

Official Title of Study: Reduction of Bladder Injection Pain with Belladonna Opiate Suppository: A Randomized, Double-Blind, Placebo-Controlled Trial (ROBIN Trial)

NCT Number: NCT02600715

Document Date: 5 November 2015

Wichita Medical Research and Education Foundation IRB
Approval Date: 9/16/2015

University of Kansas Medical Center IRB
Approval Date: 11/6/2015

Title

Reduction of Bladder Injection Pain with Belladonna Opiate Suppository: A Randomized, Double-Blind, Placebo-Controlled Trial (ROBIN Trial)

Version Date: 5 November 2015

Principal Investigator: Edgar LeClaire, MD

Co-Investigators: Rachel Wykes, MD, PGY-3, Jennifer Duong, MPH

Clinical Site: Wichita Women's Pelvic Surgery Center at Associates in Women's Health

Introduction, Background, Study Rationale

Introduction

Overactive bladder (OAB) and urge urinary incontinence (UUI) affect 17% of women in the United States [1]. The economic burden of these conditions is estimated at well over \$24 billion and is expected to increase [2, 3]. Moreover, the devastating impact on patients who suffer from OAB and UUI are well established. Clear associations with depression, sleep disorders, sexual dysfunction, and decreased quality-of-life scoring on validated surveys have all been observed in epidemiologic studies [4].

Bladder injection with Onabotulinumtoxin A (BoNT), also known as Botox (Allergan®), is an effective, Food and Drug Administration (FDA) approved for the treatment of OAB and Neurogenic Bladder (NB) (also known as neurogenic detrusor overactivity) that has failed first-line medical management. Additionally, the American Urologic Association endorses BoNT bladder injection for the treatment of refractory Painful Bladder Syndrome (also known as Interstitial Cystitis) [5, 6]. Bladder injections with BoNT may be done under general anesthesia in operating room settings. However, BoNT treatment is increasingly performed as an office procedure [7]. The safety and efficacy of BoNT injection for the treatment of bladder symptoms has been well established [7, 8]. Studies have assessed overall patient satisfaction with BoNT treatment results, but not specifically pain or discomfort during the procedure [9, 10].

Currently, trans-urethral lidocaine gel and bladder instillation of lidocaine-bicarbonate solution is recommended as standard analgesia for office injection of BoNT during cystoscopy [11, 12]. While this regimen allows relatively painless instrumentation of the urethra, evidence supporting its efficacy is lacking [13]. Furthermore, the experience of BoNT injection providers suggests standard analgesia is inadequate for controlling bladder injection pain. Pain experienced during the procedure may deter subsequent, cost-effective, office treatments. Bladder injection pain experience has not been substantively addressed in the literature.

Belladonna & opiate (B&O) suppositories have been commonly used to treat spastic lower urinary tract pain. This medication contains a naturally occurring plant alkaloid derivative which relaxes the bladder and an opioid analgesic such as opium or

morphine. B&O suppositories have been investigated in robotic prostatectomy studies that demonstrating diminished need for IV analgesia and improved post-op pain control [14, 15]. The most common version of the B&O suppository is comprised of belladonna and opium. The B&O suppository that will be used in this particular study will be belladonna and morphine, in which the morphine will be the pharmacologic equivalent of opium. The belladonna and morphine suppository is a commonly used and is pharmacologically equivalent to other belladonna and opiate suppositories. ***For the remainder of the protocol, B&O suppository will be used to generically reference belladonna and opiate suppositories unless otherwise stated.***

This randomized trial is designed to assess the effectiveness of B&Os as an adjunct to standard analgesia for improved BoNT injection pain.

Background

Overactive bladder (OAB) and urge urinary incontinence (UUI) affect 17% of women in the United States [1]. The economic burden of these conditions has been estimated at well over \$24 billion and is expected to increase to nearly \$82.6 billion in 2020 due to the aging population [2, 3]. These costs are largely due to the routine management of the symptoms (i.e. pads). Treatment costs account for a mere 14% of the overall cost. Cost reduction measures may include increasing access to diagnosis and treatment of OAB. Furthermore, the devastating impact on patients who suffer from OAB and UUI are well established. Clear associations with depression, sleep disorders, sexual dysfunction, and decreased quality-of-life scoring on validated surveys have all been observed in epidemiologic studies [4].

OAB is defined as urgency, with or without urge incontinence, usually with frequency and nocturia [16]. This affects up to 17% of women. The mechanisms contributing to urge incontinence include intrinsic malfunction of detrusor (bladder wall muscle) activity, overstimulation of detrusor muscle by acetylcholine, sensory urgency caused by abnormal sensory processing, or abnormal neuronal input to the detrusor. First line treatment involves bladder training, with the addition of oral anti-muscarinic agents if needed. These oral therapies improve symptoms and quality of life, with the NNT of 5-9 [17]. Albeit effective, these medications have reportedly poor adherence due to side effects with as many as 83% of patients discontinuing medication within the first 30 days. Second-line management includes BoNT intravesical injections, percutaneous posterior tibial nerve stimulation, and percutaneous sacral nerve stimulation. BoNT is one of the safest, least invasive, and effective options for refractory OAB [18].

Neurogenic bladder (NB), also known as neurogenic detrusor overactivity (NDO) is the urodynamic finding of uncoordinated bladder contractions. Those most commonly affected are young males with spinal cord injury and young females with multiple sclerosis. Of the estimated 273,000 people in the US with spinal cord injury, 81% experience urologic symptoms [19]. Additionally, 50-90% of persons with MS; 50% of persons with diabetic neuropathy; 24% of those with brain tumors; and 50% of patients with spinal stenosis will experience NB [20]. Among cerebrovascular accident sufferers, 8-11% will experience NB symptoms [21]. For NB patients who are able to empty their

bladder, oral medication in the form of anticholinergics. BoNT injection into the bladder has been shown to reduce the frequency of urinary incontinence episodes and daily urinary frequency at 4-6 weeks and 12 weeks following the injection [22]. Thus, BoNT injection is indicated for patients who fail first-line therapy with oral anticholinergics.

Onabotulinumtoxin A (BoNT) is a neuromuscular blocking agent acting on the presynaptic membrane of the neuromuscular junction, preventing calcium dependent release of acetylcholine. FDA-approved indications include treatment of urinary incontinence caused by detrusor overactivity due to a neurologic condition and treatment of overactive bladder (OAB) (including symptoms of urge urinary incontinence, urgency, and frequency) in adults who show inadequate response to oral medication or do not tolerate the common side-effects of first-line anticholinergics (i.e. dry-mouth, constipation, confusion). The American Urologic Association also endorses BoNT bladder injection for the treatment of refractory Painful Bladder Syndrome (also known as Interstitial Cystitis) [5, 6]. In terms of effectiveness, study participants undergoing BoNT treatment experienced a 3-4 fold reduction in daily incontinence episodes compared placebo. A treatment effect size of this magnitude has not been demonstrated with first line agents (anticholinergics or beta-3-agonists) [23]. Studies repeatedly reinforce the safety and efficacy of BoNT at doses of 100-200U administered 10-30 sites [7, 8]. BoNT treatment has also demonstrated improved quality of life measures 6 weeks following injection and improved sexual function in women with MS [24, 25]. Studies have established the effective dosage of BoNT at 100-200 units, injected in 1 to ½ unit increments throughout the bladder wall (totaling 10-20 injections per treatment) [7, 8].

