# Cover Page for Protocol

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PROTOCOL TITLE: The SLIM Study: Sling and Botox® Injection for Mixed Urinary Incontinence

## PROTOCOL TITLE:

The SLIM Study: Sling and Botox® Injection for Mixed Urinary Incontinence

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# 1.0 Objectives

Primary Aim: To determine whether synthetic retropubic midurethral sling (MUS) combined with concomitant detrusor injections of onabotulinumtoxinA is more effective than midurethral sling alone in improving mixed urinary incontinence (MUI) symptoms.

Secondary Aims:

a. To compare incontinence episode frequency on a 3-day diary in women who undergo midurethral sling plus onabotulinumtoxinA to those who undergo midurethral sling alone.

b. To compare urinary incontinence symptoms and quality of life in women who undergo midurethral sling plus onabotulinumtoxinA to those who undergo midurethral sling alone.

c. To identify baseline factors associated with persistent urgency incontinence in women after midurethral sling alone and midurethral sling plus onabotulinumtoxinA.

Hypotheses:

1. By using a double-blind randomized controlled trial, we will be able to show that retropubic midurethral sling surgery with detrusor muscle onabotulinumtoxinA injection will be more effective at controlling mixed urinary incontinence symptoms than sling surgery alone.

2. Patients who receive both midurethral sling and onabotulinumtoxinA injection will have objectively have fewer incontinence episodes than those who receive midurethral sling alone

3. Patients who receive both treatments will have better quality of life as it relates to urinary symptoms than those who receive midurethral sling alone

4. Patients who have persistent urgency urinary incontinence after either midurethral sling alone or both midurethral sling and onabotulinumtoxinA injection alone will have significantly different baseline urine microbial content than those who do not have persistent urgency symptoms after treatment

# 2.0 Background

Project Abstract:

This double-blind randomized controlled trial looks to find a better treatment for women with mixed urinary incontinence. The primary aim of this study is to determine whether midurethral sling, the predominant incontinence surgery performed worldwide, combined with injections of onabotulinumtoxinA (Botox®) into the large muscle of the bladder improves symptoms of mixed urinary incontinence better than sling surgery alone. Secondary aims are to

compare objectively the frequency of incontinence episodes in patients who receive onabotulinumtoxinA injection versus those who do not. We will also compare urinary incontinence symptoms and quality of life measures in patients who receive the injections versus those who do not. Lastly, we plan to try to identify baseline factors associated with persistent urgency urinary incontinence in women after sling surgery alone and sling surgery plus injection.

We plan to enroll women who have mixed urinary incontinence and randomize them into either treatment with sling surgery alone or sling surgery with bladder onabotulinumtoxinA injection at the time of surgery. Patients will then be followed with scheduled, in-person follow-up with a physician at 2-weeks, 3-months and at 1 year. During these visits and prior to surgery, the patients will complete standardized surveys on urinary symptoms, quality of life, pelvic floor function, and sexual health. A urine sample will also be collected from each patient for a detailed analysis of the microbial content that is beyond the scope of a normal hospital laboratory.

After this study, we hope to have developed a new and better treatment for mixed urinary incontinence that can be provided to women suffering with this malady both nationally and internationally. There is currently no standard of care for treatment of mixed urinary incontinence and we aim to provide this to the urogynecologic community. Additionally, differentiating those patients who will have persistent or worsening urgency urinary incontinence after sling surgery from those who have improvement in symptoms has been difficult. By examining the detailed microbial content of participants' urine, we hope to better understand this phenomenon.

Project Background:

Mixed urinary incontinence (MUI) is a clinical conundrum for providers and patients alike. The International Continence Society defined MUI as "involuntary loss of urine associated with urgency or urgency incontinence AND urine loss associated with physical exertion, sneezing or coughing or stress incontinence". While some women ONLY experience one type of incontinence (stress OR urgency), many experience leakage with both, and it is unclear if these MUI symptoms are one disease with a continuum of symptoms or two separate diseases making treatment algorithms challenging. Despite our lack of understanding regarding the disease process or optimal treatment, MUI accounts for up to 50% of incontinence in women. The annual burden of MUI on the national economy is significant and growing.

