Development of the Impact of Nighttime Urination (INTU) questionnaire to assess the impact of nocturia on health and functioning

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Aims: This study describes development of the Impact of Nighttime Urination (INTU) questionnaire to assess nocturia impacts on health and functioning.

Methods: Development of the questionnaire followed an iterative patient-directed process as recommended by current guidance for patient-reported outcome (PRO) measures. An initial 15-item questionnaire was devised based on reviewing the published literature, and then modified through four rounds of semi-structured interviews of 28 individuals with nocturia. In each round, open-ended concept elicitation, followed by cognitive debriefing, was used to assess the questionnaire. Items were modified based on participants’ responses and incorporated into the next round of interviews.

Results: In all rounds, participants reported that their experiences were easy to recall and report on a daily basis and that the burden of completing the questionnaire was low. The final questionnaire has a same-day recall period. It includes six daytime impact items—having limited concentration, a sense of feeling tired, difficulty getting things done, irritability, not feeling rested, and drowsiness—and four items that measure the nighttime impact of nocturia—patient concern, waking up too early, difficulty getting enough sleep, and feeling bothered by having to get up at night to void. Responses follow a 5- or 4-point scale. The final INTU captures the key concepts associated with nocturia as confirmed by cognitive debriefing.

Conclusions: Development of the 10-item INTU, a nocturia-specific PRO measure, was based on direct input and feedback from patients and has demonstrated that it captures the patient-reported impacts of nocturia.

KEYWORDS

cognitive debriefing, concept elicitation, functioning, health, health-related quality of life, nocturia impact, patient-reported outcome measure

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1 | INTRODUCTION

Nocturia entails excessive urination at night resulting in awakening at least once during the night to void, and is one of the most common reasons for interrupted sleep, especially in individuals older than 50 years of age. It is associated with increased daytime fatigue and a poorer quality of sleep, resulting in a significant negative impact on patients’ health-related quality of life (HRQoL). Patients often report being concerned about bothering their partners and others when getting up at night, and view nocturia as an inevitable consequence of getting old and a cause for embarrassment, worry, or frustration. Although the frequency and impact of nocturia varies among individuals, studies have suggested that voiding two or more times a night substantially impairs patients’ health and functioning and may warrant clinical intervention.

Patient-reported outcome (PRO) measures play a key role in the assessment of nocturia and the potential benefits of therapeutic intervention. The Nocturia Quality of Life Questionnaire (N-QOL) is the first of several tools that specifically measures the impact of nocturia and related conditions on HRQoL. The N-QOL was developed based on input from men with benign prostatic hyperplasia (BPH) only, and hence may not be representative of the overall nocturia population. Furthermore, the N-QOL has a 2-week recall period, which increases the likelihood of recall bias. Regulatory guidance for PRO measures notes that items for which patients report their recent or current state, including those with short recall periods, are generally preferred over those with longer recall times. For these reasons, the N-QOL may not be well suited to assessing improvements in health and functioning in both women and men in response to interventions in a clinical trial setting intended to support labeling claims. The Nocturia, Nocturnal Enuresis and Sleep-interruption Questionnaire (NNES-Q) also measures the impact of nocturia, but primarily focuses on the impact of nocturnal enuresis and thus only provides limited information on nocturia, such as the frequency of voiding at night and associated bother.

Here we describe the development of the Impact of Nighttime Urination (INTU) questionnaire, a new PRO measure designed to assess the impacts of nocturia on health and functioning in accordance with current established methodological guidance.

2 | MATERIALS AND METHODS

2.1 | Instrument development

Four rounds of individual interviews were conducted between June and September 2013 with participants recruited from four clinical sites, including both primary care and urology practices in the United States. Each interview, lasting approximately 60 min, was conducted by two investigators in accordance with the study protocol. The interviews were audio-recorded and transcribed, with transcripts verified through an iterative process of technical and editorial review. The interviews began with concept elicitation through open-ended questions regarding the participant's experience with nocturia. Building upon the concepts identified during the development of the N-QOL and in consultation with the United States Food and Drug Administration (FDA) review division and the Study Endpoints and Labeling Development (SEALD, now the Clinical Outcome Assessment [COA] Staff), a preliminary set of 15 items (questions) was considered in the first round of interviews (Figure 1). These items pertained to concepts related to difficulty in
concentrating, difficulty in getting enough sleep, reduced participation in enjoyable activities, and being careful about the amount of liquids consumed. During the first round of interviews, participants were provided the items for the cognitive debriefing phase to assess their interpretation, relevance, and ease of understanding, as well as identify any missing concepts regarding the impact of nocturia. Participants were also asked how easy it would be to recall their experiences over the recall periods specified in the questionnaire and how burdensome it would be to complete the questionnaire every evening for three consecutive days, as would be done in a clinical trial setting to take into account nocturia fluctuations over time.

