Official Title: A Randomized Clinical Trial of 100 Units of Intradetrusor Onabotulinum Toxin A for Refractory Overactive Bladder – Is 10 Injections less painful than 20 Injections?

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Background, Rationale, and Context:

Non-neurogenic Overactive bladder (OAB) is a chronic condition characterized by urinary urgency and frequency and can be associated with urinary incontinence. It can be a particularly bothersome syndrome with a worldwide prevalence of approximately 10.7% and is projected to be as high as 20.1% in 2018 [1]. The American Urological Association (AUA) and the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) have established a combined set of guidelines for the treatment of OAB, amended in 2015, to help the clinician diagnose and treat patients in a tiered approach [2]. First line treatments are aimed at behavioral modifications (fluid management, bladder retraining, urge suppression techniques, pelvic floor muscle exercises, and physical therapy). Second line therapies are oral pharmacologics, and the two classes of medications are the antimuscarinics and a beta-3 agonist. Third line therapies, used to treat the patient with OAB that is refractory to first and second line therapies, include these three options: intradetrusor onabotulinumtoxinA (Botox®, *Allergan, Inc*.), sacral neuromodulation (SNM), and peripheral tibial nerve stimulation (PTNS).

The United States Food and Drug Administration (FDA) has approved a dose of 100 units of Botox® for refractory OAB based on rates of improvement of continence episodes while weighing adverse events [the most common being urinary tract infections (UTIs) and urinary retention requiring clean intermittent catheterization (CIC)]. However, what is not known is the optimal number of injections of the 100 units. The AUA/SUFU OAB guidelines do not recommend a specific number of injection sites. The European Association of Urology consensus report [3] recommends 10 Units/ml per injection (10 one ml injections for 100 units). However, this was not based on randomized trials, and no studies have been done that directly compare different numbers of injection sites. The package insert for Botox® recommends 100 units combined with 10 cc of saline to be distributed in 20 injections (0.5 cc per injection) [4]. However, a literature search involving the methods of administration shows a range of 10 - 30 injections for 100 units of Botox® [3,5,11].

One of the concerns about administering Botox® into the bladder is the patient's comfort during the procedure as he or she is usually awake during this office based procedure. Patient experience is becoming a more important aspect of patient care, and is a marker for which provider are being measured. Currently, there are ongoing studies to assess whether or not 10 injections of Botox delivers the equivalent efficacy of 20 injections of Botox in a national, multi-institutional trial. Uniquely, we would like to assess if there is a difference in the pain of procedure with 10 injections versus 20 injections.

Our hypothesis is that Botox® distributed in 10 injections will result less pain of procedure perceived by the patient compared to the pain perceived by the patients receiving 20 injections.

Objectives:

- **Primary endpoint:** The primary endpoint to be assessed is the difference in pain of procedure experienced by those receiving 100 units of Botox ® in 10 injections versus those receiving 100 units of Botox in 20 injections. Our hypothesis is that those receiving 10 injections will perceive less pain.

- Pain of procedure:
  - Pain of procedure: To assess pain of procedure, we will use the 11 point Numeric Pain Rating Scale (NPRS). We expect that the patients receiving 10 injections will have less pain associated with the procedure. The patients will rate their level of pain immediately following the completion of bladder injections by selecting a whole number from 0 to 10 that represents their level of pain (0 is no pain at all and 10 is the most severe pain) during the procedure. This scale has been validated, and correlates similarly to other pain scales [7].

