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Refractory Overactive Bladder: Sacral NEuromodulation v. BoTulinum Toxin Assessment (ROSETTA)

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A. STUDY AIMS

The purpose of this randomized, open-label, active-control trial is to compare the effectiveness of intra-detrusor botulinum toxin A (Botox A[®], Allergan) versus sacral neuromodulation (InterStim[®], Medtronic) for the treatment of refractory urge urinary incontinence. In addition, the study will evaluate select technical attributes of the interventions as well as the effect of these two interventions on other lower urinary tract and pelvic floor symptoms.

A.1 Primary Aim

To compare the change from baseline in the number of urge urinary incontinence episodes (UUIE) over the six month follow-up period in women randomized to sacral neuromodulation (InterStim[®]) therapy, versus those randomized to intra-detrusor injection with 200 units of botulinum toxin A (Botox A[®]).

Hypothesis: InterStim[®] therapy will result in a greater reduction in daily urge urinary incontinence episodes over the 6-month follow-up period as compared to Botox A[®] injection

A.2 Secondary Aims

1. **Long Term Efficacy:** To compare the long-term (12 and 24 month) efficacy outcomes in women randomized to sacral neuromodulation (InterStim[®]) therapy, versus those randomized to intra-detrusor injection with 200 units of botulinum toxin A (Botox A[®]). Secondary efficacy outcomes, collected at 12 and 24 months as well as at 6 months, include adequate control of their urge urinary incontinence, change in bothersome symptoms of urinary urge incontinence (UUI), severity of urge incontinence, urinary frequency, nocturia, subject satisfaction with therapy, quality of life measures and bowel and sexual function.
2. **Cost Effectiveness:** To compare utilization of medical resources for cost effectiveness analysis and cost-utility between treatment groups.

3. **Treatment Safety and Burden:** To assess safety profile and treatment burden of both interventions by comparing adverse event incidence between treatment arms, and also by obtaining estimates of incidence of treatment-specific safety and burden outcomes. Safety and burden outcomes for Botox A[®] injections include receipt of additional injections and intermittent catheterization due to voiding dysfunction/partial urinary retention. Safety and burden outcomes for InterStim[®] device include infection, pain, lead migration, reprogramming (and reasons for) and surgical revision (and reasons for).
4. **Optimize InterStim[®] programming:** To establish InterStim[®] programming parameters that resolve adverse experiences, optimize effect and avoid surgical revision.
5. **Predictors of poor outcomes:** To determine if baseline urodynamic parameters, other clinical factors or selective “biomarkers” predict poor clinical response or adverse events within each treatment group.

B. BACKGROUND AND SIGNIFICANCE

Overactive bladder (OAB) typically manifests with the symptoms of urgency, with or without urge incontinence and usually with frequency and nocturia. Urge incontinence afflicts 17% of women over the age of 45 in the United States and 27% of all U.S. women over the age of 75.¹ Furthermore, women affected by urge incontinence suffer significant reduction in quality of life.² As opposed to stress urinary incontinence (SUI), which is predictable in occurrence and severity, urge incontinence usually occurs with little warning and is variable in the amount of leakage. The monetary ramifications of incontinence are likewise considerable. Among community dwelling and institutionalized patients in the United States, an estimated \$32 billion is spent caring for complaints of urinary incontinence, which is largely resultant from overactive bladder.³ Using population projections from the US Census Bureau from 2010 to 2050, it has been forecasted that the number of American women with urinary incontinence will increase 55% from 18.3 million to 28.4 million during this time period.⁴

Conservative first line treatments for urge incontinence include behavioral therapy including pelvic floor training +/- biofeedback and medications. Behavioral therapy treatments for urge UI consist of several components: pelvic floor muscle (PFM) training, bladder control strategies, bladder retraining to delay voiding and management of fluids. A 2004 Cochrane review concluded that, although limited, the evidence is favorable that bladder training reduces incontinent episodes; however, no recommendations could be made as to which technique is best or whether adding bladder training to another treatment enhances any effect.⁵ A multi-component approach (combining behavioral training and pelvic floor muscle exercises or biofeedback with either of these therapies) has been reported to be most effective at reducing incontinent episodes.^{6,7} Behavioral training and pelvic floor training are ideally recommended for a person who is motivated and able to attempt these interventions, both physically and cognitively. In addition, the clinical effects of the conservative therapy tend to wane over time and there lacks evidence in the literature for any long term benefit for this therapy.

