation coefficients between 0.4 and 0.8 are considered appropriate. Correlation coefficients lower than 0.4 reflect very weak or no correlation between the methods, which probably means that we are measuring some other construct with our new ePRO than is measured with the conventional method (current 'gold standard'). On the contrary, correlation coefficients higher than 0.8 reflect very strong correlations, meaning that we are more or less measuring exactly the same construct. In this case, there is no rational for replacing the conventional methods by the new (more intensive) method. For each correlation coefficient its significance will be checked as well.

3. To assess internal consistency of the developed ePRO.

   Hypothesis: We hypothesize that internal consistency of the ePRO will be moderate to good, since items were based on theoretical constructs as described in literature. Therefore, we expect to find correlation coefficients (Cronbach's α) of >0.6.

4. To assess test-retest reliability of the developed ePRO.

Hypothesis: Since OAB symptoms might fluctuate within the study period, we do not expect to find perfect test-retest reliability (i.e. test-retest reliability coefficients close to 1.00). However, it is hypothesized that symptoms will show certain subject-specific patterns, so consistency between the first half-week and the second-half week is expected. Therefore, we hypothesize to find test-retest reliability coefficients around 0.70-0.80.

5. To assess how well the developed ePRO differentiates between OAB and healthy subjects, by determining the accuracy of the discriminatory model using a confusion matrix.
   Hypothesis: We hypothesize that the accuracy of the ePRO to differentiate between OAB and healthy subjects will be comparable with ICS criteria, i.e. moderately to good. There are no studies that examined the sensitivity or specificity of these criteria. However, since OAB-like symptoms often occur in healthy subjects we expect that the ePRO might classify some healthy subjects as OAB (i.e. false positives) resulting in moderate sensitivity and high specificity.

2. STUDY DESIGN

Focus group research in OAB patients was previously done for item selection and to evaluate the quality of the PROMs according to the ESM principle (METC 16-4-189). The outcomes of the focus groups have been discussed in an expert meeting and a final questionnaire has been constructed, specifically for the ESM in the urological patient population. Now, this OAB-specific ESM tool should be tested to see if there is a difference between symptom scores on ESM and the currently used retrospective reports and SR-BDs. The ESM study is a multi-centre, prospective, cross-sectional study in Maastricht UMC+, Zuyderland Heerlen/Sittard and University Hospital Antwerp.

OAB patients will be recruited at the outpatient Pelvic Care Centre at Maastricht UMC+, the outpatient clinic Urology at Zuyderland Heerlen/Sittard and the outpatient clinic Urology at University Hospital Antwerp. Eligible patients are patients that are referred to the urologist by their general physician, other medical specialists or other hospitals with a differential diagnosis of OAB or urinary urgency incontinence. Presently, all new patients that are seen in the outpatient clinic Urology in the MUMC+, the outpatient clinic Urology at Zuyderland Heerlen/Sittard and the outpatient clinic Urology at University Hospital Antwerp are triaged by the staff members of the urology department following the standard of care on the basis of the guidelines for urinary incontinence. [36,37] Patients that are referred with a differential diagnosis of OAB or urinary urgency incontinence receive SR-BDs and a HADS questionnaire by post, together with the information about the date of the outpatient clinic appointment in an information package sent by the outpatient nurse. They are asked to fill these out and take these with them for their first urologist appointment.

Since the patients already need to fill out these SR-BDs (and HADS) for their first regular urologist visit, patients will receive a recruitment letter within the information package to inform them about the study (see ‘E3. Wervingstekst_ESM_Urologie_Versie 2.0 (27.10.2017)’). They will also receive written information (see ‘E1. Proefpersoon informatie_ESM studie Versie 2.0(18.10.2017)’) about the purpose of the ESM study in this information package. During the study, patients have to fill out a lot of questionnaires and repeated assessment of the ESM app. By contacting them prior to the first urology visit, there is no any additional burden of filling out an extra SR-BD (and HADS) for study purposes solely. Patients are asked to contact the coordinating investigator by email or telephone in case of interest in participation. If this is the case, the first visit will be scheduled with one week respite at the medical centre to sign the informed consent form (by the participant as well as the researcher) and to instruct the participant about the study procedures. No study procedures will be performed until the informed consent form is signed. After signing the informed consent form they will receive the login codes of the ESM app and the additional

(retrospective) questionnaires. This way of inclusion ensures that patients are not entrusted with filling out an extra SR-BD for study purposes solely, since they already need to fill these out following the standard of care for their regular scheduled visit.

