Protocol Number	KPSC-US-IBT-01
Title	Intradetrusor Botulinum Toxin A: Are less injections better?
Study Phase	N/A
Investigator Name	Carly Crowder, MD
Department	Obstetrics and Gynecology
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Street Address	6650 Alton Pwky
City, State and Zip code	Irvine, CA 92618
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Email Address	crowderc@hs.uci.edu
Study Site Name	Kaiser Permanente- – Sand Canyon
Street Address	6650 Alton Pwky
City, State and Zip code	Irvine, CA 92618
Version Number and Date	V2_09 Mar 2022

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Contract Research Organization
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
BTA	Botulinum Toxin A
UTI	Urinary Tract Infection
OAB	Overactive Bladder
UUI	Urinary Urgency Incontinence
PVR	Post Void Residual
SNM	Sacral Neuromodulation
PTNS	Percutaneous Tibial Nerve Stimulation
OAB-Q (LF)	Overactive Bladder Questionnaire (Long Form)
VAS	Visual Analogue Scale
PGI-I	Patient Global Impression – Improvement

PROTOCOL SUMMARY

Title	Intradetrustor Botulinum Toxin A: Are less injections better?
Short Title	Bladder Botox
Protocol Number	KPSC-US-01
Study Phase	N/A
Study Site(s)	Kaiser Permanente – Sand Canyon, Kaiser Permanente -Anaheim, UCI
Number of Subjects	Approx 40 at KPSC, 60 at UCI, 20 at PSJH
Study Arms	2 arms: One Botox® injection site (study) or 10 Botox® injection sites (control/standard of carl)
Indication	Overactive Bladder (Urinary urgency and frequency) and urinary urgency incontinence
Primary Purpose	Our primary objective is to evaluate the efficacy of intradetrusor Botox® for treatment of OAB or UUI based on patient questionnaire scores (OAB-q) in one versus ten Botox® injection [s].
Overview of Study Design	We plan for a prospective, single-blinded, non-inferiority analyzed, randomized controlled trial. We will evaluate the efficacy, safety, and tolerability of one intradetrusor Botox® injection (study) versus ten injections (control/standard of care). The patient will be blinded . There will be 1:1 randomization.
Investigational Product Administration	Not applicable, no investigational product.
Eligibility Criteria	Inclusion criteria: Female, at least 18 years old with diagnosis of overactive bladder (urinary urgency or frequency, OAB) or urinary urgency incontinence (UUI) Exclusion criteria: • Have a diagnosis of neurogenic bladder • Received intravesical botox injections within prior 6 months • Current treatment with either: SNM, PTNS, or OAB medications – need wash out as below • SNM – turn device off for at least 2 weeks prior to procedure, off during 3-month follow up window • PTNS – no treatments within 2 weeks of start, none during 3-month post-procedure follow up window • OAB meds – 2 week wash out period prior to injection, none during 3-month post-procedure follow up window

	• Currently pregnant or trying to get pregnant • Contraindications to Botox® - hypersensitivity to Botox®, inability to self-catheterize/refusal to have indwelling catheter • Have a UTI (can enroll after treatment) • Have urinary retention (PVR>150cc on two occasions) • Do not speak English or Spanish
Study Endpoint	The primary outcome variable will be the OAB-q symptoms severity subscale score (urinary symptom questionnaire) as a marker of efficacy. The secondary outcome variables will include UTI rate, PVR, urinary retention, inter-injection interval, catheter use within 3 months, PGI-I, and VAS pain score.
Statistical Methods	The target sample size was determined by using the typical standard deviation of the OAB-q score (20 points per literature review) and the known minimally important clinical difference of 10 points of the OAB-q severity subscale, our primary outcome. Using this data, we calculated the sample size of N=102 maximum total (expect to enroll ~40 at KP, ~60 at UCI, ~20 at PSJH), 51 subjects in each arm for a 80% power with 5% significance level. With an estimated 15% lost to follow up rate, we calculated need to enroll 116 subjects.