BoNT is well tolerated and most common adverse events are limited to transient urologic conditions; urinary tract infection (UTI) and urinary retention (the latter in dose dependent fashion). UTIs have been reported in 2-32% of patients after initial treatment. The risk of urinary retention occurs in 6-17% of patients and may present in days or weeks following injection and can last up to 12 weeks. Thus, patients must be willing and capable of performing intermittent self-catheterization should retention occur. Contraindications to BoNT injection are reviewed in Table 1 [3, 11, 24].

Table 1. Contraindications to BoNT injection of the bladder
<ul style="list-style-type: none"> • Presence of infection at proposed injection site • Known hypersensitivity to BoNT toxin preparation or any components in the formulation • Urinary tract infection • Urinary retention • Post void residual > 200ml in patients NOT routinely performing clean intermittent self-catheterization (CISC) • Patient unwilling or unable to use CISC • Patient unable to discontinue anti-platelet therapy for 3 days prior to injection • Anti-coagulation therapy that cannot be adjusted for the procedure • Non-compliance with prophylactic antibiotics

Onset of action is 2-4 weeks with and expected treatment duration of 42-48 weeks. Injection can be repeated as needed as soon as 12 weeks after injection. Clinical follow-

up is recommended 1-2 weeks following the procedure and again at 2-3 months [26, 27].

BoNT injection of the bladder can be performed under general anesthesia, but in its most cost-effective form it is administered an in-office procedure [7]. Though studies have evaluated patient satisfaction with results of in-office treatment, limited data exist to guide optimum pain management during injection [9, 10].

B&O suppositories (NDC-054-7045-12 and NDC-0574-7040-12, Case# 665219) have been commonly administered to treat spastic lower urinary tract pain. B&O combines the anti-muscarinic properties of a naturally occurring plant alkaloid derivative to relax the bladder with opioid analgesia. B&O suppositories have been used safely in robotic prostatectomy studies and have demonstrated diminished need for IV analgesia and improved post-op pain control [14, 15]. B&O suppositories have not been studied for pain control during urogynecologic office procedures, although they are frequently utilized in office procedure analgesia protocols.

The antimuscarinic (anticholinergic) effects of belladonna alkaloid are dose dependent and include relaxation of smooth muscle, bronchodilation, pupil dilation, decreased gastric motility, transient tachycardia, and, most significant for this study, decreased tone and amplitude of ureteral and bladder contractions. B&O suppositories pair the belladonna anti-spasmodic with analgesia of an opioid to minimize discomfort associated with ureteral spasm. B&O suppositories have been used safely in robot assisted laparoscopic prostatectomy studies [15]. Administration of B&O suppositories prior to urologic procedures has been shown to decrease IV pain medication requirements and overall pain postoperatively [14]. The common B&O suppository formulation contains 16.2mg Bella Donna and 30 or 60 mg of opium and may be dosed as 1 suppository 1-4 times a day. The cost of this medication is approximately \$400 for 12 tabs.

Contraindications to this medication include hypersensitivity to belladonna, opiate, or any component of the formulation; glaucoma; severe renal or hepatic disease; bronchial asthma; respiratory depression; convulsive disorders; acute alcoholism; premature labor. Adverse reactions occur with an undefined frequency but may include palpitations, dizziness, drowsiness, pruritus, urticarial, constipation, nausea/vomiting, xerostomia, urinary retention, blurred vision, photophobia. The anti-cholinergic effect of BoNT, when therapy administration is closely monitored, is not likely since a single B&O dose will have worn off long before the 2-4 week onset period of BoNT is complete. Minimal systemic effect has been noted with suppository administration. Additionally, patients undergoing this therapy have theoretically already withstood an anticholinergic trial as a first line treatment for OAB/NB [28, 29].

Study Rationale

Data are lacking to demonstrate the ideal pain control regimen during office injections of BoNT. This is likely due to the relatively new application of this procedure in office. One study comparing average pain during intravesicle injections with use of alkalized lidocaine vs lidocaine gel demonstrated no result [13]. Additionally, it is difficult to accurately represent the patient pain experience. The Numeric Rating Scale (NRS) is a

valid and reliable measure of pain intensity [30]. The primary outcome of our study will be determined by the patient experience objectified with the NRS. The overall goal of this study is to improve the patient experience with cost-effective evidence-based treatment.

Research Plan and Design

Study Objectives

The primary objective is to determine the effectiveness of B&O suppositories in decreasing bladder injection pain at time of BoNT injection.

Our null hypothesis: Among patients given standard analgesia for BoNT treatment of overactive bladder (OAB), neurogenic detrusor overactivity (NDO), or refractory interstitial cystitis (IC), there is no difference in bladder injection pain scores with the addition of B&O suppository when compared to placebo suppository.

H₀: Mean Δ pain during procedure in active suppository group = mean Δ pain during procedure in placebo suppository group.

Change in pain (*Mean Δ pain*) is considered to be the difference in pain from the baseline pain level after analgesia, and after the first 10 injections.

Outcomes

The primary outcome will be bladder injection pain. Pain will be measured using numeric rating scales (NRS). Participants will score their preoperative baseline pain level when they check into the clinic for their procedure (P_o). Participants will report pain 40 minutes after administration of standard analgesia and suppository (just prior to bladder injection) (P_a). This will allow calibration of our primary outcome for patients with higher levels of baseline pain not related to the procedure (using themselves as controls). They will then be asked to rate bladder pain after the first 10 injections (midpoint of the procedure) intraoperatively (P_{10}). After the procedure is completed, which would be after 20 injections, the patient will again be asked to report their pain (P_{20}).

The operational definition of our primary outcome will be calculated difference in NRS pain score prior to procedure (P_a) and midway through procedure (P_{10}): Δ pain (intraoperative pain score – preoperative pain score).

Secondary outcomes will include: pre-analgesia pain score (P_o), post-operative pain score (P_{20}), patient intolerance to the procedure, postoperative voiding trial results (pass/fail), and post void residual (PVR) results at 2 week follow-up (measured in ml, pass/fail), and diagnosis of urinary tract infection (accepted clinical definition of acute cystitis or a positive urine culture) at 2 week follow-up. PVRs < 200ml at 2 week follow-up will be considered passing result [31].

Participants will also rate their level of satisfaction with pain control immediately after the procedure using a simple Likert scale. This will be a 4-level scale ranging from 'not at all satisfied,' 'slightly satisfied,' 'mostly satisfied,' and 'very much satisfied.'

Expected Results

Investigators believe that participants randomized to the B&O suppository group will experience less bladder pain (average pain) during the BoNT injection procedure than those that were assigned to the placebo group.

Study Type and Design

This study is a randomized, pilot trial. Clinical investigators and participants will be blinded to the randomization groups. Participants, whom have elected to receive BoNT injection therapy, will be randomized to receive either a placebo or B&O suppository prior to the procedure. Pain will be assessed prior to the procedure, during the procedure, and after the procedure.