Healthy volunteers will be recruited by advertisements on bulletin boards at Maastricht University Medical Centre, other public bulletin board in Maastricht and on the website 'www.digiprik.nl' (see 'E3. Advertentie gezonde controles_ESM_Versie 2.0 (18.10.2017)'). Persons that are interested in participating after reading an advertisement are asked to contact the coordinating investigator via email and will then receive the written patient information letter and informed consent form E1. Proefpersoon informatie_ESM studie_Vrijwilligers Versie 2.0(18.10.2017) and E2. IC_ESM_Versie 2.0 (18.10.2017)). One week after receiving this information, a telephone call will follow to answer any additional questions and to verify whether or not the subject is still interested in participating. If this is the case, the first visit will be scheduled at the medical centre to sign the informed consent form (by the participant as well as the researcher), receive the ESM login codes and additional retrospective questionnaires, and to instruct the participant about the study procedures. No study procedures will be performed until the informed consent form is signed.

Study participation will comprise two appointments with the coordinating researcher. During the first visit written informed consent will be obtained and instructions about the study procedures (*i.e.* ESM and retrospective questionnaires) will be given. Hereafter, the participant will complete ESM and the SR-BD during the following week. At the end of the study, the single-time symptom questionnaires will be completed. At the end of this week another appointment ('last visit') follows during which a debriefing session concerning ESM will take place. In the case of included new patients, this appointment directly takes place after the patient is seen by the urologist for their regular outpatient visit. At that moment, all data are collected and study participation is completed. A timeline of the study period is given in **figure 1**.

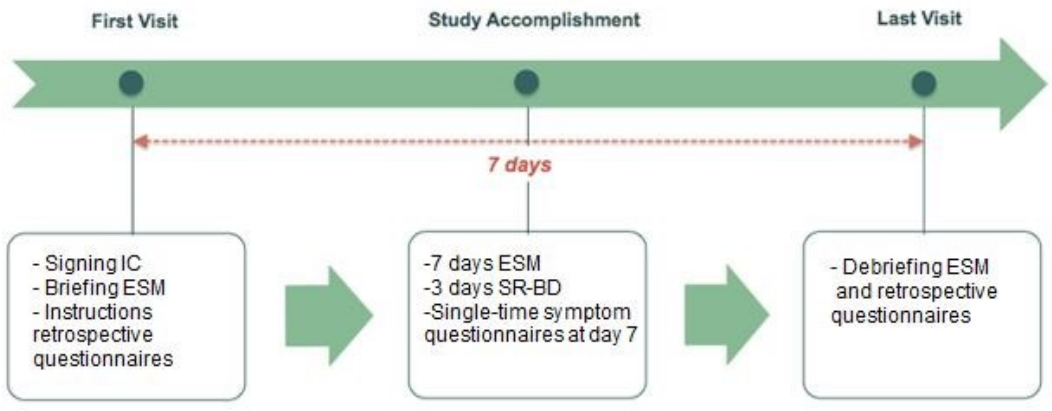

Figure 1: Timeline of study participation period.

3. STUDY POPULATION

3.1 Population

Thirty-three male and thirty-three female OAB patients will be recruited at the outpatient Pelvic Care Centre in Maastricht UMC+ the outpatient clinic Urology at Zuyderland Heerlen/Sittard and the outpatient clinic Urology at University Hospital Antwerp. Patients will be diagnosed with OAB by their urologist using the ICS criteria for OAB[5].
Furthermore, thirty-five male and thirty-five female healthy volunteers will be included in order to exploratively evaluate the ability of ESM to discriminate between OAB patients and healthy controls, in terms of triggers for the occurrence and/or persistence of urological symptoms. This control group will be sex- and age-matched to the group of OAB patients.

3.2 Inclusion criteria

3.2.1 Inclusion criteria OAB patients

Patients between 18-70 years with either subjectively experienced OAB for which they have sought medical help or have been diagnosed with OAB by a medical physician. Participants need to be able to understand written Dutch and speak the Dutch language, since the ESM app will be conducted in Dutch. They also have to understand how to practice the ESM tool.

3.2.2 Inclusion criteria healthy volunteers

- Age between 18 and 70 years;
- Male and female
- Ability to understand and speak Dutch;
- Ability to understand how to utilize the ESM tool.

3.3 Exclusion criteria

3.3.1 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Patients with a clear anatomical or other urological cause for OAB (e.g. bladder cancer, benign prostate hyperplasia (BPH), prostate cancer, urolithiasis, chronic or acute urinary tract infections (UTI), neurological disease).
- Patient with severe stress incontinence
- Pregnancy

3.3.2 Exclusion criteria healthy volunteers

- Current or past diagnosis of lower urinary tract symptoms;

- No more than one urinary tract infection in half a year.
- Start-up of regularly used medication from one month before inclusion until the end of study participation.

3.4 Sample size calculation

The outcome of the ESM is multidimensional; it gives information about the (urological) complaints but also the context in which the complaints arise. An inter-individual analysis can be made with the use of ESM, and because of this extensive data can be collected per patient.

An appropriate sample size can therefore not be made.