More importantly, women with MUI are more bothered and suffer more dramatic quality of life impact. Yet, optimal treatments for MUI lag behind. Definitive treatments for stress incontinence are typically surgical, while those for urgency incontinence are behavioral or medical. As early as the 1980s, investigators sought to determine if surgical or non-surgical treatments should be used first for MUI. In one small trial, women with MUI were randomized to medical treatment (e.g. anticholinergic medications designed to relax the bladder muscle) for urgency incontinence or surgery for stress incontinence. Forty-three percent of women in the medicine group continued to have incontinence symptoms, while

only 12-13% of the surgical patients had persistent incontinence symptoms. Further complicating treatment decisions, continence procedures designed to treat stress incontinence have historically worsened urgency incontinence in some women.

There is no high-quality evidence or consensus amongst specialists on how to approach treatment for women with MUI. The optimal treatment strategy for women with MUI is unclear. Historically, health care providers tried to identify which type of incontinence, stress or urgency, was most bothersome to the patient and treated the bothersome subtype first. Those with stress predominant incontinence underwent surgery, while those with urgency predominant incontinence received medications and behavioral/physical therapy.

Currently, the primary surgical treatment of stress incontinence is midurethral slings. Greater than 66% of women undergoing midurethral sling surgery for stress incontinence also report baseline urgency incontinence. Investigators report improvement in urgency incontinence in some women with MUI undergoing midurethral sling, however, subjective outcomes are worse in women with MUI compared to pure stress incontinence and the lower cure rates are associated with persistent urgency incontinence. Studies also demonstrated that urgency incontinence is the major cause of patient dissatisfaction of surgery for stress incontinence and prolapse. Reduced satisfaction and treatment failure after midurethral sling surgery is associated with higher baseline urgency and urgency incontinence. Additionally, one study showed that 33% of women who did not have urgency incontinence symptoms prior to midurethral sling developed urgency symptoms after surgery. This study further complicates the issue, as it is possible that midurethral sling may cause urgency symptoms in some patients. Overall, studies have shown a wide range in improvement of urgency incontinence symptoms after midurethral sling placement between 46-74%. The wide range of anticipated improvement coupled with the not insignificant rate of de novo in urgency incontinence symptoms after midurethral sling, make counseling women with MUI contemplating surgery challenging. Essentially, surgeons can counsel women with MUI that although their stress incontinence symptoms are likely to improve after midurethral sling (90% satisfaction), their urgency incontinence may get better, stay the same, or get worse.

Other strategies for treating MUI have also been proposed including treatment with anticholinergic medication in addition to traditional sling surgery. In an AHRQ funded study, anticholinergic medical therapy had minimal to moderate efficacy for treatment of urgency incontinence symptoms. Furthermore, many women taking anticholinergic medications suffer bothersome side effects, such as dry mouth and constipation, and over 50% stop taking the medication during their treatment course. In our prior work, we found that women treated with anticholinergic medications prior to traditional continence surgery were more likely to have urgency symptoms post-operatively, suggesting poorer outcomes in women with MUI. Understandably, patients with persistent urgency symptoms post-operatively are significantly less satisfied with their symptoms and surgical outcomes than patients who have complete resolution of their symptoms.

Given the known treatment shortcomings of anticholinergic medications for treatment of urgency incontinences, clinician-investigators began injecting onabotulinumtoxinA into the bladder in an attempt reduce urgency incontinence while minimizing side effects. OnabotulinumtoxinA is a neurotoxin, which inhibits acetylcholine release and temporarily relaxes the bladder muscle to inhibit urgency incontinence. A large NIH funded multicenter double-blind randomized controlled trial investigated the role of detrusor injections with 100 units of onabotulinumtoxinA compared to anticholinergic medications for the treatment of urgency incontinence. More women in the onabotulinumtoxinA group were completely dry (no incontinence episodes) without having the bothersome side effects of the anticholinergic medications. Women in the onabotulinumtoxinA group also had higher rates of transient urinary retention requiring self-catheterization and urinary tract infection; however, these rates were significantly lower than earlier studies using higher doses of onabotulinumtoxinA. Several studies suggest the optimal dose of onabotulinumtoxinA, which maximized resolution of urinary incontinence while minimizing complications, is 100 units per injection. As a result, onabotulinumtoxinA injections are a standard treatment for urgency incontinence.

Given the superior efficacy and side effect profile of onabotulinumtoxinA and the high rates of persistent urgency incontinence and dissatisfaction after sling surgery in women with MUI, we hypothesize that a combined treatment approach for women with MUI is superior to simply treating the stress incontinence alone. Specifically, women with MUI undergoing sling plus intradetrusor onabotulinumtoxinA will have fewer bothersome incontinence symptoms than women undergoing sling alone. The aim of this double-blind randomized comparative efficacy trial is to determine if women with MUI planning sling surgery sustain greater improvement in their urinary symptoms with the addition of onabotulinumtoxinA injection at the time of sling.