Sample size

Sample size is calculated assuming the group receiving the B&O suppository reports an average intra-procedural pain (P_{10}) score of 4.5, and assuming the control group (placebo) reports an average intra-procedural pain (P_{10}) score of 8. The assumed standard deviation is 3. Based on a power of 0.8, the required sample size per randomization group is 13. The total sample size required to achieve a power of 0.8 for this pilot trial would be 26 (13 per group).

Randomization

Eligible participants will be assigned with equal probability to one of two treatment groups: belladonna and opiate (B&O) suppository and inactive placebo suppository. Block randomization will be utilized to maintain balance between study group sizes over time and to enhance blinding of the clinical investigators; a repeated run of placebo or active suppositories may lead to an anticipatory bias effect on subsequent participants. An online randomized block generator will be utilized. Block size will be randomized and will not be revealed to clinical investigators. As the proposed study is double-blinded, selection bias is unlikely.

Study drug suppositories will be randomized in sequential pill canisters. Aside from standard indications to do otherwise, treatment allocation will remain concealed until enrollment and follow-up visits have been completed.

Working with the compounding pharmacy, an unblinded data coordinator will label, and track, the active and placebo drug assignments. Once the patient has consented to participate in the study, the Principal Investigator will assign the participant sequentially, and will notify the data coordinator and compounding pharmacy. Based on a sequential numbering system, the participant will be randomized to receive either the B&O suppository or the inactive placebo suppository based on the block assignment. The Principal Investigator will complete an authentic prescription in order to comply with all Drug Enforcement Administration (DEA) requirements for securing Schedule 2

narcotics. The prescription will be provided to the compounding pharmacy, which will fill the prescription based on the pre-determined randomization scheme. The compounding pharmacy will document and deliver the pill canister matching the participant's ID number, to the clinic and provide it to the Principal Investigator to store in a locked medicinal refrigerator in a locked room until the day of the procedure. Prior to administering the suppository to the patient during the procedure, the Principal Investigator will open the pill canister and document the pill canister number and the number labeled on the suppository in the patient's medical record, and study documents. If unveiling the randomization for a participant is required, the Principal Investigator can call the data coordinator or the compounding pharmacy, and the coordinator or the lead pharmacist will reveal the participant's randomization assignment over the phone. Monthly meetings will be conducted to audit the enrollment and to ensure randomization procedures are conducted appropriately.

Statistical Analysis

Preoperative demographic variables including age, race, parity, body mass index (kg/m^2), menopausal status, smoking status, medical comorbidities, and indication for BoNT treatment (OAB vs. NDO) will be compared between active and placebo patients. Continuous variables will be compared using Student t-tests. Categorical variables will be described as frequency data (proportions & percentages) and compared using Chi-square or Fisher's exact test (when expected values in any cell are less than 5). Ordinal variables will be compared using Wilcoxon Rank Sum tests.

An intent-to-treat analysis approach will be used. Results for the active group versus the control group will be compared with paired t-tests if the data are normally distributed and with Mann-Whitney tests if the data are skewed. Regression modeling will be used to analyze the relationship between our primary outcome with the following predictor variables; active vs. placebo, indication for BoNT injection (OAB vs. NDO), demographic variables, and pain scores (before-during-after procedure). Interactions between variables will be assessed and, if significant, included in the model.

Confounding variables will be included in the model if point estimates change by more than 20% with their inclusion. Continuous variables will be assessed for linearity and converted to categorical variables as indicated by model fit statistics (c-statistic, Deviance, Pearson, Hosmer-Lemeshow). Cochran-Armitage and Goodness of Linear Fit tests will be used to evaluate for linear trends between suppository treatment and our primary outcome.

All statistical analyses will be two-sided. P-value of less than 0.05 is considered to be statistically significant. An interim analysis will be performed one year after Institutional Review Board if the study has not completed data collection within one year. Results will not be given to participants.

Participants

Patients will be approached for participation once they have selected BoNT therapy for treatment of overactive bladder (OAB), neurogenic detrusor overactivity (NDO), or refractory interstitial cystitis (IC).

To be included in this study, patients must be 18 years old or older at the time of the informed consent discussion, have met clinical criteria under outside care or during the Principal Investigator's routine standard of care for BoNT injection therapy (failed initial medical management), and there must be no contraindication to BoNT therapy as outlined by drug manufacturer guidelines (Table 1). Patients will have elected to have the BoNT injection therapy prior to being offer enrollment into the study for either OAB, NDO, or IC.

Patients will be excluded for pregnancy, currently nursing a baby, age less than 18 years, or anticipated geographic relocation within the first 3 months following treatment. Patients will be excluded if the patient reports an allergy to morphine, belladonna, or opiates. Patients will also be excluded if participating in another research study. Individuals unable to provide informed consent or to complete two-week follow-up bladder testing (post-void residual) or data collection will also be excluded. Prior to randomization, a data coordinator will verify eligibility and completeness of baseline data.

Participants will be withdrawn or terminated from participating in the study by a clinical investigator if they fail to undergo the BoNT injection procedure and do not reschedule before the conclusion of the study.

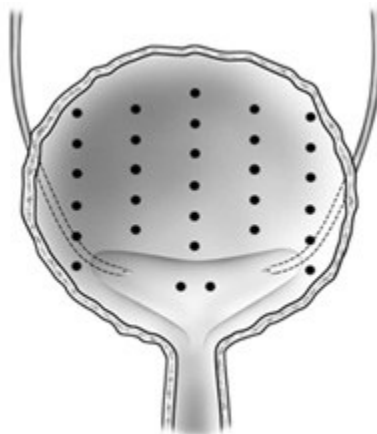
Potential confounding factors will be considered and treated appropriately during the statistical analysis. Additional confounding factors such as variability in pain and narcotic usage will be discussed in the manuscript. Investigators do not anticipate potential confounders will significantly affect the results of the study.

Standard of Care Procedures

All participants will receive injection with BoNT (Botox, Allergan) as standard clinical care. OAB participants will receive 100 units and NDO participants will receive 200 units per FDA guidelines. All participants will also undergo standard recommended preoperative analgesia per manufacture guidelines, intravesical instillation of 2% lidocaine (60ml) + sodium bicarbonate (10ml), administered 40 minutes prior to cystoscopic bladder injection. Viscous lidocaine will be used to anesthetize the urethra.

BoNT will be prepared and injected per manufacturer guidelines. After reconstitution in 10ml of normal saline, BoNT is injection in 0.5ml increments (20 injections total) into the detrusor muscle layer of the bladder dome in a standardized square pattern (Figure 1). Injection pattern will also not differ from clinical standard practice, and all patients receive the same, trigone sparing injection pattern [32].

Figure 1. Bladder injection pattern.



Regardless of participation, patients will undergo the injection procedure with BoNT, and will receive the analgesia per standard of care, both of which will be billed to the patient's insurance company. Costs associated with the BoNT therapy, including the in-office procedure visit, follow-up visit, physician fees, bladder testing conducted during two weeks follow-up, and any additional follow-up care, will be billed to the patient's insurance company, or will be the responsibility of the patient.

Information regarding volume of BoNT used in the procedure, as well as analgesia information will be collected for research purposes. Voiding trial samples, if clean, will be discarded as standard office procedures. If an infection is present, the sample is sent to the lab as standard office procedures required for appropriate medical management.