In previous literature the sample size differs from N=5 [27], N= 10 [38], N = 19 [39], N= 26 [1] to N=40 [40]. In the study of Cabrita et. al. random slopes could not be included in the multilevel regression analysis because of the sample size being too small to validly estimate all associated parameters, but an individual analysis with linear regression models with random intercept has been made.[38] Other studies using ESM in a population between 19 to 40 patients have shown that clinically relevant differences could be detected using an alpha of 0.05.[1,39-41] However, epidemiologic literature suggest that as a rule-of-thumb, a sample of at least N = 50 is required to evaluate construct validity[42,43] and to recognize a factor pattern.[44] Therefore, we need to include at least 50 participants.

Empirical studies using ESM showed that about 5% to 23.2% of the patients did not comply (defined as completing the ESM questionnaire in less than 50% of the beeps).[1,27,38-41] Taking into account a conservative non-valid ESM data rate of 23%, a sample size of 66 patients is needed to obtain 50 ESM questionnaires that can be used for the analysis.

4. METHODS

4.1 Study parameters/endpoints

Divided in three parts in accordance with the study objectives.

4.1.1 Part I Comparison of the ESM vs. SR-BDs

Main study parameter/endpoint

- Urgency scores as measured by two self-report measures:
  - The ESM tool (*i.e.* momentary measurement)
  - The sensation-related bladder diary (*i.e.* retrospective measurement with a recall period of several minutes)

Secondary study parameters/endpoints (if applicable)

- Symptom scores (other than urgency) as measured using the ESM tool:
  - Micturition habits, *i.e.* number of micturitions each day and the force of the urinary stream using the Visual Prostate Symptom Score (VPSS)
- Symptom scores (other than urgency) as measured using the single-time retrospective questionnaires:
  - Urological symptoms:
    - Female participants: OABq, ICIQ-FLUTS, 3IQ
    - Male participants: OABq, ICIQ-MLUTS, 3 IQ, IPSS, IIEF-5

4.1.2 Part II Validation

Main study parameter/endpoint

- Urgency scores as measured by two self-report measures:
  - The ESM tool (*i.e.* momentary measurement)
  - The sensation-related bladder diary (*i.e.* retrospective measurement with a recall period of several minutes)

Secondary study parameters/endpoints (if applicable)

- Symptom scores (other than urgency) as measured using the ESM tool:
  - Micturition habits, *i.e.* number of micturitions each day and the force of the urinary stream using the Visual Prostate Symptom Score (VPSS) (see Figure 2).
  - Gastrointestinal symptoms
  - Psychological symptoms
  - Gynaecological symptoms
  - Extra-intestinal somatic symptoms

- Data on context and environment at each time an ESM questionnaire is completed

- Symptom scores (other than urgency) as measured using the sensation-related bladder diary:
  - Micturition habits, *i.e.* number of micturitions each day
- Symptom scores (other than urgency) as measured using the single-time retrospective questionnaires:
  - Urological symptoms:
    - Female participants: OABq, ICIQ-FLUTS, 3IQ
    - Male participants: OABq, ICIQ-MLUTS, 3 IQ, IPSS, IIEF-5
  - Psychological symptoms: HADS
  - Gynaecological symptoms : Questionnaire Werkgroep Bekkenbodem NVOG
  - Extra-intestinal symptoms and Quality of Life scores: SF-36

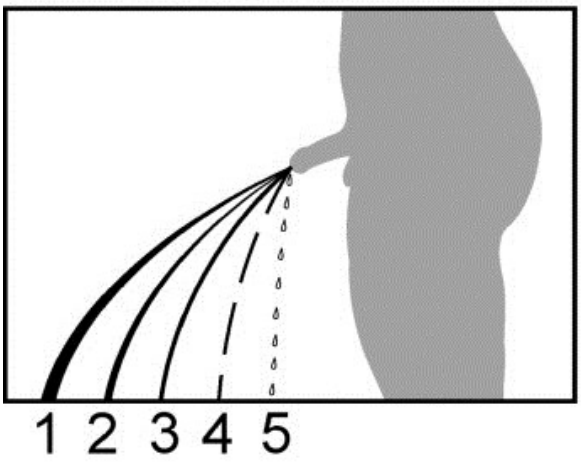

Figure 2. The Visual Prostate Symptom Score.

4.1.3 Other study parameters (if applicable)

Baseline parameters include: sex, age, body weight, type of disorder, socio-economic status, comorbidities and medication use.

4.2 Study procedures

Participants will accomplish the Experience Sampling Method for seven consecutive days during their regular daily life. Previous ESM validation studies validated for the use of the ESM for seven days too.[43]

During the last three consecutive days of the ESM, patients will also keep a SR-BD following the standard of care. A 7-day voiding diary is a reliable and valid method for documenting the change in symptoms of overactive bladder in men and women with predominantly urge incontinence. However, 3-day voiding diaries are as accurate as the 7-day diary, but patient burden is reduced. Therefore, a 3-day sensation-related bladder diary is used in the standard of care of the department of Urology of MUMC+, Zuyderland Heerlen/Sittard and University Hospital Antwerp.[46,47] Furthermore, during the first four days of the study, ESM outcomes are not influenced by outcomes reported with the sensation-related bladder diaries. This is in alignment with previous studies.[4,43]

On the last day of the study period, participants will fill out the several retrospective symptom questionnaires.