A secondary aim is to identify subsets of women who may be prone to persistent urinary symptoms after treatment. Although classic teaching is that the urine is ‘sterile’, recent studies identified that urine of normal asymptomatic women contain bacteria; in other words, similar to all other organ systems in the body (gastrointestinal tract, skin, etc) urine is NOT sterile rather it has a microbiome. Recent data suggests that patients with urgency symptoms have a different bladder microbiome (different bacteria) than those who do not suffer from this ailment. Our unit recently found that the microbiome of women with urgency and bladder pain differs from age-matched controls.

## 3.0 Inclusion and Exclusion Criteria

All women with MUI planning surgical intervention with midurethral sling will be approached for study participation. MUI will be defined as an answer of “moderately’ or “quite a bit” bothered to Urinary Distress Inventory (UDI) items (2) “urine leakage with a feeling of urgency” AND (3) “urine leakage related to coughing, sneezing, or laughing”.

Enrolled participants must meet all the following criteria:

- Undergoing mid-urethral sling surgery
- Have symptoms of both stress and urgency urinary incontinence
- Able to consent, fill out study documents, and complete all study procedures and follow-up visits
- At least 18 years of age
- English speaking
- Be able and willing to learn clean intermittent self catheterization technique

Women will be excluded for any of the following reasons:

- History of recurrent UTI (defined as three culture proven UTIs within last 12 months)
- Systemic neuromuscular disease known to affect the lower urinary tract
- Undergoing concomitant prolapse surgery
- Previous incontinence surgery
- Treatment with anticholinergic medication in the last 2 months
    - Darifenacin/Enablex
    - Oxybutynin IR/Ditropan
    - Oxybutynin ER/Ditropan XL
    - Oxybutynin Patch/Oxytrol
    - Oxybutynin Gel/Gelnique
    - Solifenacin/Vesicare
    - Tolterodine IR/Detrol
    - Tolterodine ER/Detrol LA
    - Trospium IR/Sanctura
    - Trospium ER/Sanctura XR
    - Fesoterodine/Toviaz
    - Mirabegron/Myrbetriq
- Previous bladder injection with onabotulinumtoxinA
- Prisoner status
- Pregnancy
- Patients on SGLT2 Inhibitors
    - (canagliflozin, dapagliflozin, and empagliflozin)

## 4.0 Study Timelines

Individuals will participate and remain enrolled in the study for approximately 1 year or until they have completed their one year post-operative visit.

We estimate that it will take two years to enroll the total number of subjects required to complete this study.

We expect to be able to complete primary analyses of this study 3 years from the date of IRB approval.

## 5.0 Study Endpoints

Primary endpoint will occur at 3 months. Secondary endpoint is at 1 year, or when the subject completes her 1 year post-operative visit.

## 6.0 Procedures Involved

Women with MUI undergoing midurethral sling for bothersome SUI will be randomized to 100 units onabotulinumtoxinA or placebo (saline) injections in the detrusor at the time of sling surgery. Specifically, the retropubic midurethral slings used will be either the Gynecare TVT Exact Continence System by Ethicon or the Boston Scientific Advantage Fit Transvaginal Mid-Urethral Sling System based on surgeon preference. Surgeons and participants will be masked to study assignment. Primary outcome will be the Patient Global Assessment of Improvement (PGI-I), a global, patient oriented measure that assesses symptoms of SUI and UUI at 3-months. The primary outcome, PGI-I asks subjects to best describe how their urinary tract condition is now, compared to how it was before treatment for urinary leakage. Response choices are: (1) 'very much better', (2) 'much better', (3) 'a little better', (4) 'no change', (5) 'a little worse', (6) 'much worse', and (7) 'very much worse'. Construct validity of the PGI-I was demonstrated in incontinence trials.32

We selected a subjective, patient oriented outcome as our primary outcome measure secondary to the complex nature of MUI, and the association between dissatisfaction after incontinence surgery and persistent or new onset urgency. We felt the patient's overall impression of their continence status represented a more clinically meaningful outcome than traditional objective measures. In addition, we will compare subjective and objective urinary symptoms and quality of life amongst treatment groups 3-months and 1-year after surgery.

All women with MUI planning surgical intervention with midurethral sling will be approached for study participation. MUI will be defined as an answer of "moderately' or "quite a bit" bothered to Urinary Distress Inventory (UDI) items (2) "urine leakage with a feeling of urgency" AND (3) "urine leakage related to coughing, sneezing, or laughing".