There have been various classes of drugs used for the treatment of urinary urge incontinence; however, the medical therapy with the most supporting evidence is anticholinergic medication. Anticholinergic medications target the action of acetylcholine (Ach) on the bladder.² These drugs appear to work at the level of the detrusor muscle by competitively inhibiting Ach at the M₂ and M₃ receptors to reduce the number and volume of incontinence episodes. Symptom improvement has been shown to be statistically significantly better than placebo; however, reductions in baseline urge incontinent episodes/day reflect a modest margin of benefit above placebo.⁸ Furthermore, no one anticholinergic drug has been found to be superior than any other even when comparing the newer selective agents and there is little information on the long term benefit from continued use of the anticholinergics.⁸ Side effects and poor efficacy often lead to discontinuation of these medications in a significant number of patients. A population-based study found that only 56% of women felt their OAB medication was effective and half stopped taking the medication.⁹ In addition, anticholinergics are contraindicated in individuals with uncontrolled narrow angle glaucoma, significant cardiovascular disease and other disorders common to the older population.

Women with refractory UUI have spent years participating in pelvic floor muscle training, bladder control strategies, restricting their fluids and worried about doing activities outside the house where bathroom availability is unknown. In addition, they have tried anticholinergic therapy without significantly improving their incontinence. Studies performed on patients with refractory urinary urge incontinence have shown significant baseline impairments in their quality of life on a number of disease specific quality of life questionnaires such as the Urogenital Distress Inventory, King's Health Questionnaire and the SF-36 Health Survey while on first line therapy.

^{14,18,29,39-42} In addition, when objectively documenting frequency and severity of incontinent episodes, these refractory patients report a mean number of large incontinent episodes/day of between three and eight. ^{13-15,29,39-41,43,44,54} Prior to the 1990's, the only alternative therapy was invasive surgical procedures such as bladder denervation, autoaugmentation, augmentation cystoplasty, and urinary diversion. These procedures were extensive and irreversible with poor efficacy and increased morbidity. Neuromodulation techniques were initially investigated beginning in the 1980's, in spinal cord injury patients. However, the techniques were found to have limited success and troublesome side effects, as a posterior sacral root rhizotomy was necessary to abolish all reflex activity of the anal sphincter during intradural anterior sacral stimulation. Unintended functional results occurred such as fecal incontinence and sexual dysfunction, as well as autonomic hyperreflexia hypertensive crisis during stimulation. ¹⁰ Nevertheless, the technique was refined in the non spinal cord injured patient and in 1990. Schmidt RA et al. reported on placement of an electrode through the sacral foramen to access extradural sacral nerve roots and stimulate the bladder. ¹¹

B.1 Sacral Neuromodulation for Refractory Overactive Bladder

Control of urine storage and bladder emptying is achieved by a complex interaction between the detrusor muscle, muscles of the urethra and pelvic floor, peripheral nerves, spinal cord and higher brain centers. A disruption at any level can interfere with lower urinary tract function. Electrical nerve stimulation (neuromodulation) has been used to overcome these problems. The only implantable neuromodulation system FDA approved in the United

States for the treatment of refractory urge incontinence is InterStim[®] (Medtronic, Minneapolis, MN) therapy, or sacral neuromodulation stimulation (SNS). InterStim[®] Therapy was commercially released in Europe, Canada and Australia in April 1994 and in September 1997, the FDA approved InterStim[®] Therapy for the treatment of refractory urinary urge incontinence. There have been over 40,000 devices implanted worldwide and in 2009, 9,500 devices were implanted in the US alone.

With this stimulation, an electrode is placed via the sacral foramen alongside a sacral nerve (usually S-3). In a second procedure, the lead is connected to an implanted programmable pulse generator (IPG) that provides stimulation within set stimulation parameters. The mode of action when the nerve is stimulated is thought to involve signals travelling toward the periphery and central nervous system activating somatic afferent axons in the sacral spinal roots, direct inhibition of bladder pre-ganglionic neurons, and by inhibiting interneuron transmission in the afferent limb of the micturition reflex.¹² Patients who are selected to have treatment undergo a therapeutic trial in which the S-3 sacral nerve root is stimulated by an external pulse generator. This period of test stimulation (usually 5 – 10 days) is critical to determine if a patient has an adequate clinical response. An optimal response during test stimulation, defined as $\geq 50\%$ improvement of baseline urge urinary incontinence episodes (UUIE), will qualify the patient for permanent implantation of the generator.