Criteria for whether an item was retained, modified, or deleted included patient feedback and the ability of the item to capture treatment effects in a clinical trial setting. After each round of interviews conducted at a single site, the preliminary set of items were revised based on participants’ responses. These items were then evaluated in the next round of interviews involving participants from another of the four sites. At the end of the final round of interviews, a concept elicitation grid was developed to summarize the concepts endorsed by each participant during the open elicitation portion of the interviews.

### 2.2 Participants

Participants were recruited from four clinical sites in the United States between June and September 2013. Patient selection criteria were designed to be similar to that of a planned clinical trial for which the developed PRO measure would be used. Participants were between 50 and 85 years of age with a documented diagnosis of nocturia (defined as having at least two voiding episodes per night for at least 6 months), could read and write in English, and were willing to participate and complete the interviews. Exclusion criteria were diabetes insipidus, uncontrolled diabetes mellitus or congestive heart failure (New York Heart Association Class III or IV). Also excluded were individuals who consumed >3000 ml of liquids during the day, used loop diuretics, voided >5 times per night or >8 times per day, had a history of a sleep disorder or a syndrome that disrupts sleep (within the past 6 months), or engaged in work or lifestyle activities that interfere with nighttime sleep. Each center aimed to recruit at least two individuals meeting the following criteria to ensure the cohort consisted of a diverse sample: male, aged 65 years or older, no more education than a high school diploma or equivalent, and at least two non-white individuals including at least one Hispanic participant. Seven adults were recruited from each of the four clinical sites. All participants provided informed consent and the study received Institutional Review Board approval.

### 3 RESULTS

A total of 28 participants completed the interviews across the four clinical sites. Mean (SD) age was 64.3 (±7.8) years, 50% (n = 14) of the participants were female, and 75% (n = 21) were white (Table 1). Eight (29%) participants were employed full-time, four (14%) were working part-time, three (11%) were unemployed, and 13 (46%) were retired. Overall, participants reported 2-5 nocturic episodes per night, with those in Round 4 of interviews having the greatest severity (3-5 nocturic episodes/night). Of the seven participants in Round 4, three reported using pads or adult diapers at night for convenience to avoid getting out of bed.

#### 3.1 Concept elicitation

Concept elicitation identified topics primarily related to nighttime and daytime impacts. Nighttime impacts largely reflected adverse effects on sleep. Typical participant responses were: “My sleep is terribly broken and for me, broken, sleep doesn’t work.” and “I feel real sleepy, but I know I can’t lay there... it’s hard to get up but I know I have to get up.” (Table 2). Of the 28 participants, 13 (46%) reported having an inadequate amount of sleep, 11 (39%) reported interrupted or disturbed sleep, 10 (36%) had difficulty getting back to sleep after getting up, and nine (32%) reported not wanting to get up to void. In addition, six (21%) reported getting up early in the morning to use the bathroom.

Daytime impacts largely reflected feeling tired but also included effects of tiredness on disposition. Typical statements made by participants included: “I can be real tired. I can find myself being kind of lethargic in the morning.” and “A lot of times I’ll feel tired.” (Table 2). Twenty participants (71%) described feeling tired during the day, eight (28%) mentioned needing a nap during the day, six (21%) mentioned feeling sleepy, five (18%) described feeling lethargic, and five (18%) described having to go to bed early because of feeling tired. Feeling drowsy, sluggish, low energy, dragging, groggy, fatigue, irritable, grumpy, and cranky were each mentioned by 1-3 participants.

Three participants described finding daytime activities more difficult or being less inclined to do them because of nocturia-related symptoms and three mentioned symptoms affecting their performance at work. Two stated that they found concentration to be “painful”.