- **Secondary endpoints:** Secondary endpoints to be assessed will be efficacy, OAB symptoms (nocturia, urgency, and frequency), post void residual volume (PVR) at 2 weeks and 12 week post-procedure, disease specific bother, health related quality of life (HRQoL), the patient's perceptions of change, and adverse events as detailed below:
  - Efficacy: The reduction in mean urge incontinence episodes which will be calculated by averaging the amount of urge urinary incontinence episodes over 3 days as recorded in a bladder diary. Success will be defined as a greater than 50% reduction in urge incontinence episodes after intradetrusor Botox® based on 3-day bladder diaries collected at baseline and 12 weeks post-injection. This outcome measure is consistent with results reported in previous trials involving Botox® for overactive bladder [6].
  - Disease specific bother and HRQoL: To assess OAB symptoms other than incontinence and impact on quality of life, we will administer the Overactive Bladder Questionnaire Short Form (OABq-SF) at baseline, at 2 weeks, and at 12 weeks post-procedure. This is an abbreviated version of the Overactive Bladder Questionnaire (OABq) developed to evaluate the bother and health related quality of life for patients with overactive bladder. The OAB-SF contains 6 items to assess symptom bother and 13 items to assess HRQOL. This questionnaire is commonly used, and has been validated for use in clinical practice [8].
  - PVR at 2 weeks and 12 weeks: To measure PVR at 2 weeks and 12 weeks, we will use a bladder scanner which measures volume based on ultrasound. The provider may also chose to measure PVR by straight catheterization at his or her discretion.
  - Patient's Global Impression of Change (PGIC) scale: In order to help determine the clinical significance of change, we will utilize the PGIC scale [16] administered at 2 weeks and 12 weeks post-injection.

- Adverse events: Specific to intradetrusor injections of Botox®, the most common adverse events are urinary retention requiring intermittent catheterization (approximately 4%) [9] and urinary tract infections (approximately 15.5%-35%) [10]. Patients will be closely monitored for urinary tract infections as they will undergo urinanalysis and assessment of symptoms at their post-operative visits.

Methods and Measures

- **Design:**
  - This study is a randomized clinical trial to assess whether or not 10 injections of 100 units of intradetrusor Botox® toxin is perceived as less painful compared to 20 injections of 100 units of intradetrusor Botox® toxin for the treatment of refractory OAB. Refractory OAB is defined as persistent urinary frequency and urgency despite behavioral modifications, failing a trial of 2 medications (anticholinergics or beta 3 agonists), have a contraindication to the medications, or are unable to tolerate medications due to allergies or side effects.
  - The primary outcome will be assessed by the patient completing the pain of procedure questionnaire, the NPRS, to be completed by the patient immediately after the procedure. The patient will receive the questionnaire from the nurse or medical assistant after the provider has performed the procedure. We will then compare mean value of the NPRS for the 10 injection group to the 20 injection group.
  - Efficacy will be assessed by comparing study participant's reduction in urge urinary incontinence episodes based on a 3 day voiding diary to be shared by the participant at baseline and 12 weeks post-procedure. This diary is dispensed to all patients during their visit prior to procedure visit as a part of standard of care. If subjects demonstrate a 50% reduction in urge incontinence episodes on a 3-day bladder diary, they will be categorized as "treatment success" whereas those who do not will be categorized as "treatment failure." This dichotomous outcome will define efficacy as a secondary endpoint.
  - All eligible participants will be considered for the study. Patients will be counseled about the study in the office setting. Upon enrollment, patients will share a 3-day voiding diary. Diary is dispensed to all patients when they decide to undergo injection procedure. Disease specific bother and health related quality of life questionnaires will be completed following consenting. As per standard of care, urinalysis and post-void residual volume will be measurement. The only assessment in this list that is not part of standard clinical care are the questionnaires. If patients are on medications for

overactive bladder, they will be required to stop at least 3 weeks prior to undergoing the baseline 3 day voiding diary.