There have been two studies that randomized urge incontinent participants (total=142) to either an immediate implant or a delayed implant.^{13,14} Those in the delayed group had initially responded to the test stimulation procedure and underwent the full implant after six months and served as the control arm during that time. At 6 months, both studies reported about half of the implanted group was dry (47% and 56%) v. 4-5% in the control; in addition both studies found a statistically significant improvement from baseline to 6 month in the implanted group compare to the control group. In the first study¹³, mean leakage episodes decreased in the implanted group (mean \pm SE: 9.7 \pm 6.3 to 2.6 \pm 5.1, $p < 0.0001$) and pad usage (mean \pm SE: 6.2 \pm 5.5 to 1.1 \pm 2.0, $p < .0001$) compared to the control group (mean \pm SE leakage episodes: 9.3 \pm 4.8 to 11.3 \pm 5.9, $p = 0.2$; and mean \pm SE pad usage:

5.0±3.7 to 6.3±3.6, p=0.3). In both RCTs, a second efficacy test (therapy evaluation test) was performed 6 months after implantation and consisted of deactivating stimulation for a minimum of 3 days. The effects of inactive stimulation on voiding behavior were documented for 3 days and then stimulation was reactivated. Both studies reported that upon discontinuation of stimulation a significant rebound was observed in mean leakage episodes, leakage severity and pad usage to levels comparable with those prior to implant. With resumption of stimulation these outcome measures decreased significantly again. Sustained improvement in baseline incontinence parameters has been documented at 3-5 year follow-up. For patients with urge incontinence, a 3 year study reported a 57% reduction in incontinence episodes/day (mean±SE: baseline 11.6 +/- 6.6 to 5.0 +/-6.1 at 3 years)¹⁵. In another study, 58% of those initially implanted had follow up at 5 years and the mean leakage episodes decreased from 9.6±6.0 (mean±SE) to 3.9±4.0 (mean±SE) at five years (p<0.001).¹⁶ A systematic review of sacral nerve stimulation for urgency, frequency and urge incontinence, reported that the results of the seventeen case series studies at follow up periods up to three to five years after implantation were similar with the evidence from the randomized studies with approximately 39% cured and 67% with a >50% improvement in incontinent symptoms.¹⁷ One study evaluated satisfaction and its correlation to objective data, it found that 84% of patients implanted were satisfied with their device at a mean of 27 months.¹⁸ The amount of pad weight reduction at the time of implantation (84.5% reduction in satisfied group v 60.6% reduction in dissatisfied group) was found to affect satisfaction.

No life threatening or irreversible adverse events have been reported, although in a retrospective review spanning 11 years, 53% of patients experienced a mild to moderate reportable event.¹⁹ The majority the events did not affect continued use of the therapy. The applicability of the long term studies is limited because the technology has changed over time. Initially, this device was implanted using larger incisions and the lead was threaded through plastic devices sutured directly to the lumbodorsal fascia. In 2002, the tined lead became available, which allowed for leads to be implanted with a minimally-invasive technique. Over the last decade generators have also changed in size and location of implantation. With these advances,

surgical revision rates are reported to range from 3-16%.^{20,21,22,23} with a 6% explantation rate due to lack of efficacy²² and 5-11% due to infection.^{21,24} A retrospective cohort study spanning 2001-2008 evaluated predictors for complications with the InterStim[®] device.²⁵ This cohort included those undergoing InterStim[®] for urge incontinence, urgency/frequency, retention and pain. Significant predictors were a history of trauma ($p < 0.001$), a change in body mass index ($p < 0.001$), enrollment in a pain clinic ($p = 0.008$), the duration of follow up ($p = 0.002$) and a history of adverse events ($p < 0.01$). The authors found that 67/202 patients (30%) experienced an adverse event categorized as pain, lack of efficacy, lead migration, hematoma, infection, trauma, and elective removal. The mean follow up was 36.9 months and most adverse events were experienced within the first 17 months. They concluded that patient selection is important to avoid adverse events since 16/67 patients (24%) had two or more than two AEs.

The tined lead has facilitated SNS testing via staged implantation of the chronic lead, rather than exclusively using percutaneous nerve evaluation (PNE). In studies where both procedures were performed and the authors reported separate test stimulation outcomes, the two stage approach had a higher response rate during the test phase (67-88% success rate) compared to PNE (20-46% success rate).^{19,22,26,27} One study used Medicare CPT codes associated with the test stimulation procedures (PNE and 2 stage) and ICD-9 diagnosis codes for urinary retention, urgency, frequency or urge incontinence to analyze success rates for the test stimulation procedures in the Medicare population.²⁸ The 2 Stage procedure achieved more success in females, when performed by a urologist, on those under the age of 79, and for a neurogenic bladder diagnosis, while poorest success was seen in patients with the diagnosis of interstitial cystitis. Overall this study using Medicare data reported success rates of the test stimulation procedure (PNE and 2 Stage) of 40%, the authors concluded that their cohort may represent an older and more disabled population.