1 INTRODUCTION

1.1 Background

Intradetrusor (bladder) Botulinum toxin A (BTA or Botox®) is a well-established treatment for urinary urgency incontinence (UUI). [1,2] While this treatment's efficacy in comparison to alternative therapies including anticholinergic medications and sacral neuromodulation for treatment of UUI has been studied, the ideal number of injection sites within the bladder has not been well established.[3,4] Intradetrusor BTA injections are often completed as an office procedure while the patient is awake. Each injection site can cause discomfort for the patient during the procedure. Urinary tract infection and urinary retention are risks associated with this procedure and could potentially be related to number of injection sites. Currently, there is a lack of information in the literature regarding the optimal number of intravesical BTA injection sites.

Prior studies evaluated efficacy using 100u BTA spread across 20 injections sites, however current practices at local institutions safely use 10 injections sites based on studies showing similar effect and adverse event profiles between use of 10, 20, and 40 injection sites.[5,6] Research using animal models has shown diffuse distribution of BTA within the entire detrusor muscle after just a single BTA injection at one site.[7] This has been corroborated in human studies.[8] A recently published observational pilot study shows promise for single site intradetrusor Botox® injection as it reported a lower rate of urinary retention and similar durability.[9] Similar clinical efficacy with only one to three intravesical BTA injection[s] has also been reported.[10]

1.2 Hypothesis

We hypothesize that one injection of intradetrusor Botox® will have similar efficacy to ten injections, better tolerability, due to decreased procedure time and less pain, along with potential for lower adverse event rates, specifically urinary retention and urinary tract infections.

2 OBJECTIVES AND PURPOSE

2.1 PRIMARY OBJECTIVE

Our primary objective is to evaluate the efficacy of intradetrusor Botox® in an outpatient population based on patient questionnaire scores (OAB-q) in one versus ten Botox® injection [s].

The primary outcome variable will be the OAB-q (urinary symptom questionnaire) symptom severity subscale score. The secondary outcome variables will include UTI rate, PVR, urinary retention, inter-injection interval, catheter use within 3 months, PGI-I, and VAS pain score.

3 STUDY DESIGN

We plan for a prospective, single-blinded, non-inferiority randomized controlled trial. We will evaluate the efficacy, safety, and tolerability of one intradetrusor Botox® injection (study) versus ten injections (control/standard of care). The patient will be blinded. There will be 1:1 randomization. The physician doing the procedure will not be blinded.

3.1 Treatment Arms

There will be two arms for this trial: study arm (one injection) and control arm (10 injections). Across all sites we will plan to enroll 116 maximum participants with anticipated enrollment at Kaiser Permanente being approximately 40 participants.

3.2 Study Duration

We anticipate completion of enrollment with approximately 1.5 years. Each subject will participate in the study for 3 months (one 3 week post-procedure visit and one 3 month post-procedure visit). Charts will be reviewed for approximately 6-12 months after procedure completion.

4 STUDY PRODUCT INFORMATION

4.1 Description

Botox® (onabotulinumtoxina) is an FDA approved treatment of OAB, urinary urgency and frequency, and urinary urgency incontinence via intradetrusor injection. A standard approved dose of 100units will be injected into the detrusor muscle. There is no investigational drug being studied in this trial.

4.2 Dosage, Preparation and Administration

The physician will inject 10 mL of (100u/10mL) Botulinum Toxin A in either one or ten sites located in the midline, supra-trigonal posterior bladder wall at a depth of 3mm into the detrusor. Each participant will undergo one injection procedure for the duration of the study.

4.3 Toxicity and Safety Information

The most common adverse reactions associated with intradetrusor administration of Botox® include urinary tract infection and urinary retention. These will be monitored as described below in adverse events section.