After consenting to enrollment in the study, the patients will be scheduled for Botox® injections in the office. Randomization will be performed using random sequence number generation in blocks of 10 with randomization assignment concealed in sequentially numbered opaque envelopes. Randomization will be performed before the study startup by the coordinator using online available tool (sealed envelope). Envelopes with 50% carrying 10 injections instructions, and 50% carrying 20 injections instructions are prepared in advance, sealed, numbered 1 to 50, and stored in a locked cabinet at the Urology clinic at Charlois Blvd. Three envelopes will be carried to the Greensboro Wake Health System during coordinator's scheduled clinic days. And then coordinator will bring those packets back to the Charlois Blvd Urology clinic on a regular base. On the day of the procedure, the provider will select the next numbered envelope that will contain the randomization assignment for the number of injections. Subjects will be blinded to the randomization result. All patients will undergo a urinalysis prior to the procedure. If there is concern for an acute, untreated urinary tract infection, the patient does not undergo the procedure, and is treated with antibiotics while a urine culture is sent. All participants will be given preoperative antibiotics (except aminoglycosides). 100 units of Botox® will be combined with 20 cc saline for the purposes of 20 injections, or 100 units of Botox® will be combined with 10 cc of sterile saline for the purpose of 10 injections. Lidocaine Jelly locally. And the bladder will be instilled with 30ml of Marcaine and 5ml of NaHCo3 solution through a catheter for at least 15 minutes prior to the procedure. Cystoscopy with either a rigid or flexible cystoscope (per surgeon preference) will be performed using sterile technique. The Botox® will be injected in a grid like pattern avoiding the trigone as seen below. Study patients do not know the number of injections received in the bladder. There are two providers in the room for each procedure. Injection counting will be verbalized as Injection 1, Injection 2… to up to Injection 20 by non-injecting provider. A patient and a provider who is injecting will hear total of 20 counts. Providers will know the randomization prior to procedure, and a decision will be cleared between two providers whether to account pseudo injection at odd or even number for patients receiving 10 injections. A patient randomized to 10 injections will receive 10 injections at alternate count. All patients will be informed in advance about the procedure at the time of consenting.The patient will be allowed to void on her own post-procedure. Immediately after the procedure, the patient will receive a questionnaire to rate the pain of procedure using the numeric pain scale. The patient will then be discharged to home.**Figure 1:** Diagram showing sites of injections for patients undergoing 10 injections of 100 units of Botox®.

Figure 1: Diagram showing sites of injections for patients undergoing 10 injections of 100 units of Botox®.