There is a paucity of literature regarding predictors for success with not only the testing phase but with long term use of the device. A retrospective study evaluating fifty- five refractory urge incontinent women found a statistically significant difference in long term cure or "dry" rates in women aged < 55

years (65% versus 37% for older individuals ; $p=0.05$).²⁹ Women having three or more chronic conditions or a neurologic condition had a lower cure rate in both younger and older individuals. The absence or presence of detrusor overactivity, seen on urodynamics, has not been found to predict success of the test stimulation period nor clinical outcome 6 months after implantation.^{30,31} However, South et al. reported, that in a cohort of 104 patients, age and severity of incontinence were found to be associated with success. Women older than 65 years of age were 3.5 times less likely to respond; furthermore, those with >4 UUIE/day were 3.1 times less likely to respond.

Although InterStim[®] is routinely used to treat refractory overactive bladder symptoms, prospective studies evaluating predictors for response and improved management of the device to potentially avoid adverse events are needed. In addition, there have been no randomized studies comparing the efficacy of this therapy to any other.

B.2 Botulinum A Toxin for Neurogenic Overactive Bladder

In recent years there has been increasing use of botulinum toxin for the treatment of neurogenic and nonneurogenic refractory overactive bladder symptoms. Botulinum toxins are potent neurotoxins with a high affinity for acetylcholine producing nerve cells and act by inhibiting acetylcholine release at the presynaptic neuromuscular junctions. Early studies have shown promising results for a condition where there have been few options between pharmacotherapy and surgery. Currently, Botulinum toxin type A (Botox A[®]) is marketed under the trade names of Botox A[®] and Dysport (not available in the US). The FDA approved uses include cervical dystonia, blepharospasm, strabismus, essential hyperhidrosis, and for cosmetic treatment of glabellar lines.³² Recent clinical trials have demonstrated efficacy in other conditions including achalsia, anismus, and urinary disorders such as detrusor sphincter dysynergia and neurogenic and non neurogenic detrusor over activity.

In August 2011, Botox A[®] was approved for the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g. SCI, MS) in adults who have an inadequate response to or

are intolerant of an anticholinergic medication. Two double-blind, placebo-controlled, randomized studies reported significant improvements compared to placebo in the primary efficacy variable of change from baseline in weekly UIIE at the primary endpoint of 6 weeks. Schurch et al. introduced Botox A[®] injection to treat neurogenic detrusor overactivity (NDO) and performed the first randomized, placebo controlled study in 59 patients, 89% of whom were spinal cord injured.³⁴ After 2 weeks, 63% of the treated patients were continent v. 23% of the placebo group. In the Botox treated group, statistically significant improvements in IE/day, maximum cystometric capacities and quality of life measures were seen throughout the 24 week follow up. The dosage of Botox A[®] was not standardized, 200 and 300 units were used, and both doses resulted in a 54-58% reduction in mean incontinent episodes. In another placebo controlled study evaluating a population of both spinal cord injured as well as patients with multiple sclerosis, Botox A[®] dosage was randomized to 200 units or 300 units. At 6 weeks, 38-39% of patients receiving either dose of Botox A[®] were continent compared with 7.6% placebo. At 3 months, 70% of the patients receiving either dose had a >50% decrease in UIE and the mean duration of effect was 42 weeks.³⁵ Other studies have confirmed urodynamic changes including decreased detrusor pressure and increased bladder capacity following treatment with botulinum toxin in NDO.^{36,37,39}

B.3 Botulinum A Toxin for Refractory Idiopathic Overactive Bladder

Since the original descriptions of the effects of Botox A[®] on subjects with NDO, there have been three placebo controlled studies showing the effectiveness of 200 units of Botulinum A Toxin for refractory idiopathic detrusor overactivity (IDO). (Table 1) All three studies reported a significant improvement in incontinence parameters and patients' assessment of their improvement as early as 4 weeks after injection.^{39,40,41}

The Refractory Urge Urinary Incontinence and Botulinum A Injection (RUBI) trial demonstrated that approximately 60% of women who received 200 units of Botox A[®] had a clinical response based on the patient global improvement of incontinence score, PGI-I, and the median duration of their response was 373 days. The mean PGI-I two months post initial injection was significantly better in the Botox A[®] group v. placebo (2.7 versus 4.0, p=0.003). Baseline UIE on a 3 day bladder diary was similar between Botox