To accomplish the ESM, they need to carry their own smartphone or (in case they do not have one) another digital device, which will be lent to them for this period. On the smartphone or digital device an application, specifically developed for this project, will be downloaded. This application will run the PROM as follows.

The concerning device will send out an auditory signal 10 times a day at random moments between 07:00 am and 22:00 pm. During 10 minutes following the signal participants can complete a questionnaire, *i.e.* the developed PROM, on the device (see F1. 'ESM_Vragenlijst_Versie 1.0 (11.08.2017)'). After these 10 minutes the questionnaire will not be available until the next beep and is considered missing data. Therefore, subjects are instructed to complete as many questionnaires as possible each day, as soon as possible following each beep, but to pass over questionnaires when completing is impossible. For example, subjects should not fill out questions when driving a car. The questions will be identical between the different moments during the day.

Additionally, participants will be instructed to complete a different ESM questionnaire in the morning when they wake up (see F1. 'ESM_Ochtend Vragenlijst_Versie 1.0 (11.08.2017)'). A timeline portraying which questionnaire has to be filled out at what time during the study period is reported in figure 2.

4.2.1 PROM development

The process of question selection for the development of an OAB specific ESM tool is a crucial step since content, construct and criterion validity are dependent on these questions. The questions that will be used were derived from previously published ESM studies and currently used OAB symptom questionnaires and further selection took place based on patients input during focus group interviews. Following, the items were evaluated by a multidisciplinary expert group consisting of highly esteemed and experienced investigators in the fields of urology, gastroenterology, psychiatry and gynaecology. Herewith, the number of items was further reduced in order to minimize the burden associated with completing the questionnaire at regular intervals.

This stepwise approach was performed according to guidelines for symptom assessment tool development.

4.2.2 Tool development

To apply ESM as a symptom assessment method in this study, an application suitable for smartphones has been developed. This application runs the previously selected set of items, as described in section 5.2.1.1. 'PROM development'.

The application can be downloaded freely on the personal smartphone of each participating subject. Once the application is downloaded and activated, it will work both online and offline to ensure that no assessments will be missed when not connected to the Internet. In online situations the answers will be directly and automatically sent to the general database; when offline the answers will be temporary stored at the smartphone and will be sent to the database as soon as an Internet connection is available. Encryption of data to assure on patient's privacy is described in detail in section 9.1 'Handling and storage of data and documents'.

Questions in the application will be designed in a hierarchical order, *i.e.* if the patient has no symptoms at that particular moment, there is no rationale for assessing triggers and therefore these questions will be automatically set to a default of "no" or "none". Further, if patients find an auditory signal

disturbing during their daily activities, they will be able to choose a vibration signal instead.

4.2.3 Retrospective symptom assessment – conventional questionnaires

Apart from ESM, participants will be instructed to complete a SR-BD during last 3 consecutive days of filling out the ESM (see 'F2. ESM_sensation-related bladder diary_Versie 1.0 (11.08.2017)'). The SR-BD has to be filled out after each micturition. This is a voiding diary where people fill out at what time they had to void, how high the voided volume was and how high the urgency and perception of bladder fullness was what they experienced. Furthermore they have to fill out if and how much urine loss they had. Furthermore, participants will be instructed to complete additional (single-time) retrospective questionnaires, at the end of the test period of 7 days:

- Baseline questionnaire for demographic characteristics (see F1. 'ESM_Algemene Vragenlijst_Versie 1.0 (11.08.2017)').
- *Sensation-related bladder diaries* (see 'F2. ESM_sensation-related bladder diary_Versie 1.0 (11.08.2017)'). Besides urinary frequency and voided volume, these diaries also include the degree of urge and the perception of bladder fullness during each void. It has been recommended that evaluation of bladder sensations during daily activities is the most representative. [48-50] Sensation-related bladder diaries (SR-BDs) are a non-invasive tool that is used to evaluate these bladder sensations in daily life.
- *Overactive Bladder Questionnaire (OAB-q)* (see F1. 'ESM_OABq_Versie1.0 (2016.10.17)'). 33-item questionnaire on LUTS and Health-related quality of life (HRQL) items.[51]
- *3 Incontinence Questionnaire (3IQ) (see 'F1. ESM_3IQ_Versie 1.0 (11.08.2017)')*[52]
- *Female participants only :*
    - *International Consultation on Incontinence Modular Questionnaire – Female LUTS* (see F1. 'ESM_ICIQFLUTS_Versie 1.0 (11.08.2017)').13-item questionnaire on lower urinary tract symptoms [53,54].
    - *Vragenlijst Werkgroep Bekkenbodem NVOG* (see 'F1. ESM_VragenlijstNVOG_Versie 1.0 (11.08.2017)'). 47-short item questionnaire on pelvic symptoms.