Women will undergo standardized urologic evaluation at baseline including assessment of urinary symptoms and quality of life using short forms of the Urinary Distress Inventory (UDI-6) and Incontinence Impact Questionnaire (IIQ-7); assessment of overall severity of their incontinence symptoms with the Patient Global Impression of Severity (PGI-S);32 post void residual urine volume; urine analysis and culture; multichannel urodynamic testing; and pelvic exam with prolapse quantification using pelvic organ prolapse quantification system (POP-Q)33. All patients will also complete a 3-day urinary diary at baseline quantifying the number of incontinence episodes (stress and urge). Three months and 1-year after surgery, patients will again complete all baseline measures, including UDI, IIQ, PGI-I, PGI-S, and 3-day diary to report symptom and objective urinary symptoms after treatment. A sample of urine will be obtained for microbiome analysis at each visit.

Scheduled in-person follow-up visits will occur at baseline, 2 and 6-weeks, 3-months, and 1-year after surgery. At the baseline, 3-month, and 1-year visits,

research staff will collect the 3-day diary information and record any adverse events that have occurred during the post-operative period. Subjects will also complete the general and condition specific symptom and QOL questionnaires. In addition, an update of current medication and assessment as to whether any evaluation or treatment for pelvic floor disorders or adverse outcomes from surgery have occurred since the previous evaluation will be assessed by clinical staff at the in-person visits. All patient and survey data will be recorded in RedCAP.

## 7.0 Data and Specimen Banking

Data will be collected at Northwestern Medicine. All study data will be recorded on Case Report Forms by research coordinator and securely maintained in a locked cabinet. CRFs will be derived from source documentation and/or participant self-report. Data will be entered by the research coordinator at Northwestern into a REDCap database that will be stored on a secure sever at the Data Coordinating Center. All collected data must be entered into REDCap within 5 business days. Any queries to data entered into REDCap will be addressed by site staff within 5 business days. It is each site's responsibility to regularly check REDCap for data queries.

Both data and specimens will be banked for further use. Patient specimens will not have any directly identifiable patient information on them, but will remain coded for future studies if the specimen is unused in this study. Argonne National Laboratories will have no access to any patient identifying information. All patient identifiers will be removed prior to transferring microbiome samples to Argonne National Laboratories for processing.

## 8.0 Data and Specimen Management

All analyses will be conducted using SPSS version 20 (Chicago, IL). Histograms will be used to determine distribution of data and appropriate non-parametric or parametric tests will be selected. Primary outcome will be analyzed dichotomously with responses of "very much better" and "much better" considered an optimal outcome. A chi-square test of association will be used to compare primary outcome (PGI-I) between treatment groups. Questionnaire data will be compared between sling alone and sling plus onabotulinumtoxinA groups using Mann Whitney test. All test results will be considered significant with a p-value of less than or equal to 0.05.

In a study of women with MUI undergoing retropubic midurethral sling, 66% of patients reported a PGI-I of "very much better' or 'much better' at 3-months.23 Similarly, in a randomized trial of intravesical onabotulinumtoxinA 55% of participants had PGI-I scores of "very much better' or 'much better'. Therefore, assuming "optimal outcomes' (PGI-I scores of "very much better' or 'much better) in 66% of women undergoing sling alone and 93% in those undergoing sling plus onabotulinumtoxinA, we will need to recruit 34 patients in each group

to show a significant difference with 80% power at a 0.5 significance level. Assuming a significant attrition rate, we will recruit approximately 100 women (50 in each arm).

Data will be collected at Northwestern Medicine. All study data will be recorded on Case Report Forms by research coordinator and securely maintained in a locked cabinet that only the study coordinator has access to. CRFs will be derived from source documentation and/or participant self-report. Data will be entered by the research coordinator at Northwestern into a REDCap database that will be stored on a secure sever. Only study staff will have passwords to access the project data on REDCap.

The data that is banked locally will be entered into an electronic data capture website. All users of REDCap need an institutional username and password to log in and to enter data. Research personnel, including study staff as well as study doctors will be able to collect and have access to subject data.

All specimen collected will be stored locally in the clinic storage facility until patient de-identification and subsequent transfer to Argonne National Laboratory for analysis can be completed. Any specimens that are not used for this study will be stored for future study use. Only the study coordinator and physicians participating in the study directly will have access to the storage facility for the purposes of adding specimens and sending them out only. Specimens will be batch-shipped to Argonne National Laboratories when enough have accumulated to do so.