A[®] and placebo (17.12 +/-13.4 versus 16.15 +/-14.7). One month after injection, there was a highly significant difference in the number of urge incontinence episodes (IE's) ($P < 0.0001$) and total IE's ($p < 0.0001$) on a 3-day bladder diary compared with placebo, with 72% of subjects receiving Botox A[®] experiencing a 75% reduction in UIIE. Urinary retention was defined as a post void residual (PVR) > 200 ml irrespective of symptoms. This occurred in 12 of 28 women (43%) exclusively in the Botox A[®] treated cohort; however, 9/12 with elevated PVRs were asymptomatic.⁴⁰

In another RCT, 16 men and women received 200 units Botox A[®]. Baseline UIIE/day were similar between the two groups (BTX=4.98 versus placebo=3.91), only the BTX arm had a statistically significant decrease in UIIE at 12 weeks and at 6 months 50% of those receiving Botox A[®] continued to have improved continence. Although urodynamic parameters improved in all patients receiving Botox A[®], 12.5% of the group were perceived as having a poor clinical response. Acute retention was not reported but 33% had increased PVRs > 200 ml.

In the last RCT study⁴¹ (Botox A[®] v. placebo), the authors reported on their 6 week data. The dose of Botox A[®] was randomized to 200 or 300 units. Baseline UIE/day were similar [Botox A[®] 8 (5.1) v placebo 7.9 (3.6)]. Sixty percent of those receiving Botox A[®] experienced a mean improvement between 60 to 80% in the pad weight, QOL and incontinent episodes/day and no significant change was seen in the placebo group. Minimal response to Botox A[®] was seen in 4/15 patients (27%); there was a statistically significant increase in PVR in the Botox A[®] group from a baseline of 25 ml to 107 ml ($p = 0.0025$) with no significant change in the placebo group (30 ml to 27 ml [NS]). Four (26.6%) subjects receiving Botox A[®] experienced PVR values > 200 ml at the 6-week evaluation. One was symptomatic and required intermittent catheterization at 3 weeks.⁴¹

These three randomized placebo controlled studies evaluated a refractory IDO population with similar baseline incontinence severity, based on IE/day. Using 200 units, each study reported early statistically significant improvements compared with placebo and two of the studies with longer follow up showed durability past 6 months. The findings regarding increased

PVRs were also similar with 30-40% having PVRs > 200 ml but a smaller percentage experiencing symptoms.

There are 3 case series (Table 1) published totaling 123 NDO and 58 refractory IDO patients, in which 300 units was used for NDO and 200 units for refractory IDO.^{42,43,44} Mean baseline UUIE/day were similar between the three studies [NDO 3.5 (0.7) v IDO 4.0 (1.1)]. All three studies reported statistically significant reductions in UUIE/day in both NDO and refractory IDO at 4 weeks. Total continence was reported in 55% NDO and 57% IDO at 4 months.⁴³ The mean time to return of baseline symptoms was 10.4 months and to reinjection 13.5 months.⁴² Two of these studies reported on the need for intermittent catheterization with similar results (88% and 69% NDO v. 12.5% and 19% IDO).^{42,44} These studies highlight the similarities in baseline incontinence parameters between NDO and refractory IDO populations and the long term durability of a single dose injection at the respected doses. However, a difference in need for intermittent catheterization was seen between the NDO and refractory IDO populations.