- *Male participants only:*
  - *International Consultation on Incontinence Modular Questionnaire – Male LUTS* (see 'F1. ESM_ICIQMLUTS_Versie 1.0 (11.08.2017)').13-item questionnaire on lower urinary tract symptoms [53,54].
  - *International Prostate Symptom Score* (see 'F1. ESM_IPSS_Versie 1.0 (11.08.2017)'). 7 item questionnaire on LUTS and 1 item questionnaire on Quality of Life[55].
  - *International Index of Erectile Functions 5 (IIEF-5)* (see 'F1. ESM_IIEF5_Versie 1.0 (11.08.2017). 5-item questionnaire to screen for erectile dysfunction. [56]
- *Hospital Anxiety and Depression Scale (HADS) ((*see 'F1. ESM_HADS_Versie 1.0 (11.08.2017)').[57]
- *Short Form-36* (SF-36) (see F1. ESM_SF36_Versie 1.0 (11.08.2017)'). Self-survey after general quality of life (not disease-specific)[58]

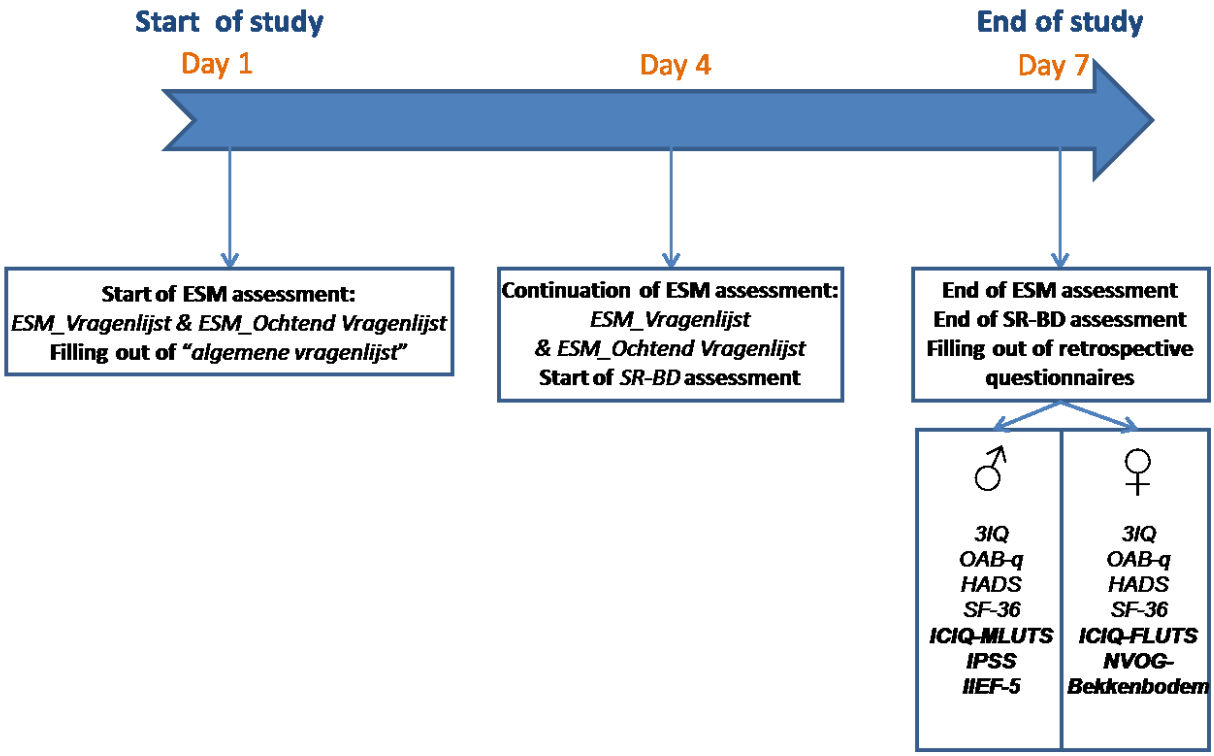

Figure 2: Questionnaire timeline.

4.3 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.

4.4 Replacement of individual subjects after withdrawal

We do not expect many dropouts, because the study is not very burdensome in a physical way and so, is not very difficult to complete. However, accomplishing ESM for 7 days is quite time-consuming and might intervene with daily activities, so possibly, not all subjects will be perfectly compliant to the method (i.e. completing the PROM at 10 random moments during 7 consecutive days). In case a subject decides to end participation before the 7-day participation period is completed, this subject will be considered a drop-out. Data can still be used in the comparison of assessment methods (part I), to determine the test-retest reliability and to assess the accuracy of the discriminatory model using a confusion matrix.

4.5 Follow-up of subjects withdrawn from treatment

Since there is no intervention involved in the study, there is no need for follow up of withdrawn participants.

4.6 Premature termination of the study

There are no expected reasons for premature termination of the study.

5. SAFETY REPORTING

All safety reporting will be handled in accordance with METC protocol

5.1 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.