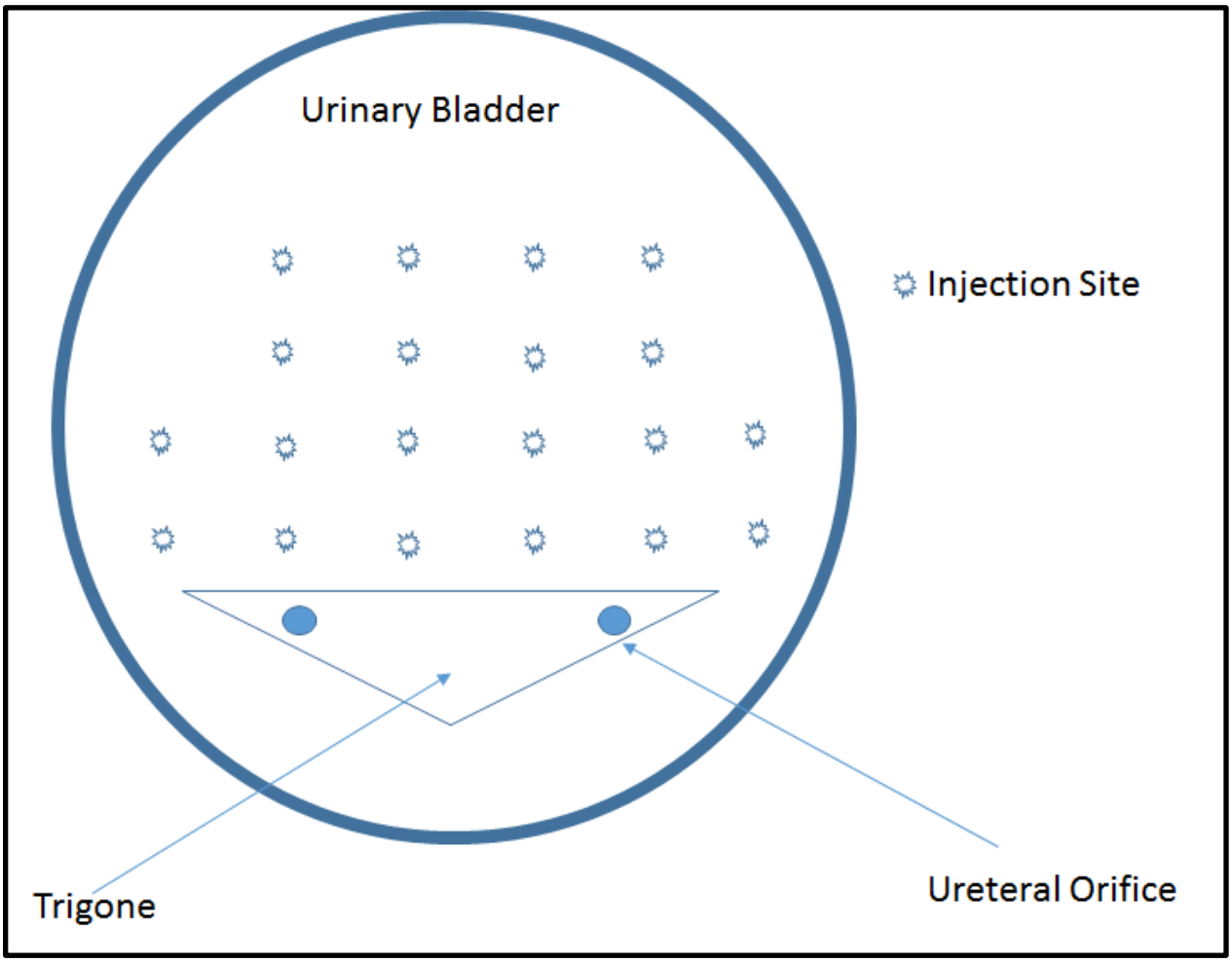

Figure 2: Diagram showing sites of injections for patients undergoing 20 injections of 100 units of Botox®

- At two weeks, the patient will return to clinic for a standard office visit. She will have a post void residual checked using either a bladder scan or catheter, and a urinalysis (urine culture will be sent per clinic protocol). If a urine culture grows any bacteria, and the patient is symptomatic, she will be treated with culture specific antibiotics. She will then be asked about symptoms of a urinary tract infection, if they have been treated for a urinary tract infection, difficulty emptying the bladder, or required intermittent or an

indwelling Foley catheter since the Botox® therapy. Subjects will complete the PGI-C and the OAB-SF. The patient will be sent home with a 3-day bladder diary to complete just prior to the 12-week visit.

- At 12 weeks, the patient will return to clinic and her 3-day bladder diary will be reviewed. A post void residual volume will be checked using either a bladder scan or catheter, and a urinalysis will be sent per standard practice (urine culture will be sent per clinic protocol). If a urine culture grows any amount of bacteria and the patient is symptomatic, she will be treated with culture specific antibiotics. She will then be asked about symptoms of a urinary tract infection, if they have been treated for a urinary tract infection, difficulty emptying her bladder, or required intermittent or an indwelling Foley catheter since the Botox® therapy. She will again take the OABq-SF and PGIC.

- **Setting:**

  - This study will take place at two Urology clinic locations at Wake Forest Baptist Medical Center, 140 Charlois Boulevard in Winston Salem, NC and 3903 North Elm Street in Greensboro, NC.

Subjects Selection Criteria

- **Inclusion criteria:** Subjects must meet the following inclusion criteria in order to be eligible for the study
  1. Female gender
  2. At least 18 years of age
  3. Have already decided to undergo intradetrusor Botox® injections for treatment of refractory overactive bladder.
  4. Able and willing to learn clean intermittent catheterization (or care provider is willing and able to perform intermittent catheterization).
  5. Understands and is willing to undergo follow up and complete questionnaires as described in this protocol
  6. Able to give informed consent
- **Exclusion Criteria:**
  1. Male gender
  2. Neurological conditions (Examples: Cerebral vascular accident within 6 months prior to treatment, Parkinson's disease, Multiple Sclerosis, and Spina Bifida).
  3. Acute urinary tract infection
  4. Treatment with Botox® toxin for other conditions
  5. Allergy to Botox® toxin
  6. Hematuria that has not been worked up
  7. Known bladder malignancy

8. Previous history of bladder augmentation
9. Currently pregnant (with no plans to become pregnant within 6 months of enrollment) or breastfeeding
10. Currently taking aminoglycoside antibiotics
11. PVR >150 cc (measured by bladder scan or by catheterization) prior to enrollment
12. History of bladder pain syndrome.