## 9.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

Adverse events associated with midurethral sling surgery in conjunction with onabotulinumtoxinA injection will be recorded, but only include events such as post-operative urinary retention requiring catheterization, post-operative urinary tract infection, and persistent urinary urgency. Adverse events will be recorded at each follow up visit on Case Report Forms and subsequently will be added in to REDCap electronic data capture system. The PI will be notified of any adverse events, which will be resolved with the patient.

## 10.0 Withdrawal of Subjects*

Subjects will be withdrawn from the research without their consent if they do not return for the scheduled 3 month post-operative visit. In this case, subjects will be notified that they can no longer participate and their insurance billed for the cost of the onabotulinumtoxinA used during the procedure, with the subject covering any cost not covered by insurance.

## 11.0 Risks to Subjects*

Risks associated with the project are minimal. Patients participating in the project will already be undergoing a retropubic midurethral sling for bothersome stress

urinary incontinence, and will already have been counseled on and have understood the risks associated with that surgical procedure. None of the risks associated with that surgical procedure will change (increase or decrease) by participating in this study.

This additional risks associated with the procedure are for the patients in the onabotulinumtoxinA arm. Intravesical injection incurs a 5% increased risk of urinary retention requiring clean intermittent self catheterization. All patients will be taught this technique prior to the procedure regardless of study arm. Those with urinary retention have an increased risk of urinary tract infection. This is time-limited and last for less than 2 months on average. All patients will be informed of these risks as part of the consent process.

Another risk to subjects is that we will be collecting their personal health information in a database. All of the data will be kept confidential and will be stored on password protected, secure servers, or in locked cabinet files that only study staff on the project have access to. Personal health information will be stored on files that are separate from the subject's name, all health information will be coded. Coded list will be kept on secure, password protected file.

## 12.0 Potential Benefits to Subjects

Given the superior efficacy and side effect profile of onabotulinumtoxinA and the high rates of persistent urgency incontinence and dissatisfaction after sling surgery in women with MUI, we hypothesize that a combined treatment approach for women with MUI is superior to simply treating the stress incontinence alone. Specifically, women with MUI undergoing sling plus intradetrusor onabotulinumtoxinA will have fewer bothersome incontinence symptoms than women undergoing sling alone. It is possible that subjects will have significant improvement in quality of life due to the improvement in urinary symptoms that they would not have been offered without this study.

## 13.0 Sharing of Results with Subjects

Results will not be directly shared with subjects

## 14.0 Setting

Research will be conducted in Northwestern Medical Group's outpatient clinic, the Integrated Pelvic Health Program (IPHP). Potential subjects will be identified and recruited by physicians within the practice. Once potential subjects are identified, the study coordinator will provide the patient with information about the study. If the patient is interested in joining the study, the study coordinator will consent the patient in the IPHP clinic. The patients will complete questionnaires per the study either at home or in the clinic in a private room. Demographic and medical and surgical data will be collected from the patient's medical record and recorded on the RedCAP secure server.

After consenting to the study, the surgical procedure that subjects are undergoing as part of their standard of care will be performed at an NMHC facility. The onabotulinumtoxinA injections will be performed in the operating room by one of the study physicians. Randomization will be performed via RedCAP on a secure online server through a hospital computer.

The subjects post-operative visits will take place in the Integrated Pelvic Health program, and NMHC outpatient clinic, as part of standard of care. Additional questionnaires will be completed at these visits and data will be collected from these visits as well.

## 15.0 Resources Available

The staff that will be involved in this research are highly qualified. The Principle Investigator, Dr. Kimberly Kenton, is the chief of Female Pelvic Medicine and Reconstructive Surgery and is nationally and internationally recognized for research in pelvic floor disorders and has served as primary investigator on many studies funded by the National Institute of Health. She has authored or co-authored 150 scientific papers and currently serves on the editorial board of Obstetrics & Gynecology and the Journal of Female Pelvic Medicine & Reconstructive Surgery. The other study physicians assisting in recruiting efforts have completed their fellowships in Female Pelvic Medicine & Reconstructive surgery and are both involved in numerous research studies and serve as reviewers for several scientific journals. The nurse practitioner on staff at the IPHP has worked on several other protocols during her time at Northwestern. The study coordinator on staff has over 3 years of research experience and 1 year of experience working in clinical trials and consenting patients.