4.4 Concomitant Medications/ Treatments

Current treatment with either: SNM, PTNS, or OAB medications – need wash out as below:

1. SNM – turn device off for at least 2 weeks prior to procedure, off during 3-month follow up window
2. PTNS – no treatments within 2 weeks of start, none during 3-month post-procedure follow up window
3. OAB meds – 2 week wash out period prior to injection, none during 3-month post-procedure follow up window

5 SELECTION AND WITHDRAWAL OF PATIENTS

Inclusion Criteria

1 Female
2 18 years old or greater
3 Diagnosis of overactive bladder (urinary urgency or frequency, OAB) or urinary urgency incontinence (UUI)

Exclusion Criteria

1 Have a diagnosis of neurogenic bladder
2 Received intravesical Botox® injections within prior 6 months
3 Current treatment with either: SNM, PTNS, or OAB medications – need wash out as below
4 SNM – turn device off for at least 2 weeks prior to procedure, off during 3-month follow up window
5 PTNS – no treatments within 2 weeks of start, none during 3-month post-procedure follow up window
6 OAB meds – 2 week wash out period prior to injection, none during 3-month post-procedure follow up window
7 Currently pregnant or trying to get pregnant
8 Contraindications to Botox® - hypersensitivity to Botox®, inability to self-catheterize/refusal to have indwelling catheter
9 Have a UTI (can enroll after treatment)
10 Have urinary retention (PVR>150cc on two occasions)
11 Do not speak English or Spanish

Withdrawal Criteria

Subjects are only receiving one procedure as part of the study, thus would only be withdrawn prior to undergoing the procedure if they had exclusion criteria or voluntarily withdrew.

6 STRATIFICATION/ RANDOMIZATION SCHEME

Subjects will be randomized via permuted blocks in a 1:1 fashion to either the study group (1 injection) or the control/standard of care group (10 injections). The pre-assigned randomization by permuted block design will be determined at the time of the procedure by opening of a sealed, opaque envelope containing the group allocation.

7 ASSESSMENT OF EFFICACY AND SAFETY

7.1 Adverse Events Reporting

7.1.1 Adverse Event Definition

Adverse Event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

All adverse events, including those that are reported by the patient spontaneously, those the study investigator observes, and those that the study investigator elicits in response to open-ended questions. Recorded adverse events should be assessed by the study investigator indicating the causal relationship of the event with the study drug and whether it meets the criteria for a Serious Adverse Event.

7.1.2 Time Period and Frequency for Event Assessment and Follow-up

Adverse events will be collected from the procedure date through at least 3 months after the Botox® injection procedure.

7.1.3 Serious Adverse Event Definition

SERIOUS ADVERSE EVENT (SAE) is an adverse event or suspected adverse reaction if, in the view of either the study investigator, meets one or more of the following criteria:

- Results in death
- Is a life-threatening adverse event (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in a congenital anomaly/ birth defect
- An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

7.1.4 Serious Adverse Event Reporting

If the site personnel identifies a potential SAE the Investigator will be notified immediately. If the study investigator determines that the adverse event meets the criteria for an SAE, the Investigator will report the event as follows: document the SAE in the adverse event log. t The study investigator will also notify the KPSC Institutional Review Board (IRB) of unanticipated SAEs within 10 business days per the KPSC IRB SOP 502, Principal Investigator Reportable Event and Incident Requirements.

8 STUDY SCHEDULE: CLINICAL/ LABORATORY EVALUATIONS

8.1 Study Procedure

8.1.1 Informed Consent

Subjects will typically have the time between their clinic initial/consultation visit and their procedure appointment (typically at least 1 week) to consider whether to consent. If the study is not discussed at their prior visit or via telephone script prior to procedure appointment, subjects will be given up to 60 min to consider and ask the Investigator questions. Participants will be consented by the Principal Investigator or any of the physician co-investigators who will be performing the Botox® procedure. The participant will be provided a copy of the signed informed consent.