Table 1. Summary of Studies with Botulinum A Toxin Dose of 200 units

Author	Design	N	Baseline UUIE/day	Outcome Definition	Outcome	Retention or PVR
Brubaker ⁴⁰	RCT:	BTX: 28 Pbo 15	5.17 (based on 3 day diary	Failure = PGI-I score >=4;	60% Botox; resp Med resp time 373 d (BTX) vs 62 d (Pbo)	12/28 (43%) BTX vs 0 Pbo (PVR>200), Med time 62 d
Sahai ³⁹	RCT:	BTX 16 Pbo 18	4.98 (BTX); 3.91 (Pbo)	MCC; UUI episodes on diary, QoL by IIQ-7, UDI-6	Increase in MCC (264 vs 168); Sig changes in freq and UUIE;	6/18 (33%) with PVR > 150
Flynn ⁴¹	RCT:	BTX 15 Pbo 7	8 (BTX) 7.9 (Pbo)	UUIE/day, UDI/IIQ at 6 weeks, 2nd 24 hour pad weight,	IIQ-7, UDI-6 and pad weight and pads/day sig chg; no change in MCC & UUIE	26.6% PVR>200 at 6 weeks, 1 symptomatic requiring ISC
Kalsi ⁴²	CS	101	2.6 (IDO) 3.4 (NDO)	Primary: > 25% improvement in 2/5 parameters (freq, urg, # UI/24hrs, max cap or max Pdet) on 4d diary Secondary: >50% improvement	IDO Prim Improvement: 1mo: 30/38 (79%) 4 mo: 20/38 (53%). IDO Sec improvement: 1mo: 26/38 (68%) 4mo: 16/38 (42%) Sec Duration (Kaplan Meier mean) 13.5 mo	at 4 months CISC: IDO 2/16 (12.5%) NDO 15/17 (88.2%)
Kalsi ⁴³	CS	24	6.3 (IDO) 3.3 (NDO)	bladder diary	sig dec in freq, nocturia by 4 weeks	NC
Popat ⁴⁴	CS	75	3.2 (IDO) 3.9 (NDO)	Primary: > 25% improvement in 2/5 (see above); continent = no IE on 4-d diary	Meds: IDO: 11 on meds, 4 d/c'd at 4wks but 2 restarted at 16wk	IDO: 6/31 (19%) CISC. NDO 9/13 (69%)
Rajkumar ⁴⁵	CS	15	NC	UDS 6 wks; BFLUTS and KHQ 6wk and q mo and diaries	6 wks: DOA eliminated 6/15 (40%) Return of Symptoms: 13/15 (87%) with mean 24wk time (range 10-52)	PVR > 200 3/15 (20%)
Kuo ⁴⁶	CS	20	NC	Excellent = continent w/o diff void, improved = PS improved ≥ 50% or incont grade ↑ by 1 grade; success = excel or improv	IDO pts: 3 mos: 7/9 (78%) success; "treatment failure in 3/20 (15%)"	2ks: 10/20 (50%) PVR >250; 6mos, 30% PVR > 1/3 capacity
White ⁴⁷	CS	21	NC	>50% improvement in pads/day and voiding frequency	Baseline pads/day 4 (.89), 1 mo 13, 6 mo 2.8; 9 mo 4.06; mean duration of efficacy(>50% improvement) was 7.12 mo (range 5-11)	no retention; no reported increase in PVR; mean PVR at one month was 61cc.
Makovey ⁴⁸	Cohort	85	NC	Patient reported symptomatic improvement and requests for future repeat injections	Improvement: 58/85 (68%); duration of efficacy 6.9 mo (range 4 to 11)	No patients had incomplete bladder emptying requiring ISC
Khan ⁴⁹	CS	81	NC	primary: UDI and IIQ; secondary need for reinjection and CISC	Significant improvement in all QOL scores;); median inter-injection interval was 15 mo, after 1st injection; 12 mo after 2nd injection; 14 mo after 3rd injection; 13 mo after 4th	PVR>100 required CISC: overall rate 43%; if a pt needed CISC after BTX, it was always needed after subsequent injections

NC=Not commented on in this study

Long term efficacy after a single Botox A[®] injection has been reported in other publications using 200 units. (Table 1) Four case series, totaling 104 patients, published follow up until at least 6 months.^{45,46,47,48} The study outcomes varied and included urodynamic and objective bladder diary and pad usage parameters but in general all reported 60-76% of patients experiencing a $\geq 50\%$ improvement. The mean duration of the effect was consistent amongst the studies to be 6-7 months (range 5-11). However, Khan reported on a longer duration of effect in a refractory IDO using 200 units when the criteria for reinjection were subjective reporting of recurrent UUI symptoms. The median interinjection interval was 15 months after the first injection with minimal decrease in interval time between repeat injections 2 through 4.⁴⁹

There are publications reporting on improved subjective and urodynamic outcomes in refractory IDO using 100 or 150 units.^{50, 51, 52, 53,54} (Table 2) Two of these studies used 150 units and had similar three month continence rates of 58% and 57%.^{53,54} Cohen's study population was randomized to either 150 units versus 100 units. The group receiving 100 units had a significantly lower continence rate at 3 months of only 25%.⁵² Furthermore, nearly all subjects were back to baseline incontinence by 6 months in Flynn's study.⁵⁴ Of the studies reporting on 100 units, Kuo randomized subjects to detrusor, suburothelial or bladder base injections. Although patient satisfaction was 93%, 80% and 67% at 3 months post injection, there was no statistically significant change in UUIE/day from baseline in the detrusor or suburothelial injected groups and by 6 months satisfaction was 67%, 47% and 13%.⁵² Other studies using 100 units, one study included dry OAB patients, reported 3 month satisfaction outcomes in 80-88% of patients.^{50,51} The studies using lower doses highlight early satisfaction and improvement in symptoms; however, both outcomes appear to decrease after 3 months.