- **Sample Size:**

  - This study is unique as there are no previous trials assessing pain of procedure associated with intravesical administration of bladder Botox. To calculate sample size in the study, we will assume an effect of size of 1. We expect that patients receiving 20 injections will be within the moderate pain range (between 5 to 7 on the NPR scale). Therefor we will assume a mean NPR rating for patients receiving 20 injections would be 6 with a standard deviation of 2. Patients receiving 10 injections will be expected to have less pain and be in the mild pain range (from 1 to 4 on the NPR scale). Based on this, we would need 16 patients in each group. Accounting for a 20% drop out rate, we would need to accrue 20 patients in each group.

- **Statistical Analysis:**

  1. Primary endpoint: Each patient will be asked to rate her pain level of procedure by completing the NPRS immediately after her procedure. The mean NPRS score of each group (10 injections vs 20 injections) will be calculated and compared using a paired T test.

  2. Secondary endpoints

     - Each patient's mean number of urge urinary incontinence episodes will be calculated by averaging the number of urge urinary incontinence episodes collected over 3 days as recorded on a bladder diary. This will be calculated pre-intervention at baseline and at 12 weeks. As previously described, "treatment success" is defined achieving greater than 50% reduction in the number of urge urinary incontinence episodes at 12 weeks after treatment with Botox®. A "treatment failure" will be defined as achieving less than 50% reduction in the number of urge urinary incontinence episodes at 12 weeks after treatment with Botox®. Our hypothesis is that there will be more significantly "treatment responders" in patients receiving 20 injections compared to 10 injections. To assess for clinical significance Chi square (X^2) will be used.

- OABq-SF and PGIC collected from the group receiving 20 injections and the group receiving 10 injections. The mean will be calculated for each of the outcomes and for each of the groups. The result will be compared using paired t-test.

- We will compare the mean number of patients with urinary retention and UTIs in patients in both groups (those receiving 20 injections and those receiving 10 injections). To test for significance we will use the t-test.

Interventions and Interactions

- This study will use the FDA approved dose for refractory overactive bladder which is 100 units of onabotulinum toxin A (Botox®).
- Per surgeon preference, a flexible cystoscope or a rigid cystoscope will be used to inject the Botox® in the wall of the bladder.
- Injections will be in a grid-like fashion.
- We will use a 3 day bladder diary obtained from the International Urogynecological Association (IUGA) for baseline and 12 week follow up. (Appendix 1)
- Immediately after the treatment, patients will be asked to rate their pain using the Numeric Pain Scale. Please see appendix.
- Patients will be assessed for adverse events, symptom specific and global quality of life using the form in the appendix.
- All surveys will be handed to the patients by nursing. Patients will fill out the forms before seeing a physician.

Outcome Measures: Outcome measures to be assessed include: pain of procedure, urge urinary incontinence episodes, efficacy, bother, HRQoL, PGIC, urinary tract infection, urinary retention requiring catheterization.

Calendar of Events:

Form/Intervention	Baseline	Day of Procedure (Botox Injections)	2 weeks	12 weeks
ICF	x			
PVR	x		x	x
Urinalysis	x	x	x	x
Study Inclusion Form	x			
Bladder Diary	x	*		x
Randomization		x		
Pain Scale		x		
OABq-SF	x		x	x
PGIC			x	x
Adverse Events Questionnare			x	x
Completion of Study Form				x

*: Collect the completed Diary

Human Subjections Projection

Subject Recruitment Methods: Patients evaluated in the office setting and who are diagnosed with refractory overactive bladder will be counseled regarding their options for treatment. The 3 treatment options include: intradetrusor injection of onabotulinum toxin, sacral neuromodulation, and percutaneous tibial nerve stimulation. After weighing the risks and benefits of all procedures, patients opting for therapy with onabotulinum toxin A will be considered for the trial. A member of the study team will discuss eligibility, review the inclusion/exclusion criteria, and answer questions. Informed consent will be signed. Three day diary provided during the at visit as per Standard of Care will be reviewed belonging all participants in order to capture the information. Any patient who wishes to withdraw from the study may do so at any time. If the patient chooses to withdraw, they will be presented with the option to allow the data collected up to that point to be retained, or have it removed.