8.1.2 Eligibility Review

Eligibility will be assessed by review of inclusion and exclusion criteria posted in all recruitment locations by co-investigators. After consent and enrollment the participants will be screened and randomized via permuted blocks in a 1:1 fashion to either the study group (1 injection) or the control group/standard of care (10 injections). The pre-assigned randomization by permuted block design will be determined at the time of the procedure by opening of a sealed, opaque envelope containing the group allocation.

Pre-Procedure Requirements
Prior to the procedure each subject will have the following (at either prior/consultation visit or procedure visit see study calendar below):

[ ] sign consent form
(prior to any non-standard of care procedures)
[ ] Post-void residual
[ ] Urinalysis (formal UA OR poct udip)
[ ] OAB-Q LF Questionnaire completion

8.1.3 Study Procedure

Botox Injection Procedure

Arm 1: 1 injection
Subjects will be blinded to the allocation group by turning the cystoscope screen away from patient. Cystoscopic injection will be standardized using an injection cystoscope and 100-200 mL of intravesical fluid. Subjects undergoing the procedure in clinic will receive a lidocaine instillation prior to the procedure along with a urethral lidocaine jelly. The physician will inject 10 mL of (100u/10mL) Botulinum Toxin A in one midline, supra-trigonal posterior bladder wall site at a depth of 3mm, as diagramed below. The bladder trigone and ureteral orifices will not be injected. Each subject will undergo a single injection procedure as part of this trial. Each subject will void prior to leaving clinic.

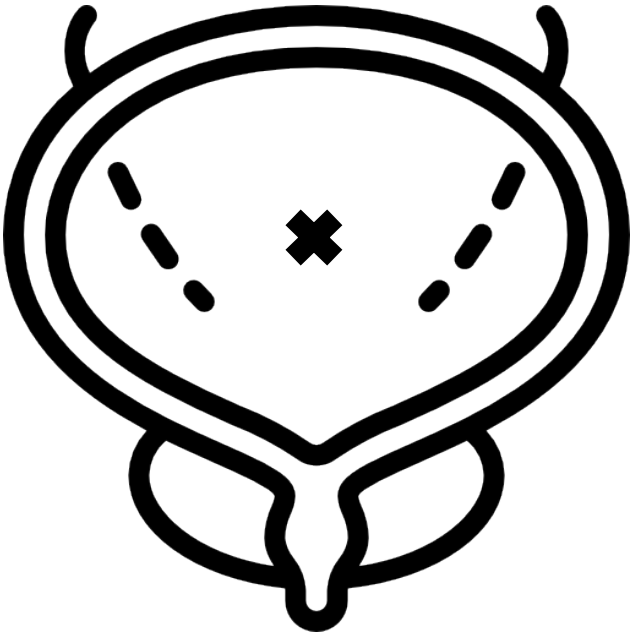

Fig 1: 1 injection location

Arm 2: 10 Injections

Subjects will be blinded to the allocation group by turning the cystoscope screen away from patient. Cystoscopic injection will be standardized using an injection cystoscope and 100-200 mL of intravesical fluid. Subjects undergoing the procedure in clinic will receive lidocaine instillation prior to the procedure along with a urethral lidocaine jelly. The physician will inject 10 mL of (100u/10mL) Botulinum Toxin A in ten 1mL aliquots at ten supra-trigonal posterior bladder wall sites at a depth of 3mm, as diagramed below. The bladder trigone and ureteral orifices will not be injected. Each subject will undergo a single injection procedure as part of this trial. Each subject will void prior to leaving clinic.