5.2 AEs, SAEs and SUSARs

5.2.1 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 investigational product / the experimental intervention]. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

5.2.2 Serious adverse events (SAEs)

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

- 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;
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse events.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse event. This is for a preliminary report with another 8 days for completion of the report.

5.3 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

6. STATISTICAL ANALYSIS

Part I – Comparison of the ESM to SR-BDs and other retrospective questionnaires

In case of incomplete ESM data, we will not use imputation techniques as these techniques have similar assumptions on the mechanisms of missing data as the statistical model described in the remaining text.

Experience Sampling Methods produce complex multilevel data structures, and analysis techniques need to take the variation between subjects and repeated measures within subjects into account. Associations between urological symptom scores of the SR-BD and corresponding ESM scores will be tested using linear mixed-effects models, with a random intercept to account for clustering of measurements within patients, and an autoregressive (AR1) covariate structure to account for correlations of measurements over time. Currently the SR-BD can be seen as the standard method and will therefore be used as dependent variable in the analysis. For each participant, ESM day-mean scores of individual symptoms will be used as predictor, to test whether average symptom scores of the day reflect the day-mean SR-BD scores.

To quantify the difference of scores between the two methods, ESM data will be subtracted from corresponding day-mean SR-BD scores, resulting in a delta score, which will be statistically tested using the same multilevel analysis, adjusting for repeated measures. In like manner, the differences between the mean SR-BD scores and ESM maximum scores of the day will be tested.

To investigate if certain patient characteristics lead to a different retrospective perception of urgency, possible predictors of a larger delta-score (i.e. the differences in urgency reporting between ESM day-mean scores and the day-mean SR-BD scores) will be tested: i.e. gender, age, presence of comorbid panic disorder and psychological symptoms (HADS).

Part II Validation

The COSMIN guidelines are used to validate the Experience Sampling Method as a health-related ePRO. In this COSMIN (COnsensus-based Standards for selection of health Measurement INstruments) checklist manual, the methodology to examine responsiveness, i.e. “the instruments ability to detect change over time in the construct to be measured” gives the following instructions.[59-61] Studies evaluating the measurement properties of an instrument should be of high methodological quality to guarantee appropriate conclusions about the measurement properties of the instrument. Therefore, the COSMIN initiative developed a taxonomy of measurement properties relevant for evaluating health instruments, with three domains: reliability, validity and responsiveness. Each domain contains one or more measurement property:[59]

6.1 Primary study parameter

Data used for analysis will comprise patient-reported scores from ESM, paper SR-BDs and single-time paper symptom questionnaires. The PROM will be psychometrically evaluated with regard to validity and reliability. These parameters will characterize the ESM measure and allow insight into the potential role of this method in clinical practice. Validity and reliability will be assessed according to following components [29,62,63]:

- Content validity reflects the extent to which the instrument as a whole measures all the relevant aspects that are indicative to the specific condition and population. This can be determined by taking into account evidence from qualitative studies, performing cognitive interviews to evaluate patients’ understanding with the instrument and by taking into account experts’ opinions [62,63]. In this study, content validity is assured by basing ESM items on theoretical constructs from the literature as well as by performing patient focus groups and expert meetings.
- Concurrent validity reflects the correlation between a new test and an existing test that purport to measure the same construct. ESM scores will be correlated with scores of so-called ‘concurrent’ instruments. In the present study, ESM measures will be compared to scores obtained from SR-BDs and symptom questionnaires. Since ESM data have a hierarchical structure, with repeated measurements (level 1) nested within subjects (level 2), these analyses will be performed using linear mixed-effects models, including a random intercept and an autoregressive (AR1) covariate structure. [62,63].
- To quantify the difference of scores between the two methods (ESM and SR-BD), a delta score is calculated. Using the same multilevel analysis, thus adjusting for clustering within patients and for correlations between repeated

measures, we will test whether this delta score is different from 0. In like manner, the differences between SR-BD scores and ESM maximum scores of the day will be tested.

- Internal consistency is a reliability measure to analyse correlations between single items of an instrument/scale that are supposed to measure similar symptoms or domains. The homogeneity of a scale (*e.g.* internal consistency) is analysed by Cronbach's α-statistic. A coefficient of at least 0.6 is generally considered as acceptable, values above 0.8 are considered as good to very good [29,64-66]. As subjects are usually not able to respond after every beep (for example because of driving a car), completion of ≥6 of the 10 beep-questionnaires per day will be considered as being compliant. Not completed beep-questionnaires will be considered as missing values in the analyses.[1,67]
- Test-retest reliability reflects the consistency between repeated measurements of the same outcome in the same test conditions, but at different times. We will ascertain on individual response consistency over the study period. Scores of the first half-week will be correlated with scores of the second half-week. A test-retest reliability coefficient of more than 0.70 will be considered adequate [29].
- Differences between OAB symptom scores assessed by the OAB-q / ICIQ-FLUTS / IPSS and ESM could only be analysed on subject level, by paired sample t-test, due to lack of intra-subject variation in the OAB-q scores (only one measurement per subject). Scoring scales of the retrospective questionnaires and ESM will be harmonized by rescaling the ESM data from a 11-point to a 6-point and 5-point scale. In order to assess whether the rescaling affected the reliability of urological symptom related questions in ESM, a Cronbach's a was calculated for the original and rescaled data.
  Subject-means (i.e. means over 7 days) of ESM data were calculated and compared to the corresponding OABq / ICIQ-FLUTS /IPSS scores.
- Following the COSMIN guidelines it should be aimed to assess the responsiveness of the ESM tool too. However, since responsiveness is the sensitivity of an instrument to detect difference between two points in time within groups[68], this psychometric property, it is not meaningful to assess this, since the ESM measures repeatedly over a longer period of time (10 times a day for 7 days). It is expected that there will be a fluctuation of symptoms during the assessment period, however 'big' differences that could be assessed with statistical analysis are not expected to occur. The