Research Intervention

Participants randomized to the active group will receive a rectal belladonna & opiate (B&O) suppository along with standard analgesia 40 minutes prior to bladder injection.

Participants randomized to placebo will also receive standard analgesia as well as a rectal suppository composed of inactive base 40 minutes prior to bladder injection.

Study drug will be provided by a compounding pharmacy [REDACTED] that can produce visibly identical active and placebo suppositories. Dosage of the compounded active suppository is belladonna 16.2mg and morphine 7.5mg, which matches the commercially available belladonna and opium suppositories (belladonna 16.2mg + opium powder 60mg). Compounded belladonna dose will be the same (16.2mg) and morphine equivalent dose (7.5mg) will be used in place of powdered opium component. Using morphine, which carries a Schedule 2 narcotics classification, requires adhering to DEA restrictions for compounding purposes. The Principal Investigator will write an authentic prescription for each participant enrolled in the study (each prescription will refer to the research study, and will request "B&O suppository or placebo"), which will assist with adhering to guidelines for using Schedule 2 narcotics in clinical practice. Blinding afforded by using similar suppositories also enhances study rigor.

The B&O suppository and placebo pills participants receive will not be billed to the patient's insurance company.

Origin, Tracking, and Dispensing of Suppositories

The placebos and B&O suppositories will be purchased from [REDACTED]

The pharmacy will compound belladonna and morphine suppositories (16.2mg/7.5mg) to the same dose equivalent of opium (60 mg). Compounding the belladonna and morphine (morphine sulfate 7.5 mg is approximately equivalent to powdered opium 60 mg) would be more feasible for the study than using commercial B&O suppositories because the pharmacy cannot duplicate the exact size and shape of the commercially available B&O suppositories for research purposes. Due to the research being double-blinded to the participant and the investigators, compounded belladonna and morphine suppositories will be used. Compounded belladonna and morphine is a commonly used, and is pharmacologically equivalent to belladonna and opium suppositories.

The active suppositories and placebo suppositories will be compounded to be physically identical, and will be provided directly to the Principal Investigator located at Wichita Women's Pelvic Surgery Center at Associates in Women's Health, by the compounding pharmacy. The Principal Investigator will not know the identity of the suppositories. The data coordinator will maintain a master tracking list of the suppository with an inventory or ID number provided by the pharmacy as to which ID numbers are placebos and which are the B&O suppositories. The data coordinator will provide the randomization scheme to the pharmacy, who will fill each individual prescription based on the order the patient is consented into the study (using the participant's ID number), and will place the individual suppository into a blinded pill canister. The Principal Investigator will call the data coordinator and the lead pharmacist at the compounding pharmacy when a patient has consented and will undergo the procedure. The pharmacist associated with the compounding pharmacy will hand deliver the envelope to the clinic, and document the pill canister being delivered. The data coordinator will meet the pharmacist at the clinic to audit the container, and to confirm the appropriate container is provided to the Principal Investigator. The "unblinded" label containing the actual medication provided to the patient, including the patient name, date of birth, address, and phone number will be concealed in an envelope and carried separately from the pill canister, however, in order to comply with DEA guidelines, both will be hand delivered to the clinic. The envelope with the identity of the suppository will be in a secure container under lock and key, and will only be accessible to the data coordinator. The label will be stored with the participant's study records, and not revealed to the Principal Investigator.

All suppositories will be stored in a locked refrigerator that will be kept in a locked office. The temperature will be monitored regularly for quality assurance. The Principal Investigator will administer the suppository to the participant prior to the BoNT procedure, and will document in the participant's medical record and study documents which pill number was administered to the participant. The data coordinator will monitor

and monthly audit logs to ensure randomization assignments are adhered to during the course of the study.

A sample from each batch of compounded suppositories will be sent off for third-party testing to test the suppositories for chemical validity.

Participant Timeline

The length of participation in this study will be approximately two weeks from the day of the injection procedure. Table 2 illustrates the procedures or tasks to be completed during each appointment.

Table 2. ROBIN Trial Participant Timeline	
Appointment	Task/Objective
Patient Consents to Undergo Bladder Injection Therapy	<ul style="list-style-type: none"> • Patient elects to receive BoNT therapy as standard of care treatment for overactive bladder, neurogenic detrusor overactivity, or refractory interstitial cystitis • If patient meets inclusion criteria, patient is consented and offered enrollment into the study • Participant receives a participant ID number based on sequential numbering • Principal Investigator completes prescription and sends to compounding pharmacy to fill based on participant ID number
Day Prior to Procedure	<ul style="list-style-type: none"> • If informed consent is obtained, the blinded suppository will be hand delivered to the clinic by the compounding pharmacy • The suppository will be locked in a medicinal refrigerator until time of the procedure
Day of Procedure	<ul style="list-style-type: none"> • Participant checks in for procedure, and completes pain assessment (P_0) • Principal Investigator administers the suppository or placebo to the participant • Participant completes pain assessment after receiving analgesia for the procedure (P_a) • Participant undergoes BoNT procedure and completes pain assessment (P_{10}, P_{20}) • Participant completes voiding residual trial • Adverse effects or serious events are assessed • Participant is released from clinic
2-weeks follow-up visit	<ul style="list-style-type: none"> • Participant completes voiding residual trial and adverse effects or serious events are assessed • Participant receives \$25 gift card incentive for completing the study

Risks to Subjects

Because the patient has already given consent to receive the BoNT therapy, any risks associated with the procedure while participating in this study are within normal bounds for any patient electing to undergo the procedure. Overall, the risks involving the use of the B&O suppository are comparable to not utilizing it during the BoNT therapy

procedure. Use of this particular suppository should not significantly increase or decrease risks to the patient.

However, investigators believe that there are risks associated with this study. Physical risks associated with participating in this study, and related to study procedures include drowsiness/nausea associated with the B&O suppository if the participant is randomized to the active group. As standard of care after the BoNT procedure, patients are required to have a driver, and are advised on to operative a moving vehicle. Participants receiving the placebo may experience discomfort with the procedure, which the patient is aware of during the consent process for the BoNT therapy.

This research study involves exposure to pain and discomfort, however the risk is associated with routine clinical care since there are no established guidelines or recommendations for suppository use with analgesia during the BoNT therapy. The risk of discomfort and drowsiness/nausea associated with the study is minimal, and if the patient were to not participate in the study, would typically receive the B&O suppository as part of the Principal Investigator's routine standard of care. Researchers believe there is less than minimal risk associated with psychological, economic, social, and legal aspects of this study.

Loss of anonymity is a risk associated with research projects that involve human subjects. The research staff working on this study will take every precaution to guard patient identity in accordance with HIPPA standards. All study information and data will be grouped in aggregate and no individual information will be reported. No patient will be identified by name and protections will be in place to keep individual information confidential and anonymous.

However, risks are reasonable to the potential benefit from the study. Participation in this study will contribute to a better understanding of the treatment of bladder injection pain, which outweighs the minimal risk associated with the active group intervention. Additionally, this study may also help other patients that need to have the BoNT therapy in the future, have a better understanding of treatment options for overactive bladder, neurogenic detrusor overactivity, and refractory interstitial cystitis. Furthermore, information collected from this study would provide clinicians methods that could potentially reduce patient pain during in-office procedures, and would reduce potential healthcare costs associated with performing this type of procedure in a hospital facility.