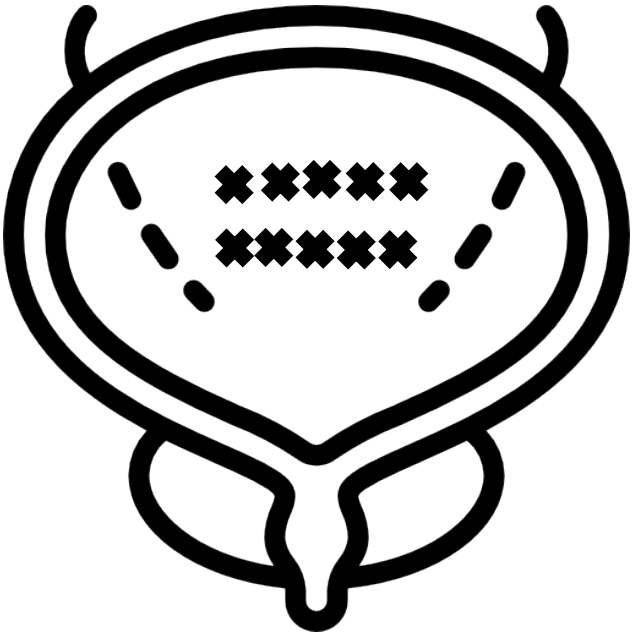

Figure 2: Arm 2: 10 injection locations

Post-Procedure Requirements
[ ] Confirm ability to void after procedure
[ ] Subject completes visual analogue scale of pain
[ ] Procedure note using study dotphrase: .procbotoxstudy
[ ] RX prophylactic antibiotic
- Macrobid 100 mg BID x 3 day
  OR 2nd line if allergies
- Bactrim DS BID x 3 day

3 week follow up visit

[ ] PVR
[ ] OAB-Q LF

3 month follow up visit

[ ] OAB-Q LF
[ ] PGI-I

8.2 Clinical Evaluations

8.2.1 Clinical Evaluation

Subjects will be screened at their initial consultation visit for inclusion in the study. If the screening exams, tests and/or procedures allow and the subject desires to enroll, then the subject will have the following procedures and tests done. This study includes 3 visits which will take

about 60 minutes each. These will include a procedure visit, a 3-week follow up visit, and a 3 month follow up.

1. Procedure visit for intradetrusor Botox® injection, collection of pre-procedure OAB-q, VAS pain scale after procedure

2. 3-week follow up visit, including collection of post-void residual via urethral catheterization or bladder scan (ultrasound) and post-procedure OAB-q

3. 3-month follow up visit, either in person or via telephone with collection of OAB-q and symptoms improvement questionnaire (PGI-I)

8.2.2 Adverse Event Assessment

Participants will be assessed for adverse events from the time of their injection procedure through at least 3 months post procedure. There will be specific evaluation for urinary retention (PVR collected at 3 week follow up visit) and UTI (UA pre-procedure and UCx post-procedure if symptomatic). See Section 7.1 regarding adverse event reporting.

8.3 Laboratory Evaluations

8.3.1 Insert Laboratory Evaluation

A standard of care lab urinalysis or clinic point of care urine dip evaluation will be collected prior to the Botox® injection procedure. There will not be any other standard required labs. If participants are exhibiting UTI symptoms, a standard of care work up with urine culture will be completed.

8.4 Schedule of Assessments

Procedures				
	Consultation clinic visit (prior to study enrollment)	Procedure Visit	3 wk Follow-Up	3 month Follow-Up
Estimated visit time	60min	60 min	60 min	60 min
Recruit	X			
Urinalysis	X			
PVR	X		X	
Sign Consent	X	OR X		
Questionnaire (OAB-q LF)	X	OR X	X	
VAS-Pain Score		X (after procedure)		

Questionnaire (OAB-q LF, PGI-I)				X
Telephone Call (if unable to present for in-person visit)				X

9 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

The outcome status (in terms of toxicity, response, reason off study, progression, and survival) of all eligible patients will be reported. All eligible patients who begin treatment will be included in the analysis of efficacy, safety, and tolerability of the Botox® procedure.

9.1 Primary Endpoints

The primary outcome variable will be the OAB-q symptoms severity subscale score (urinary symptom questionnaire) as a marker of efficacy.