aim of this study is not to detect change between two groups with the use of statistical analysis. It is rather to evaluate symptom pattern recognition of the ESM tool. Therefore responsiveness will not be assessed as psychometric property in this study.

A significance level (α) of 0.05 will be considered statistically significant. Data analysis will be performed using IBM SPSS Statistics software version 23.0 (IBM Statistics for Windows, Armonk, New York).

6.2 Other study parameters

- Baseline characteristics / descriptives will be described as means and standard deviations (in case of normal distribution) or medians and interquartile ranges (in absence of a normal distribution) for continuous variables and frequencies for categorical variables. The following patient characteristics will be investigated: gender, age, race, length, weight, highest level of education, work status, smoking, alcohol use, drug use, caffeine use and medication.
    - To investigate if certain patient characteristics lead to a different retrospective perception of urgency, possible predictors of a larger delta-score (i.e. the differences in urgency reporting between ESM day-mean scores and the end-of-day SR-BD scores) will be tested: i.e. gender, age, presence of comorbid panic disorder, psychological symptoms (HADS) .

7. ETHICAL CONSIDERATIONS

7.1 Regulation statement

This study will be conducted according to the Declaration of Helsinki (64th WMA General Assembly, Brazil, 2013), the Medical Research Involving Human Subjects Act (WMO) and EMA as well as FDA guidelines on the evaluation of treatments in OAB and development of patient-reported outcome measures.[62,69,70]

7.2 Recruitment and consent

7.2.1 OAB patients

Eligible patients are patients that are referred to the urologist by their general physician, other medical specialists or other hospitals with a differential diagnosis of OAB or urinary urgency incontinence. Presently, all new patients that are seen in the outpatient clinic Urology in the MUMC+, the outpatient clinic Urology at Zuyderland Heerlen/Sittard and the outpatient clinic Urology at University Hospital Antwerp are triaged by the staff members of the urology department following the standard of care on the basis of the guidelines for urinary incontinence. [36,37] Patients that are referred with a differential diagnosis of OAB or urinary urgency incontinence receive SR-BDs and a HADS questionnaire by post, together with the information about the date of the outpatient clinic appointment in an information package. They are asked to fill these out and take these with them for their first urologist appointment.

Since the patients already need to fill out these SR-BDs (and HADS) for their first regular urologist visit, patients will receive a recruitment letter within the information package to inform them about the study (see 'E3. Wervingstekst_ESM_Urologie_Versie 2.0 (27.10.2017)'). They will also receive written information (see 'E1. Proefpersoon informatie_ESM studie Versie 2.0(18.10.2017)') about the purpose of the ESM study in this information package sent by the outpatient nurse. During the study, patients have to fill out a lot of questionnaires and repeated assessment of the ESM app. By contacting them prior to the first urology visit, there is no any additional burden of filling out an extra SR-BD (and HADS) for study purposes solely. Patients are asked to contact the coordinating investigator by email or telephone in case of interest in participation. If this is the case, the first visit will be scheduled with one week respite at the medical centre to sign the informed consent form (by the participant as well as the researcher) and to instruct the participant about the study procedures. No study procedures will be performed until the informed consent form is signed. After signing the informed consent form they will receive the login codes of the ESM app and the additional (retrospective) questionnaires. This way of inclusion ensures that patients are

not entrusted with filling out an extra SR-BD for study purposes solely, since they already need to fill these out following the standard of care for their regular scheduled visit.

7.2.2 Healthy volunteers

Healthy volunteers will be recruited by advertisements on bulletin boards at Maastricht University Medical Centre, other public bulletin board in Maastricht and on the website 'www.digiprik.nl' (see 'E4. Advertentie gezonde controles_ESM_Versie 2.0 (18.10.2017)'). Persons that are interested in participating after reading an advertisement are asked to contact the coordinating investigator via email and will then receive the written patient information letter and informed consent form E1. Proefpersoon informatie_ESM_Vrijwilligers Versie 2.0(18.10.2017) and E2. IC_ESM_Versie 2.0 (18.10.2017)). One week after receiving this information, a telephone call will follow to answer any additional questions and to verify whether or not the subject is still interested in participating. If this is the case, the first visit will be scheduled at the medical centre to sign the informed consent form (by the participant as well as the researcher), receive the ESM login codes and additional retrospective questionnaires, and to instruct the participant about the study procedures. No study procedures will be performed until the informed consent form is signed.
Healthy volunteers can report on the informed consent form if they want to be informed in case of a random "disease" finding. In case of random "disease" finding, patients will be treated with the standard care of treatment.