Study Sites

Study sites for this study include the following locations where the investigators will perform research procedures, or analyze and store data.

Wichita Women's Pelvic Surgery Center at Associates in Women's Health (Clinical site)



University of Kansas School of Medicine – Wichita
Department of Obstetrics and Gynecology

Study Personnel

The study personnel associated with research procedures are listed in Table 3.

Table 3. ROBIN Trial Research Personnel			
Study Personnel	Affiliation	Role	Responsibilities
Edgar LeClaire, MD	KUSM-W Department of Obstetrics and Gynecology Clinical Instructor	Principal Investigator	<ul style="list-style-type: none"> • Determining eligibility • Obtaining informed consent • Providing on-going information to the IRB • Completing physical exam • Performing clinical procedures and intervention • Conducting questionnaires • Completing study data forms • Managing study database • Statistical analysis • Report generation
Rachel Wykes, MD, PGY-3	KUSM-W Department of Obstetrics and Gynecology Resident	Resident Co- Investigator	<ul style="list-style-type: none"> • Determining eligibility • Obtaining informed consent • Conducting questionnaires • Completing study data forms • Managing study database • Statistical analysis • Report generation • Chart audit
Jennifer Duong, MPH	KUSM-W Department of Obstetrics and Gynecology Staff	Project and Data Coordinator, Co- Investigator	<ul style="list-style-type: none"> • Determining eligibility • Obtaining informed consent • Conducting questionnaires • Completing study data forms • Managing study database • Statistical analysis • Report generation • Chart audit

Recruitment

Eligible female participants will be recruited from Wichita Women’s Pelvic Surgery Center at Associates in Women’s Health, P.A., a urogynecology and gynecologic-oncology clinic located in south-central Kansas with a collaborative academic relationship with University of Kansas School of Medicine-Wichita.

Based on the sample size needed to complete this study, investigators will need to consent and enroll about 3 patients a month into the study. The Principal Investigator believes that with the current number of patients treated with BoNT therapy, the number of patients needed to participate is obtainable within 12-18 months.

Screening for Potential Study Participants

The Principal Investigator will screen potential subjects based on the inclusion and exclusion criteria. Potential subjects will have met the clinical criteria to be treated with BoNT therapy prior to screening for the study.

Informed Consent Process

Clinical visits will occur at Wichita Women's Pelvic Surgery Center at Associates in Women's Health (WWPSC) in Wichita, KS. Investigators and research staff will be available to answer patient questions at the time of the informed consent interview. The consenting process will take place after patient in-processing according to standard clinic operating protocols, and after the patient has satisfied the clinical criteria and has elected to undergo BoNT injection therapy with the Principal Investigator.

After electing to undergo the injection therapy, the Principal Investigator will review the eligibility criteria to determine if the patient is eligible to participate in the study. If all inclusion criteria are met, the Principal Investigator or a member of the research team will present the informed consent form to the patient and will discuss the study with the potential subject. The patient will be informed that participation is voluntary, and their decision to participate will not affect their medical treatment or procedures related to the BoNT injection therapy. Consent will only be sought from those patients that meet fulfill the study inclusion criteria. All materials will be provided to the patient and the conversation will take place in English (Appendix A – ROBIN Consent Form).

After all questions have been answered, and the patient has had adequate time to review the informed consent form, if the patient would like to participate, the research team will ask the participant to sign the consent form. If the patient would like additional time to review the informed consent form and to consider participation, the patient can either schedule a visit to complete the form before their visit, or can sign the informed consent form when they check in for their procedure.

A copy of the signed consent will be provided to the participant. The Principal Investigator will be notified that the patient consents to participate in the study. After consenting, the investigators and research assistant will review all materials for completeness before the subject leaves the clinic site.

If consent to participate in the study is not given, no information collected during the visit will be used in the study. Instead, the information will be used for normal documentation of patient care.

Patients will be consenting to data collection and to research participation to receive an intervention or a placebo above and beyond standard clinical practice.

Alternatives to Participation

The alternative to participating in this study would be to not participate in the study. The patient will still undergo the BoNT therapy as anticipated. Even if the patient declines to participate in the study, the patient would still receive the B&O suppository as the Principal Investigator's standard of care, or patients can notify the clinician they do not want to utilize a suppository.

Costs to Subjects

The study subject will be responsible for costs associated with the BoNT injection therapy, and standard medical costs associated with their treatment. In the instance that the insurance company will not pay for the injection therapy or the associated standard of care procedures, the subject will be notified, and the subject will be responsible for the costs associated with their medical treatment. If the subject does not have insurance, the subject has previously agreed to cover the costs associated with the treatment.

The only costs that the subject will not be responsible for are those related to the study procedures. The subject is not required to cover the cost of the suppository, or the pain assessment forms.

New Study-Related Information

Although investigators do not anticipate developments in research or information related to the study, the study subject will receive new information from investigators via letter correspondence. Any correspondence will be disseminated by the Principal Investigator, and the data coordinator will track and monitor that each study subject receives the information.

Participation Incentive

Subjects will receive a \$25 gift card at the conclusion of the 2-week follow-up appointment to assist with travel/driver costs. If the subject withdraws before the 2-week follow-up, the participant will not receive an incentive for participation.

Research-Related Injury

If the study subject were to be injured as a result of study procedures (separate from the BoNT therapy), subjects will be advised to immediately contact the Principal Investigator, Dr. Edgar LeClaire [REDACTED] Dr. LeClaire will decide what type of treatment, if any, is best for the study participant at that time.

Data Collection and Protection

Data Collection Procedures

Data collection will occur after obtaining informed consent for the patient to participate in the study. Demographic data will be collected to include clinical, surgical, functional, post-procedure, charted data collected as part of routine clinical visit and standard of care (Table 4). Data will be collected on a paper form (Appendix B – Data Collection Form). Follow-up data will include newly charted clinical and functional data.

Table 4. Summary of Participant Demographic Data Collected
Date of 1st consultation
Height
Weight
Body Mass Index
Race/Ethnicity
Smoking status
Menopausal status
Diagnoses
Prior surgeries
Past medical history
Medications
Indication for BoNT injection procedure

The day of the procedure, the participant will check in at the front desk. A nurse will escort the participant back to the procedure room for preparation. The participant will be given a pain assessment form with a numeric rating scale that will ask the participant to evaluate their bladder pain prior to standard analgesia and the procedure (Appendix C – Pain Assessment Form - Po). After completing the assessment, the participant will be positioned for the procedure and will be administered standard analgesia plus active or placebo suppository (based on randomization assignment).

Aside from suppository placement, BoNT injection protocols that are in compliance with best practices established by Allergan® and the FDA will be followed. In summary, BoNT will be reconstituted in 10ml normal saline and injected in 1/2ml increments (20 injections). Standard analgesia consists of bladder instillation with 50-60ml of 1% lidocaine solution with 10ml of sodium bicarbonate. Instillation is maintained for 40 minutes prior to the procedure. During that time, the patient will rotate while on procedure table (10 minutes on supine, 10 minutes prone, 10 on each side) to maximize bladder wall contact with anesthetic. The patient will then be placed in lithotomy position for cystoscopic injection of BoNT. A 17 french 30 degree cystoscope will be used. Injection will be carried out using a flexible botox injection needle designed for the procedure. All patients will undergo standard screening for preoperative UTI and antibiotic prophylaxis per accepted guidelines.