All data will be kept on a secure password protected and encrypted hospital issued computers and contained within password protected files. Source documents will be kept in a locked drawer on Wake Forest Baptist Health property.

Informed Consent: Signed informed consent will be obtained from each subject. The principal investigator and co-investigators will obtain informed consent. The informed consent process will take place in the Urology offices in either Winston-Salem, NC or Greensboro, NC.

Confidentiality and Privacy: Confidentiality will be protected by collecting only the information needed to assess study outcomes, minimizing the collection of any information to the fullest extent possible that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, stored separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Following data collection, subject identifying information will be destroyed 3 years after closure of the study by shredding, consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring: The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff.

Reporting of Unanticipated Problems, Adverse Events or Deviations: Any unanticipated issues, serious and unexpected adverse events, deviations or protocol changes will be promptly reported to the principal investigator or member of the research team, the IRB, sponsor, and appropriate government agency if appropriate.

Bladder Diary Sample

IUGA
international urogynaecological association

This simple chart allows you to record the fluid you drink and the urine you pass over 3 days (not necessarily consecutive) in the week prior to your clinic appointment. This can provide valuable information.

Please fill in approximately when and how much fluid you drink and the type of liquid.

Please fill in the time and amount (in mls, or ounces) of urine passed, and mark with a star if you have leaked or mark with a "P" if you have needed to change your pad.

Here is an example of a filled chart to help you complete your own more easily.

Date/Time DD.MM.YY	Liquid Intake (ml)	Volume of Urine (ml)	Leaks	Pad Change
21.02.06			*	
0215		150		
0715		250		
0800	1 cup of coffee			
0820		60	*	P
0930	Cup orange juice		*	
1000		100		
1200	2 mugs coffee			
1400		300		
1430		20		
1530	Cup of tea 200ml	200		
1600				
1800	Cup of tea 200ml		*	P
1900		100	*	
2000	Glass beer 200ml	20		
2030	Glass wine 50ml		*	
2200				P
2300		150		

IUGA Office | office@iuga.org | www.iuga.org

Appendix 1: IUGA 3 day Bladder Diary Sample

Date/Time DD.MM.YY	Liquid Intake (ml)	Volume of Urine (ml)	Leaks	Pad Change

IUGA
International urogynaecological association

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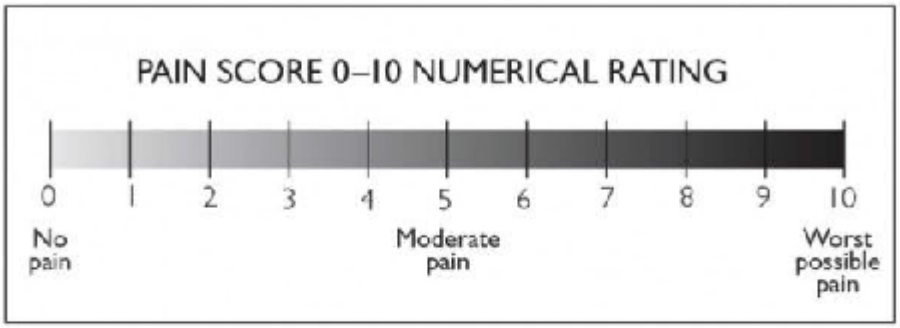
Appendix 1: IUGA 3 Day Bladder Diary to be completed by the patient.

Medical Record Number:
Date of Procedure:

Please rate the pain that you experienced during this procedure using the scale below.