7.3 Benefits and risks assessment, group relatedness

Participating in this study does not bring along important risks, since subjects only have to complete questionnaires and there are no treatments or investigational products involved. Therefore, this is a low-risk study. However, completing the PROM several times a day might be quite burdensome and time-consuming for participants and will intervene with regular daily life. Completing the SR-BD by measuring the voided volumes with the use of a measuring cup is sometimes difficult to combine with professional or social life. Therefore, this could be considered a burden. However, new patients already need to fill out these SR-BDs for their first regular urologist visit, so an extra completion of a SR-BD for study purposes solely will not be needed.
Furthermore, since data are transferred via Internet and partly stored at a participant's smartphone, there is a need for securing on an individual's privacy. This is described into more detail in section 9.1 'Handling and storage of data and documents'.

During the study period, subjects will not directly benefit from participation, since they do not receive any interventional strategy. However, it is possible that completing the ESM questionnaires makes subjects more aware of their symptom patterns and possible provoking factors in daily life. Awareness could trigger symptoms and therefore be considered as a burden. Nevertheless, for the patients it could be beneficial too to know what triggers complaints, to cope better with their disease.
All in all, the risks in this study are not disproportional in association with the benefits. Participants will be informed about the burdens before participating.

7.4 Compensation for injury

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

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

7.5 Incentives

Subjects will receive a 15 euro VVV-voucher compensation for participation in this study. Furthermore, travel expenses will be compensated. In UZA the VVV-vouchers are not valid, therefore an equal compensation will be given according to local guidelines.

8. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

8.1 Handling and storage of data and documents

Obtained data will be coded for the protection of the privacy of the participants, in accordance with the Dutch Personal Data Protection Act (Wet Bescherming Persoonsgegevens, 2000). Data will be coded ("ESM_OAB_001", "ESM_OAB_002" etc, The allocated number is associated with the order of entrance in the study.

This way it is not convertible to the subject. This code is linked to the name, address, date of birth and telephone number of the subject. The principal investigator will keep the key of the code in a locked cabinet, to which only the PI has access. Access to the data will be permitted to all members of the project team, the IGZ, the medical-ethical committee (MEC) and assigned monitors from the Clinical Trial Center Maastricht (CTCM). The data will be stored for 15 years after the end of the study.

Data that is collected on paper, *i.e.* the SR-BDs (see 9.1.1 'Retrospective symptom assessment – conventional questionnaires'), will be stored in a locked cabinet at SURO 4.15 at MUMC+. The SR-BDs from Zuyderland Heerlen/Sittard and University Hospital Antwerp will be scanned and sent by e-mail, anonymized with the study ID for the protection of the privacy of the participants via Microsoft Outlook from one computer, protected with a password, to the other computer, protected with a password. The paper version of the SR-BDs will be stored in a locked cabinet in the office of drs. Kuenen and prof. dr. De Wachter.

Data that is collected digitally, *i.e.* in- and exclusion criteria, demographic characteristics and (single-time) retrospective questionnaires (see 9.1.1 'Retrospective symptom assessment – conventional questionnaires'), will be collected using Castor EDC. Following, this data will be stored on the MIT server of the MUMC+. Backups will be automatically obtained every day, using the MIT server of MUMC+.

All data obtained from the ESM application (*i.e.* downloaded on the participant's smartphone) will be transferred to a certified and secured database using the local Internet network. Data is automatically encrypted and saved according to the NEN 7510- and ISO/IEC 27001/27002 guidelines, hereby respecting the Dutch Personal Data Protection Act (Wet Bescherming Persoonsgegevens, 2000) and Good Clinical Practice guideline. In case a participant completes an ESM assessment in the absence of an online Internet connection the obtained data are temporary stored at the concerning mobile device. For this, a specific asymmetric encryption using a logon procedure with individual username and password will be used to guarantee a subject's privacy. Data will be transferred to the secured database as soon as there is an online Internet connection again.

8.2 Monitoring and Quality Assurance

A qualified monitor of the CTCM will monitor the conduct of the study. A monitoring plan will be drafted after the first application to the METC.

8.3 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.

8.4 Annual progress report

The sponsor/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.

8.5 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.

8.6 Public disclosure and publication policy

Publication will occur in accordance with the CCMO-statement on publication policy (CCMO-statement publicatiebeleid, 2002). Because publications on the validation of a

real-time symptom assessment method in OAB patients do not exist, the results of this study will be published in a peer reviewed journal.

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