Due to the high volume of patients that present with mixed urinary incontinence in our clinic, it is feasible that the required number of suitable subjects will be recruited within the estimated window of time. Also, since study participants are undergoing surgery as part of standard of care, they will be more likely to return for their follow-up visits since these are part of their standard post-operative care. Our center will begin enrolling participants once we have IRB approval, tentatively July 2015. With the time required recruit 100 patients (approximately two years), collect outcomes data on the enrolled subjects for a year, and analyze data, this study will be active until June 2018.

The Integrated Pelvic Health Program, affiliated with Northwestern Memorial Hospital, helps individuals with pelvic floor disorders. It is the only program in the Chicago area that brings together a multispecialty approach to pelvic floor disorders in one location. Our dedicated team of physicians, nurses, and physical therapists are committed to restoring the quality of life for people with such disorders. Both the physicians and the facilities offer state-of-the-art resources to ensure the highest quality evaluation, medical and surgical care to women with incontinence and prolapsed. Our physicians are national leaders in minimally

invasive pelvic reconstructive surgery and sacral nerve stimulation for urinary and fecal incontinence.

All study staff members are in possession of the protocol and the protocol has been reviewed by all of the study members during a research conference. Research procedures have been made clear and were outlined by the study coordinator and Principle Investigator.

## 16.0 Recruitment Methods

Subjects with mixed urinary incontinence already undergoing retropubic midurethral sling for bothersome stress urinary incontinence will be identified at the Integrated Pelvic Health Program, and Northwestern Medicine. Once potential subjects are identified, the study coordinator will provide the patient with information about the study.

The source of the subjects will be those women meeting criteria for mixed urinary incontinence who are already undergoing a retropubic midurethral sling for bothersome stress urinary incontinence with one of the providers at the Integrated Pelvic Health Program affiliated with Northwestern Medicine.

## 17.0 Local Number of Subjects

This is a single center study at Northwestern Medicine. We will require up to 100 participants to meet power requirements for this study while appropriately accounting for attrition rate.

## 18.0 Provisions to Protect the Privacy Interests of Subjects

To protect privacy interests, the personal health information collected for research purposes will be collected from the subject's electronic medical record to limit the amount of people they interact with and provide personal information to.

All interviews will be conducted in a private office or examination room to ensure confidentiality. Phone conversations will be conducted from private offices. Any study correspondence with patients will not indicate disease status or focus on the envelope. All physical exams will be conducted in a private examination room. Subjects will be allowed to skip any question on a questionnaire that makes them feel uncomfortable.

The study staff, including investigators and the study coordinator, will have access to the subject's medical record and study documents. All study documents will be kept in a locked cabinet and only those with password required access to EPIC will be able to access the subject's electronic medical record.

## 19.0 Compensation for Research-Related Injury

Subjects in need of medical follow-up will be referred to their provider. There will be no compensation for research-related injury.

## 20.0 Economic Burden to Subjects

Because these patients will already be undergoing retropubic midurethral sling as an inclusion criterion for participation in this study, each participant would already be incurring the costs of visits, parking, all pre-operative and post-operative testing, and operating room fees. There are no additional tests or visits required as part of this study. All onabotulinumtoxinA used and placebo saline in addition to syringes and needles will be covered in the study budget and not incurred by the patient or the patient's insurance.

## 21.0 Consent Process

Consent will be obtained from the patient by research staff, either by the study coordinator or by one of the investigators. The informed consent process is expected to take up to 30 minutes. The person obtaining consent will verbally go through the form and also allow time for the subject to read the form in its entirety. The subject will be allowed to consult with family. The person obtaining consent will ensure the subject understands the purpose and procedures of the study. After all the subject's questions have been answered, the subject will be given time to make a decision about enrollment. The original signed written consent form will be kept separately from research data at Northwestern, and a signed copy will be given to the patient. We will not be enrolling Non-English speaking subjects. Decisionally-impaired subjects will not be enrolled in our study.

## 22.0 Process to Document Consent in Writing

We will be following "SOP: Written Documentation of Consent (HRP-091)" and will be documenting process of consent in writing.

## 23.0 Drugs or Devices

OnabotulinumtoxinA and placebo saline will be stored in the IPHP clinic in a locked cabinet (as is currently done). Once the patient is randomized, the study coordinator will inform the clinic RN who will sterilely prepare the medication and deliver it to the operating room with the patient's study number on the medication, so both the patient and the physician remain masked. Lot number and expiration date will be recorded for each study patient.