After 40 minutes of receiving the analgesic and suppository, and right before the procedure, the participant will be asked to report their bladder pain using a numeric rating scale (Appendix D – Pain Assessment Form – Pa-P20).

Patients will undergo 20 total injections at time of BoNT treatment. An investigator will perform pain assessments during the procedure. During the procedure, the participant will be asked their bladder pain using the numeric rating scale after the first 10 of 20 injections performed during the procedure and after the next 10 of 20 performed during the procedure (Appendix D – Pain Assessment Form – Pa-P20).

After the procedure is completed, the participant will be asked to complete a voiding trial, and will be given a pain assessment form, answering a Likert scale question regarding their satisfaction with their pain management during the procedure (Appendix E – Pain Assessment Form - Post BoNT). After the voiding trial is completed and the Principal Investigator has provided standard medical counseling and care after the procedure, the participant is released from the clinic.

Patient pain outcomes will be measured using numeric rating scales (NRS) and satisfaction with pain management during the procedure. The Principal Investigator will perform the clinical evaluation and in-office procedures associated with this study. The investigators will assist with the pain assessments. Patient information will be collected as part of the normal course of care associated with routine post-surgical visit and will be charted according to routine clinical practice. Pain assessments will be collected for research purposes.

Description of Follow-Up

During the informed consent process, subjects will agree to a standard of care follow-up with the Principal Investigator, two weeks after their in-office procedure where they will undergo PVR assessment. The Principal Investigator will perform a clinical exam as part of their standard of care. Adverse and serious effects will be assessed during follow-up. Both the results of the PVR assessment, adverse and serious effects, and result of urine culture will be documented (Appendix F – Assessment Form – 2-Week Follow-up).

Cessation Rules/Termination of Study

During the consenting process, subjects will be advised that they may voluntarily withdraw from this study at any time. They will not be obligated to reveal their reason for withdrawal. Additional circumstances for which a subject may not continue study participation include death, or lost to follow-up status. A subject will also be withdrawn from the study if their procedure was not performed at Associates in Women's Health. Moreover, a subject will be withdrawn from the study if the subject does not follow the study requirements. The Principal Investigator has discretion in removing a patient from the study if study requirements are not met.

Subjects terminated from the study will undergo standard treatment of care. All data collected during the study prior to cessation will be kept on hold at the discretion of the

investigator(s) and research assistant, unless the subject cancels the permission for researchers to use the collected data.

To withdrawal from the study, the subject will need to write a statement to the Principal Investigator. The mailing address to withdraw is: Edgar LeClaire, MD, KU School of Medicine- Wichita, Department of Obstetrics and Gynecology, [REDACTED]
[REDACTED]

Once a written statement has been received, the researchers will remove the subject from the current list of subjects and will be placed on the withdrawn list. Information that had already been collected from the patient will be kept. Subjects will continue to receive standard treatment of care; however, all data collected after receiving the study withdrawal statement will not be added to the cumulative study data.

Human Subjects Protections

Researchers involved with this study will have Human Subjects and HIPAA Certification. This proposal will be submitted to two IRBs; the Wichita Medical Research and Education Foundation IRB and the University of Kansas School of Medicine – Wichita Human Subjects Committee 2 IRB. This study will not commence until final approval is received from the IRBs.

Methods to Minimize Risks

To minimize the risks associated with this study, the privacy of potential subjects will be maintained as all Protected Health Information (PHI) will be protected and have limited access. Subject names and clinic record numbers will be maintained on a master list linked to a unique, assigned identification code generated independent of the medical record number. Much of the information we are seeking to collect is routinely collected and placed in the patient clinic and surgery charts. Access to PHI is necessary to connect patient surveys and assessments to information collected from the electronic medical record.

The master list will be maintained under secure conditions at all times. The master list will be stored at the University of Kansas School of Medicine - Wichita, Department of Obstetrics and Gynecology [REDACTED]

[REDACTED] Electronic copies of the master list will be password-protected and stored on encrypted computers/laptops. Only the data coordinator will have access to the master list in the department. The master list will be destroyed once all data has been deemed complete and analyzed, and it is determined that the master list is no longer necessary.

Only the listed investigators and their designated staff will have access to the master list and study data. The Institutional Review Boards, US Department of Health and Human Service, the Office of Human Research Protections, and other government and regulatory bodies, as required by law, may have access to this research data.

Research assistants enlisted to assist with this study will be closely supervised by the Principal Investigator. Those involved in direct patient care responsibilities, and assisting clinicians are located at Associates in Women's Health, and will not perform activities beyond their scope of care or expertise. Information technology protections and firewalls that are in place at this facility will protect the electronic data stored.

Data Security

Paper forms will be maintained under secure conditions at all times. The paper forms used in this study will not have participant protected health information listed, and will be kept in a locked office at all times. Data forms will be kept confidential during the conduct of this study. Research materials, such as protocols, IRB documents, participant information and data forms (after completion of data collection and analysis) will be kept in locked file cabinets in the University of Kansas School of Medicine – Wichita, Department of Obstetrics and Gynecology [REDACTED]

Documents and study related materials will be maintained under lock and key. Electronic files will be password-protected and encrypted, and will only be accessed by researchers listed on this study. Portable data devices (flash drives) will be encrypted and password-protected and will be maintained in secure locations in locked offices (either a co-investigator's office or the research assistant's office). At the conclusion of the study, all study related materials will be kept in locked file cabinets. Electronic files will have multiple firewalls and passwords to help keep information confidential. Electronic databases will be kept based on the record retention guidelines previously stated, and will be stored on password-protected and encrypted hard drives.

Information collected from paper forms will be entered into a computerized data file, and the file will be password protected and encrypted. Passwords will be subject to scheduled changes. The master list will be kept separately from the data collection forms. Access to study databases is restricted to an as needed basis to identified investigators and will be protected by appropriate firewalls. The database will be password-protected and encrypted. Files sent by email will first be password-protected and the email will be encrypted and sent via secure email.

Study Monitoring

The research staff will provide oversight, supervision, and monitoring of the data collection and will insure the integrity of the data which will ultimately ensure subject confidentiality. The study sites will be either the Principal Investigator's local clinic practice site, or those affiliated with the study personnel at the University of Kansas School of Medicine – Wichita.

Secure and Maintain IRB Approval at All Sites:

The Wichita Medical Research and Education Foundation IRB, in conjunction with the University of Kansas School of Medicine – Wichita Human Subjects Committee 2 IRB, will serve as the IRBs of record for this study, to include all the study locations listed previously. All protocol deviations, amendments, revisions, and continuing review

reports will be promptly compiled by the project coordinator, reviewed by the principal investigator and co-investigators, and provided to the IRBs. All research within the scope of this project will be conducted under IRB policies and guidelines.