Answer (Please write a number from 0 to 10): _____

Appendix 2: Pain assessment to be completed immediately after the procedure

	Medical Record Number: _____		
	Date: _____		
1	Since your last visit, have you been diagnosed with a UTI?	Yes	No
2	Do you have any of the following symptoms?		
3	- Burning with urination	Yes	No
4	- Blood in the urine	Yes	No
5	- Fever	Yes	No
6	Since your last visit, have you been evaluated in the emergency room?	Yes	No
7	Since your last visit, have you been evaluated by your primary doctor?	Yes	No
8	Since your last visit, have you required a urinary catheter, (intermittent or indwelling)?	Yes	No
9	Since your last visit, have you seen blood in your urine that lasted more than 48 hr.?	Yes	No
10	Since your last visit, have you had difficulty swallowing?	Yes	No
11	Since your last visit, have you had difficulty breathing?	Yes	No

Appendix 3: Follow up Adverse Event questionnaire to be completed at 2 weeks and12 weeks

Appendix A. OAB-q SF and Scoring Manual

OAB-q Short-Form

This questionnaire asks about how much you have been bothered by selected bladder symptoms during the past 4 weeks. Please place a ✓ or x in the box that best describes the extent to which you were bothered by each symptom during the past 4 weeks. There are no right or wrong answers. Please be sure to answer every question.

During the past 4 weeks, how bothered were you by...	Not at all	A little bit	Some-what	Quite a bit	A great deal	A very great deal
1. An uncomfortable urge to urinate?	☐	☐	☐	☐	☐	☐
2. A sudden urge to urinate with little or no warning?	☐	☐	☐	☐	☐	☐
3. Accidental loss of small amounts of urine?	☐	☐	☐	☐	☐	☐
4. Nighttime urination?	☐	☐	☐	☐	☐	☐
5. Waking up at night because you had to urinate?	☐	☐	☐	☐	☐	☐
6. Urine loss associated with a strong desire to urinate?	☐	☐	☐	☐	☐	☐

Appendix 4: OAB Short Form for Bother to be completed at baseline, 2 weeks and 12 weeks.

The previous questions asked about your feelings about individual bladder symptoms. For the following questions, please think about your overall bladder symptoms in the past 4 weeks and how these symptoms have affected your life. Please answer each question about how often you have felt this way to the best of your ability. Please place a ✓ or x in the box that best answers each question.

During the past 4 weeks, how often have your bladder symptoms	None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
1. Caused you to plan "escape routes" to restrooms in public places?	☐	☐	☐	☐	☐	☐
2. Made you feel like there is something wrong with you?	☐	☐	☐	☐	☐	☐
3. Interfered with your ability to get a good night's rest?	☐	☐	☐	☐	☐	☐
4. Made you frustrated or annoyed about the amount of time you spend in the restroom?	☐	☐	☐	☐	☐	☐
5. Made you avoid activities away from restrooms (i.e., walks, running, hiking)?	☐	☐	☐	☐	☐	☐
6. Awakened you during sleep?	☐	☐	☐	☐	☐	☐
7. Caused you to decrease your physical activities (exercising, sports, etc.)?	☐	☐	☐	☐	☐	☐
8. Caused you to have problems with your partner or spouse?	☐	☐	☐	☐	☐	☐
9. Made you uncomfortable while traveling with others because of needing to stop for a restroom?	☐	☐	☐	☐	☐	☐
10. Affected your relationships with family and friends?	☐	☐	☐	☐	☐	☐
11. Interfered with getting the amount of sleep you needed?	☐	☐	☐	☐	☐	☐
12. Caused you embarrassment?	☐	☐	☐	☐	☐	☐
13. Caused you to locate the closest restroom as soon as you arrive at a place you have never been?	☐	☐	☐	☐	☐	☐

Appendix 5: OAB Short Form for Bother to be completed at baseline, 2 weeks and 12 weeks.

MRN: _____
DOB: _____
Date: _____

Since beginning treatment at this clinic, how would you describe the change (if any) in ACTIVITY LIMITATIONS, SYMPTOMS, EMOTIONS and OVERALL QUALITY OF LIFE, related to your condition? (tick ONE box).

No change (or condition has got worse)	[ ]	1
Almost the same, hardly any change at all	[ ]	2
A little better, but no noticeable change	[ ]	3
Somewhat better, but the change has not made any real difference	[ ]	4
Moderately better, and a slight but noticeable change	[ ]	5
Better, and a definite improvement that has made a real and worthwhile difference	[ ]	6
A great deal better, and a considerable improvement that has made all the difference	[ ]	7

Appendix 6: PGI scale to be completed by patients at week 2 and week 12.

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