In Rounds 2, 3, and 4 of the interviews, participants were specifically asked about the worst aspect of nocturia. Responses were consistent with those cited spontaneously (reflecting a “typical patient response”) and largely focused on sleep disturbances, the inconvenience of having to get up at night, and feeling tired the next day.
3.2 | Cognitive debriefing

Round 1 of the cognitive debriefing interview evaluated the initial set of 15 items consisting of 14 statements and one question: 13 statements had a recall period of the whole day, one statement had a recall period of the morning, and the question had a recall period of the previous night. Following the interview, five items were omitted either due to lack of relevance or overlap with other items. All statements were rephrased as questions, and one item regarding feeling rested was added. Among the resulting 11 items, five retained a whole-day recall period, and three items each were assigned an evening or morning recall period. Minor modifications were made to the wording of the response options.
The 11 items were evaluated in the Round 2 interview. Based on participant feedback, eight items remained unchanged, two were revised slightly, and one was omitted due to potential overlap with another item. Two new items were added: one to assess if patients wake earlier than desired due to a morning void and another to determine whether the word “unpleasant” rather than “bother” better captures the experience of having to get up in the night. No changes were made to the recall period.

Of the 12 items tested in the Round 3 interview, seven were retained with no modifications and two were modified with alternative wording to be evaluated in Round 4. Three items were omitted, two due to irrelevance: being careful about liquid intake was a behavior deemed unlikely to change over the course of a clinical trial; falling was considered irrelevant to most participants. “Bother” was found to better capture the experience of having to get up at night to void compared with “unpleasant.” Hence the item with “unpleasant” (which was added for Round 3) was omitted and the term “bother” was retained.

A nine-item version of the questionnaire was evaluated in the Round 4 interviews. All seven items remained unchanged from those in the Round 1 interviews, as were the preferred versions of the two items with alternative wordings. An additional concept—“feeling drowsy”—was identified in the feedback and was added to the final questionnaire.

In its final version, the INTU consists of 10 items. These include six items that assess the effects of nocturia on daytime activities: having limited concentration, a sense of feeling tired, difficulty getting things done, irritability, not feeling rested, and drowsiness. Responses to the first four items are assessed using a five-point verbal rating scale ranging from “Not at all” to “All day” and using a four-point verbal rating scale ranging from “Not at all” to “Very much” for the remaining two items. The other four items measure the nighttime impact of nocturia: patient concern, waking up too early, difficulty getting enough sleep, and feeling bothered by having to get up at night to go to the bathroom. Responses to the nighttime impact items were on the same four-point verbal rating scale. Concepts included in the final questionnaire are shown in Table 3.

All participants reported that it was easy to recall their experiences over the recall periods specified in the questionnaire and that completing the questionnaire on three consecutive nights would not be burdensome.

### 4 | DISCUSSION

This report describes the development of the INTU, a 10-item questionnaire designed to assess the impact of nocturia on health, well-being, and functioning in men and women with clinically significant nocturia, defined as having at least two voiding episodes per night. The questionnaire covers the concepts identified as being relevant to individuals with nocturia who would seek medical treatment as well as able to detect treatment change in clinical trial. Furthermore, the INTU has a recall period of a single day, which is not only considered to be more reliable than the longer recall periods used by other instruments, but also minimizes recall bias and allows for changes over time, including response to treatment to be captured.

Each of the interviews included a concept elicitation and cognitive debriefing portion, which allowed refinement of the initial 15 items through four rounds of revision. Concept elicitation consistently identified a number of key concepts associated with nocturia. These concepts largely reflected daytime tiredness due to interrupted nighttime sleep and the associated consequences of difficulty in concentration and daytime irritability. Another commonly