Obtain IRB Approvals Prior to Implementing Changes to Protocol:

Investigators wish to assure the IRBs that any amendments to the protocol or supporting documents will be submitted for approval prior to implementation; problems associated with the research will be reported in accordance with IRBs policies.

Ensure general coordination of study conduct:

The principal investigator agrees to accept responsibility for the scientific conduct of this study and for the rights and welfare of human subjects. General oversight of the coordination of this study will be provided by the principal investigator, sub-investigators, and project coordinator.

Modifications to Study Protocol and Oversight:

Each review will consider whether or not the study should continue without change, be modified, or be terminated. Recommendations regarding modification of the design and conduct of the study might include:

1. Modification of the study protocol based upon review of the safety data;
2. Optional approaches when the incidence of primary study outcomes is substantially less than expected such as recommendations to extend study site; and
3. Corrective actions regarding the study site.

Any modifications to the study protocol will be submitted to the IRBs for approval prior to implementation of the changes.

To monitor adverse events or other unanticipated problems:

In lieu of a DSMB, investigators will serve in this capacity, in which they will be responsible for the following:

1. Interim/cumulative data for evidence of study-related adverse events;
2. Interim/cumulative data for evidence of efficacy when appropriate;
3. Performance of the study site;
4. Adequacy of compliance with goals for subject selection; and
5. Factors external to the study such as scientific or therapeutic developments that may impact participant safety or the ethics of the study.

The Principal Investigator and project coordinator will assume responsibility for:

1. Data quality, completeness, and timeliness;
2. Completeness of survey instruments;
3. Adherence to the protocol; and
4. Factors that might affect the study outcome or compromise the confidentiality of the trial data (such as protocol deviations).

Moreover, assessments for participant safety, study conduct and progress, and efficacy will be done. Periodic reviews of the same factors will be carried out. Each review will

consider whether or not the study should continue without change, be modified, or be terminated. Steps to unmask participants will be used to ensure participant safety if needed.

Investigator's Ethical and Regulatory Responsibilities:

Protocol adherence is the primary responsibility of the Principal Investigator. The co-investigators, and project coordinator will serve to support protocol adherence efforts and maintain an understanding of all protocol details. The principal investigator will consult with the other investigators regarding protocol revisions and amendments before adopting such changes. The IRBs will be notified of any problems during the conduct of this study.

Adverse Event Assessment and Reporting

The study team will be reviewing and assessing subject safety and data on a monthly basis. Participant pain assessments and clinical outcomes will be regularly reviewed to monitor patient safety. The Clavien-Dindo classification system will be used to monitor for adverse events and complications [33]. Adverse events specifically related to BoNT injection will also be monitored to include urinary tract infection and gastroparesis [31].

In the case an adverse event were to occur, the study investigator(s) will assume responsibility for reporting and documenting any complications. All serious events and adverse effects will be recorded on the participant's case record forms. In addition, all serious adverse and unanticipated adverse effects will be reported to the Institutional Review Boards by telephone, or in writing, within five (5) business days after the investigators first learn of the event by either the investigator(s) or the project coordinator.

The investigators are required to document all general medical complications, including, but not limited to the following: date of occurrence, date diagnosed, type of complication, and treatment. The investigator(s) and research assistant are responsible for complying with any reporting requirement of the reviewing IRBs.

Adverse events will be assessed after the suppository has been used, during the procedure, and during the voiding trial. During the two week follow-up visit, adverse events will also be assessed. The investigators do not believe there will be a need to stop or alter the study, but will stop the study if requested by the Institutional Review Board.

Record Retention

All study related documents (research materials such as protocols, IRB documents, participant information and data forms after completion of data collection and analysis) will be retained for fifteen (15) years from the date of initial IRB approval, and will be kept in locked cabinets located at the University of Kansas School of Medicine – Wichita Department of Obstetrics and Gynecology, [REDACTED]

[REDACTED]. At the time of document

disposal, documents will be shredded according to KUMC Research Institute Record Retention guidelines.

Dissemination of Results

Once the research is completed, it will be submitted to gynecologic journals and conferences, particularly those specializing in urogynecology.

Project Timeline

The project seeks to obtain Institutional Review Board approval from the IRBs by September 2015 (Table 5). This research project is anticipated to be completed by April 2017. The investigators anticipate conducting preliminary analysis after one year, and will complete continuing review forms as needed to complete the study.

Table 5. ROBIN Trial Project Timeline													
PROJECT LAUNCH Project Deliverables (X)	Academic Year 2015 - 2016												
	7	8	9	10	11	12	1	2	3	4	5	6	7
	J	A	S	O	N	D	J	F	M	A	M	J	J
Assemble project staff, create study protocol, submit for IRB approval and study funding													
Submit project for IRB approval and funding													
Receive IRB Approval			X										
Train study team and support staff													
Recruit patients from local providers offices													
Enroll patients and collect data													
Team meetings to discuss research plan, data quality, and progress on objectives													
Conduct preliminary analysis													
Review findings with team													
IRB Continuing Review													
	Academic Year 2016 - 2017												
Finalize data analysis and conclusions													
Draft abstract and submit to regional/national conferences		X											
Disseminate preliminary findings at regional/national conferences				X						X			
Draft manuscript													
Submit manuscript for publication							X						

Budget and Justification

Investigators will be requesting funding to cover costs related to the study and registration for the Principal Investigator and the Resident Investigator to present the findings of this study at the 2016 American Urogynecologic Society Annual Meeting. A detailed budget is provided below.

Personnel Costs: **\$0.00**
LeClaire, Edgar, MD, Principal Investigator (PI), will be responsible for managing and providing direction on all aspects of the project, ensuring that the budget and timetable targets are met, and providing direction to the other research personnel. Specifically he will facilitate communication between members of study team, and oversee conduct of the study, ensure all requirements for the Institutional Review Board are met, and contribute to reports, and dissemination. Dr. LeClaire will be performing the clinical procedures associated with this study, perform the data analysis and create reports, and disseminate results at national meetings.

Rachel Wykes, MD, PGY-3, Co-investigator, will be responsible for managing and providing direction on all aspects of the project, ensuring that the budget and timetable targets are met, support Institutional Review Board approval/revisions, and providing direction to the other research personnel. Specifically she will facilitate communication between members of study team, and oversee conduct of the study personnel, perform study procedures, assist with data analysis, and create reports, and dissemination at national meetings.

Jennifer Duong, MPH Study Personnel, will be responsible for facilitating team communication, coordinating protocol implementation logistics at the study site, and drafting/submitting Institutional Review Board reports and summaries, support Institutional Review Board approval/revisions, assist with team coordination, assist with data cleaning, assist with data analysis, review reports and submit abstracts for conference presentations.

Fringe Benefits: **\$0.00**
None requested.

Equipment: **\$0.00**
None requested.

Supplies: **\$1825.00**
Based on the quote provided by the compounding pharmacy, compounded belladonna and morphine pills will cost \$15.00 per pill the placebo pills will cost \$10.00. Thus, 20 compounded belladonna and morphine pills will cost \$300.00 and 20 placebo pills will cost \$200.00. Extra suppositories will be created to send for third-party validity testing and in the case where a suppository is deemed defective or dropped. Third-party validity testing will cost approximately \$500.00 Participants will receive a \$25 Walmart gift card from Walmart for participating. The total cost for incentives for 26 participants will be \$650.00. Paper supplies for surveys and printing will cost \$100.00. The poster

will be a 4x3 poster board used during presentations, which will cost \$75.00. Total costs for supplies will be \$1825.00.