Table 2. Summary of Studies with Botulinum A Toxin Dose of 100 to 150 units

Author	Design	N	Baseline UUIE/day	Outcome Definition	Outcome	Retention or PVR
Cohen ⁵⁴	RCT	44	9.8 (BTX) 9.3 (Pbo)	>50% reduction of UUIE at 3 months	100 units: 8/12 (67%) 150 units 9/12 (75%) (Difference not significant at 0.05 level)	CIC:PVR>100cc symptomatic or >200 and asymptomatic; 2 pts, 1 in each dose CIC for retention (PVR>350), able to void by 16 wks 0/7
Flynn ⁵⁵	CS	7	Med 7 Range 2-15	Primary: No. IE per 24 h on 3d diary; Secondary: IIQ-7, UDI-6	3 mos: ≥50% improved continence: median 1.66 UUIE/day, freq, QoL, pad tests; 6 mos: recurrent UUI; 4 UUIE/day	
Kuo ⁵²	RCT	45	6.8 (suburo) 11.3 (detrusor) 11.1 (bladder base)	Satisfaction based on symptom improvement > 75%, 50-75%, 25-50%, <25%	Satisfied (order of Detrusor, Subroth Bladder base): @ 3 mo: 14/15 (93%), 12/15 (80%) , 10/15 (67%) @ 6 mo : 67%, 47%, 13% @ 9mo: 20%, 20%, 6.7%	Acute retentn: 2 detr, 2 suburo, 0 in base; PVR>150: 33%, 47% and 13%
Dmochowski ⁵⁸	RCT	313	NC	Change from baseline in UUIE/week at 12 weeks	@ 12 weeks; mean change from baseline in UUIE was -17.4,-20.7,-18.4,-23,-19.6,-19.4 for Pbo, 50,100,150,200,300 U;	PVR>200 at any visit; 2.3% (Pbo), 8.9%(50) 18.2%(100), 28%(150) 23% (200), 25.5%(300) max PVR effect @ 2 wks; PVR volumes then declined
Kuo ⁵³	RCT	75	NC	Self reported UI 0-3 grade, 0 = continence, 3=severe UI; Voiding diff 0-3 grade, 0=no diff 3=severe diff; Excellent (E). when UI=0 and diff inc < 2; Improved (I) when UI improved by >=1 and void diff < 2	Subjective reporting of improvement IDO (E or I): 100U 73.3%; 150U 77.7%; 200U 81.8% Overall, 3mo E: 35% (100), 36%(150), 41%(200); I: 48%, 56%, 48%; Duration E/I 100U 3.5m (3-7); 5.5m (5-9); 200U 6.7m (4-12)	PVR >150: 100U 30%, 150U 72%, 200U 52%
Werner ⁵¹	CS	26	NC	f/u 1, 3 & 9 mos UDS, diary, KHQ; Fail = no UDS or subj change; (no analysis)	1 mo: 69% subj dry; 3 mo 80% subj dry; 9mo 1/5 (20%) subj dry	2 on CISC
Schmid ⁵⁰	CS	100	NC	Incontinence scale (1=none, 2 mild/mod, 3 severe); e pt scales for Urgency, Satisfaction; QOL = KHQ; Fail = no UDS or subjective change after BTX	1 & 3 mo: 88% with improved subjective and UDS parameters; @ 9 mo: absent in 7 (33%), mild 10 (50%) and severe 3 (17%); Mean efficacy 6 +/- 2 mo.	4/100 (4%) pts retention PVR > 400; return to baseline by 6-9mos

NC=Not commented on in this study

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The lack of long-term durability using a lower dose is further outlined in a study, which randomized subjects to 3 doses. (Table 2) Kuo reported on 75 patients with detrusor overactivity refractory to anticholinergics and randomized the cohort to 100, 150, or 200 units of Botox A[®].⁵³ Urinary incontinence at 3 months was graded on a self-reported scale of 0 to 3, representing mild, moderate and severe incontinence. At 3 months 34.8%, 36%, and 40.7% of patients treated with 100, 150, and 200 units of Botox A[®], respectively had excellent improvement. The duration of therapeutic effectiveness (excellent or improved) was significantly shorter for the patients treated with 100 units (3.5 months, range 3-7) compared with that for those treated with 150 (5.5 months, range 5-9) or 200 units (6.7 months, range 4-12) of Botox A[®], $p < 0.001$. A recent randomized, placebo controlled, dose ranging trial included subjects with ≥ 8 IE/week and who had failed 2 prior anticholinergic therapies.⁵⁵ Subjects were randomized to receive, placebo, 50, 100, 150, 200, or 300 units of Botox A[®].