### Table 2

Examples of typical statements obtained from concept elicitation

| Domain          | Concept                           | Item number |
|-----------------|-----------------------------------|-------------|
| Sleep           | “My sleep is terribly broken and for me, broken, sleep doesn’t work.” | 1           |
|                 | “I wake up and I’m not as fully rested because I have to wake up at intervals, so I don’t get a complete night’s sleep.” | 2           |
|                 | “It [nocturia] might force me to get up a little bit earlier that I would otherwise. I mean if I look at the clock, as I said, I normally get up at 4:30 AM. If it’s 4:00 AM, I will get up at 4:00 AM, and that will be the start of my day.” | 3           |
|                 | “I feel real sleepy, but I know I can’t lay there... it’s hard to get up but I know I have to get up.” | 4           |
| Tiredness       | “I can be real tired. I can find myself being kind of lethargic in the morning.” | 5           |
|                 | “A lot of times I’ll feel tired.” | 6           |
|                 | “But usually over in the afternoon, sometimes I have to go back to bed for a while. You have to get a little rest.” | 7           |
| Activities      | “Sometimes it’s really difficult at work... if they ask if anybody wants to go home early and I hate it because I want do my full shift and I want the money. But I mean I volunteer to go home.” | 8           |

### Table 3

Concepts included in the INTU questionnaire

| Item number | Concept                  | Domain (daytime or nighttime) |
|-------------|--------------------------|------------------------------|
| 1           | Concentration            | Daytime                      |
| 2           | Tiredness                | Daytime                      |
| 3           | Completing activities    | Daytime                      |
| 4           | Irritability             | Daytime                      |
| 5           | Nocturia anxiety         | Nighttime                    |
| 6           | Restfulness              | Daytime                      |
| 7           | Premature waking         | Nighttime                    |
| 8           | Insufficient sleep       | Nighttime                    |
| 9           | Nocturia bother          | Nighttime                    |
| 10          | Daytime drowsiness       | Daytime                      |
reported concept was related to having difficulty getting back to sleep as a result of getting up in the night and starting the day earlier than desired. Concepts in the INTU were similar to those reported in validation studies of the N-QOL instrument.\textsuperscript{2,5}

The INTU was developed through a robust process of iterative modification and testing, as recommended by current guidelines for the development of PRO instruments and according to recommendations by the FDA reviewing division and COA staff.\textsuperscript{6,9} The criteria for study participant recruitment were chosen to ensure that the instrument was developed in individuals representative of the population intended for use of the INTU questionnaire. Thus, the study population represented men and women equally, was within the expected age range, and had clinically meaningful symptoms of nocturia. In addition, the individuals included in each of the four rounds of interviews were generally representative of the whole study cohort. The findings from each round of interviews were used to modify the questionnaire, with the final INTU representing the cumulative feedback from all 28 participants. Furthermore, all participants reported that it was easy to recall their experiences over a one-day period and that completing the questionnaire on consecutive days would not be burdensome.

This study has several limitations. First, participants in this study may have provided answers that they deem to be socially desirable in an interview setting. For example, when asked how burdensome it would be to complete the questionnaire every evening for three consecutive days, most replied that it was of limited bother. Despite this limitation, querying patients to understand the potential level of burden of completing the questionnaire was important at this stage of instrument development. Another limitation is that the item generation was not informed by a separate concept elicitation phase but rather a concept elicitation process which was conducted prior to the cognitive debriefing in each round of interviews. However, the initial items were developed based on prior qualitative research in patients with nocturia and the results showed consistency across the four rounds of interviews. This suggests that item development based on an initial concept elicitation phase would not have substantially altered the final included items.

5 | CONCLUSIONS

The INTU was devised through a robust process involving iterative patient-directed feedback of a clinically representative population of men and women to ensure the development of a PRO instrument that can accurately capture the impact of nocturia on health and functioning. The INTU builds upon previous research conducted to support existing nocturia-related instruments and uses a same-day recall period to assesses the impact of nocturia on sleep, feeling tired during the day, and concern about having to get up in the night. Participants reported that recalling their experience over a one-day period was easily managed and that completion of the questionnaire in a clinical trial setting would not be burdensome. The INTU development process drew upon the recommendations of current guidance for the development of PRO instruments. The INTU may be a valuable tool in the development of much needed new therapies for nocturia.

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DISCLOSURES

Susan Martin, an employee of RTI Health Solutions, served as a study investigator and has served as a consultant/advisor to Allergan plc. Kristin Khalaf Gillard, an employee of Xcenda, has served as consultant/advisor to Allergan plc. Steven Abrams is an employee of Allergan plc; Linda Cheng and Seymour Fein are employees of Serenity Pharmaceuticals, LLC.

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