9.2 Secondary Endpoints

The secondary outcome variables will include UTI rate, PVR, urinary retention, inter-injection interval, catheter use within 3 months, PGI-I, and VAS pain score.

10 DATA HANDLING AND RECORD KEEPING

10.1 Source Documentation

Documentation that will be considered as source will be the electronic medical records and questionnaires (OAB-Q, PGI-I, and VAS-pain).

10.2 Case Report Forms

10.3 CRF attached as appendix. The electronic medical record and questionnaires (OAB-Q, PGI-I, and VAS-pain) will be considered data sources. Study data will be captured using REDCap for data management purposes.Record Retention

Data will be stored securely in REDCap and retained through presentation and publication of study results. At site for 1 year after the IRB has closed out the study. Following that all study related documents will be archived for 15 years at Iron Mountain Retention facility (8700 Mercury Lane, Pico Rivera, CA 90660).

10.4 Data Management

Data will be stored securely in KPSC REDCap. This data will be encrypted and password protected on the KPSCnetwork via REDCap. Only delegated study personnel will have access to the database.

11 STUDY OVERSIGHT

11.1 Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) has been chartered and will meet as specified in the DSMB charter agreement to assist with safety oversight. The DSMB will report back to the PI. See Appendix D, DSMB Charter for details.

11.2 Study Site Monitoring

Internal monitoring of sites will be conducted quarterly by the PI and site lead investigators, Dr. Crowder, Dr. Whitcomb, Dr. Brueseke, respectively. The monitoring will be done remotely through scheduled teleconferences with the lead investigator and/or designee. On-site visits will also be conducted quarterly. See satellite site management plan, appendix E for details.

12 STATISTICAL CONSIDERATIONS

12.1 Study Hypothesis

We hypothesize that one intradetrusor Botox® injection site has similar efficacy to ten injections sites based on OAB-Q symptoms severity score change from pre-procedure to 3-week post-procedure with a minimal clinical important difference of 10.

12.2 Sample Size Considerations

The target sample size was determined by using the typical standard deviation of the OAB-q symptom severity score (20 points per literature review) and the known minimally important clinical difference of 10 points of the OAB-q severity subscale, our primary outcome. Using this data, we calculated the sample size of N=102 maximum total (expect to enroll ~40 at KP, ~60 at UCI, ~20 PSJH), 51 subjects in each arm for an 80% power with 5% significance level. Based on review of prior clinical data at UCI and KP, we expect to complete enrollment within 1 – 1.5 years. With an estimated 15% lost to follow up rate, we calculated need to enroll 116 subjects.

12.3 Final Analysis Plan

We will describe the study population, including patient age, race/ethnicity, baseline severity scores (OAB-Q), BMI, medical history (prior surgery, menopausal status, prior Botox, etc.), overall, by arm, and stratified by study site (KPSC, UCI, PSJH). We will summarize continuous measures using means and standard deviations and categorical measures using percentages. We will compare study arms using the t-test or Fisher's exact test, as appropriate.

We will examine the outcome measures (OAB-Q and any secondary measures) to determine whether they are approximately normally distributed. If not, we will apply a

transformation prior to analysis to make the analytic variable approximately normal. If no transformation successfully achieves approximate normality, we will apply non-parametric tests for analysis, including Wilcoxon's rank-sum test instead of the t-test and quantile regression instead of linear regression.

We will analyze the main study outcome (OAB-Q score) initially using a t-test to compare the two study arms, overall and stratified by study site. We will further analyze the outcome using generalized estimating equations to account for correlation within study sites. These models will adjust for any potential differences in age, race/ethnicity, baseline severity scores, or any other baseline measures, and will account for any potential differences between study sites.

Secondary outcomes will be analyzed in the same manner as the primary outcome.

Primary analyses will be performed using intention-to-treat to determine study arm. If multiple individuals are not treated according to the randomization plan, we will perform a sensitivity analysis using as-treated, per-protocol study arms.