Other Expenses: \$900.00

Registration to the 2016 American Urogynecologic Society Annual Meeting will be approximately \$450.00 for each attendee. The Principal Investigator and the resident co-investigator will attend to present the findings from this study. The total cost of registration to the meeting will be \$900.00.

Subcontractor Costs: \$0.00

None requested.

Personnel Costs	\$0.00
Fringe Benefits	\$0.00
Equipment	\$0.00
Supplies	\$1825.00
Other Expenses	\$900.00
Subcontractor Costs	\$0.00
Total Projected Study Costs:	\$2725.00

Appendices

Appendix A – ROBIN Consent Form

Appendix B – Data Collection Form

Appendix C – Pain Assessment Form – Po

Appendix D – Pain Assessment Form – Pa-P20

Appendix E – Pain Assessment Form – Post BoNT

Appendix F – Assessment Form – 2-Week Follow-up

References

1. Coyne, K.S., et al., *The impact of urinary urgency and frequency on health-related quality of life in overactive bladder: results from a national community survey*. Value in Health, 2004. **7**(4): p. 455-63.
2. Hu, T.W., et al., *Costs of urinary incontinence and overactive bladder in the United States: a comparative study*. Urology, 2004. **63**(3): p. 461-5.
3. Wu, J.M., et al., *Forecasting the prevalence of pelvic floor disorders in U.S. Women: 2010 to 2050*. Obstetrics & Gynecology, 2009. **114**(6): p. 1278-83.
4. Tyagi, S., et al., *The overactive bladder: Epidemiology and morbidity*. Urol Clin North Am, 2006. **33**(4): p. 433-8, vii.
5. Hanno, P.M., et al., *AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome*. J Urol, 2011. **185**(6): p. 2162-70.
6. Hanno, P.M., et al., *Diagnosis and treatment of interstitial cystitis/bladder pain syndrome: AUA guideline amendment*. J Urol, 2015. **193**(5): p. 1545-53.
7. Chung, E., *Botulinum toxin in urology: a review of clinical potential in the treatment of urologic and sexual conditions*. Expert Opin Biol Ther, 2015. **15**(1): p. 95-102.
8. Chancellor, M.B., et al., *Evidence-based review and assessment of botulinum neurotoxin for the treatment of urologic conditions*. Toxicon, 2013. **67**: p. 129-40.
9. Malde, S., et al., *Patient experience and satisfaction with Onabotulinumtoxin A for refractory overactive bladder*. BJU Int, 2014.
10. Schulte-Baukloh, H., et al., *Botulinum-A toxin for treatment of overactive bladder without detrusor overactivity: urodynamic outcome and patient satisfaction*. Urology, 2005. **66**(1): p. 82-7.
11. Allergan Inc. *Botox for OAB - Dosing and Administration*. 2015 2015 [cited 2015 August 17]; Available from: <http://hcp.botoxforoab.com/the-botox-procedure/dosing-and-administration>.
12. *onabotulinumtoxinA*. McGraw Hill.
13. Nambiar, A.K., et al., *Alkalinized lidocaine versus lidocaine gel as local anesthesia prior to intra-vesical botulinum toxin (BoNTA) injections: A prospective, single center, randomized, double-blind, parallel group trial of efficacy and morbidity*. Neurourol Urodyn, 2015.
14. Lukasewycz, S., et al., *Does a perioperative belladonna and opium suppository improve postoperative pain following robotic assisted laparoscopic radical prostatectomy? Results of a single institution randomized study*. Can J Urol, 2010. **17**(5): p. 5377-82.
15. Scavonetto, F., et al., *Prophylactic belladonna suppositories on anesthetic recovery after robotic assisted laparoscopic prostatectomy*. Can J Urol, 2013. **20**(3): p. 6799-804.
16. Peyronnet, B., et al., *[Management of overactive bladder in women]*. Prog Urol, 2015.
17. Nabi, G., et al., *Anticholinergic drugs versus placebo for overactive bladder syndrome in adults*. Cochrane Database Syst Rev, 2006(4): p. Cd003781.
18. Cardozo, L., et al., *Urinary urgency - translating the evidence base into daily clinical practice*. Int J Clin Pract, 2009. **63**(12): p. 1675-82.

19. Goldmark, E., B. Niver, and D.A. Ginsberg, *Neurogenic bladder: from diagnosis to management*. Curr Urol Rep, 2014. **15**(10): p. 448.
20. Stohrer, M., et al., *EAU guidelines on neurogenic lower urinary tract dysfunction*. Eur Urol, 2009. **56**(1): p. 81-8.
21. Nakayama, H., et al., *Prevalence and risk factors of incontinence after stroke. The Copenhagen Stroke Study*. Stroke, 1997. **28**(1): p. 58-62.
22. Duthie, J.B., et al., *Botulinum toxin injections for adults with overactive bladder syndrome*. Cochrane Database Syst Rev, 2011(12): p. Cd005493.
23. Cruz, F. and V. Nitti, *Chapter 5: Clinical data in neurogenic detrusor overactivity (NDO) and overactive bladder (OAB)*. Neurourol Urodyn, 2014. **33 Suppl 3**: p. S26-31.
24. Cruz, F., et al., *Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: a randomised, double-blind, placebo-controlled trial*. Eur Urol, 2011. **60**(4): p. 742-50.
25. Giannantoni, A., et al., *OnabotulinumtoxinA intradetrusorial injections improve sexual function in female patients affected by multiple sclerosis: preliminary results*. World J Urol, 2015.
26. Giannantoni, A., et al., *OnabotulinumtoxinA intravesical treatment in patients affected by overactive bladder syndrome: best practice in real-life management*. Urologia, 2015. **0**(0): p. 0.
27. Jimenez-Cidre, M.A. and S. Arlandis-Guzman, *OnabotulinumtoxinA in overactive bladder: Evidence-based consensus recommendations*. Actas Urol Esp, 2015.
28. *Belladonna and Opium*. McGraw Hill.
29. Gilman, A.G. and L.S. Goodman, *Goodman and Gilman's the Pharmacological Basis of Therapeutics*. 1980: Macmillan.
30. Coll, A.M., J.R. Ameen, and D. Mead, *Postoperative pain assessment tools in day surgery: literature review*. J Adv Nurs, 2004. **46**(2): p. 124-33.
31. Dmochowski, R., et al., *Efficacy and safety of onabotulinumtoxinA for idiopathic overactive bladder: a double-blind, placebo controlled, randomized, dose ranging trial*. J Urol, 2010. **184**(6): p. 2416-22.
32. Karsenty, G., et al., *Technical aspects of botulinum toxin type A injection in the bladder to treat urinary incontinence: reviewing the procedure*. Int J Clin Pract, 2014. **68**(6): p. 731-42.
33. Clavien, P.A., et al., *The Clavien-Dindo classification of surgical complications: five-year experience*. Ann Surg, 2009. **250**(2): p. 187-96.