For any individuals who are lost to follow-up, we will first compare those individuals who are lost to those who complete follow-up in terms of demographics, baseline characteristics and any outcome assessments prior to the time that they are lost to follow-up. For primary analysis of OAB-Q scores, we will analyze complete data including only those who have completed the follow-up questionnaires within the prescribed timeframes. If more than 10% are lost to follow-up, we will additionally perform multiple imputation in an attempt to capture data of those lost to follow-up.

13 REGISTRATION GUIDELINE

The patients will be enrolled and registered for the study in person, however if needed this number can be used: 833-574-2273. In order to register a patient the following forms and records will be needed: informed consent, confirmation of meeting inclusion/exclusion criteria via checklist review, Screening Enrollment Log, Patient Enrollment Log,Patient Screening #, Patient ID Log, completion of pre-procedure OAB-Q. Patient will be randomized via permuted block design in a 1:1 fashion to one of the two arms, Arm 1: 1 Injection or Arm 2: 10 injections at their Botox® procedure visit.

14 BIOHAZARD CONTAINMENT

Not applicable.

15 ETHICAL AND REGULATORY CONSIDERATIONS

All institutional and Federal regulations concerning the Informed Consent form will be fulfilled. The study will be conducted in adherence to ICH Good Clinical Practice.

15.1 Institutional Review Board

This study protocol, the informed consent form(s), any information intended for distribution to subjects, and any relevant supporting information will be submitted to KPSC IRB by the Principal Investigator and review and approved by KPSC IRB prior to initiation of the study.

The Principal Investigator is responsible for submitting all reportable events as defined by KPSC-IRB SOP-502 to KPSC IRB within the appropriate reporting periods.

15.2 Informed Consent Process

Written informed consent, in compliance with 21 CFR 50 will be obtained before any study-related procedures are initiated. Informed consent will be obtained from each patient or patient's legally authorized representative (LAR) or the patient's legal guardian. Informed consent includes the principle that it is critical that the individual be informed about the potential risks and benefits of participating in this study. This information will allow individuals to make a personal risk-versus-benefit decision and understand the following general principles:

1. Participation in this program is entirely voluntary.
2. Patients may withdraw from participation in this program at any time without penalty or loss of benefits to which they are otherwise entitled.
3. Refusal to participate in this study involves no penalty.
4. The individual is free to ask any questions that will allow him/her to understand the nature of this study.

15.3 Exclusion of Women, Minorities, and Children (Special Populations)

This study will enroll women and minorities, specifically Spanish speakers. Children will not be enrolled as intradetrusor Botox® is not approved for treatment of OAB or UUI in a pediatric population. Currently pregnant or trying to get pregnant are excluded.

15.4 Privacy and Confidentiality

All subject identifiers and PHI will be recorded and maintained electronically in RedCap. Dr. Crowder as PI will have access to all PHI along with all other co-investigators during the process of their clinical duties as the physicians enrolling and completing the study procedure.

15.5 Future Use of Stored Specimens and Other Identifiable Data

There will not be specimens stored in this study. Participants will have opportunity to agree to future use of data within consent form.

16 REFERENCES/ATTACHMENTS

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17 APPENDICES

Appendix A: Case Report Form – (excel spreadsheet, uploaded to IRIS)

Appendix B: Informed Consent Form – uploaded to IRIS

Appendix C: Questionnaires - OAB-Q LF (English, Spanish), PGI-I, VAS pain

Appendix D: DSMB Charter (uploaded to IRIS)

Appendix E: Satellite Site Management Plan

18 SIGNATURE

This clinical trial protocol has been reviewed and approved in order to ensure compliance with Good Clinical Practices.

This study will be performed in compliance with Good Clinical Practices, including the archiving of essential documents.

Version Number and Date	Version 2_09 Mar 2022
Investigator Name	Carly Crowder, MD
Signature and Date	_____