Approximately fifty subjects were in each group. Continence rates were not reported but a mean change from baseline UUIE was reported at 3 months, as -17.4, -20.7, -18.4, -23, -19.6, and -19.4 for placebo, 50, 100, 150, 200, and 300 units, respectively. Although the study could not report on statistically significant differences in incontinence improvement after Botox therapy compared with placebo at many time points, when reporting on the cumulative efficacy, there was minimal additional benefit seen at 3 months with doses greater than 150 units. Longer follow up was not reported in this study.

The outcome of repeat Botox A[®] injections have been followed in both NDO and refractory IDO studies.^{37,38,50,56,57} Three studies included only neurogenic patients and used either 200 or 300 units of Botox A[®]. In one study, all 20 patients received 5 repeat injection sessions at scheduled 7 month intervals.⁵⁶ The urodynamic parameters such as maximum bladder capacity and detrusor pressure improved significantly and after each reinjection the improvement was sustained. In addition, there was an absence in the change in detrusor compliance even after the 5th Botox injection. Grouse et al.³⁸ reinjected 44 NDO patients with Botox A[®] based on recurrence of

worsening urodynamic parameters or complaints of urinary incontinence. The interval between subsequent injections was on average 9 to 11 months. Satisfaction was high and anticholinergic use decreased significantly. More recently, repeat injections were reported in a refractory IDO patients.⁵⁷ Twenty patients underwent a second Botox A[®] injection (5 at 150 units, 11 at 200 units, 5 at 25 units) and nine patients received up to 4 injections. Repeat injections appeared to be equally efficacious as the first injection, showing improvement in OAB symptoms, urodynamic parameters and QOL. In addition, there was no change in PVR between injections. The median time between injections 1 and 2 and 2 and 3 was 377 and 378 days. Using 200 units, Khan found very similar median interinjection times of 11-15 months between 1-4 injections.⁴⁹

B.4 Rationale for using 200 units in this study

We chose 200 units of Botox A[®] as the dose for this trial since our primary outcome was to evaluate the efficacy at 6 months and the published literature supported 200 units as the dose most likely to provide this durability. Botox A[®] therapy is performed via cystoscopy with 20-30 needle injections into the detrusor muscle. The placebo controlled studies reported a 16-28% urinary tract infection post procedural rate after placebo injections in this UUI population. Additionally when considering other factors such as procedural discomfort, clinical assessments and procedure visits for reinjection, a clinically reasonable interinjection period would be at a minimal of 6 months. Several studies referenced above have documented that longevity using 200 units. There have been no studies showing this benefit using lower doses when assessing objective outcomes of continence status. Many studies have shown results to the contrary.

There are no reported cases of permanent urinary retention after Botox A[®] injections; however, due to variability in monitoring PVRs in the published literature, the incidence of symptomatic partial retention remains unclear. However, studies using 200 units that have reported on the implementation of clean intermittent self catheterization (CISC) have reported a range between 0-30%.

The dose response trial also found an increase in PVR with increasing doses of Botox A[®]. The incidence of PVR > 200 ml and (CISC%) was 18% (11%) with 100 units, 28% (20%) with 150 units, 23% (21%) with 200 units, and 26% (16%) with 300 units⁵⁸. Median days of catheterization was 113 days with 100 units, 57 days with 150 units, 179 days with 200 units, and 15 days with 300 units. These findings do not support a direct correlation between increasing dose and chance of CISC nor duration of CISC. Sahai reported similar findings with twenty of 34 patients who initially received 200 units and requested a repeat injection. The study allowed for a dose reduction if the subject required CISC after the initial 200 units. Despite reduction in dosage to 150 units, 4/5 patients still required CISC after their 2nd injection. Two continued to need CISC despite being reduced to 100 units for 3rd injection, both elected to increase their dose for their 4th injection to maintain efficacy. This study further supports the need to investigate other factors, not yet determined, which may predispose a patient to voiding dysfunction after Botox A[®] injection. ROSETTA has set predetermined criteria for initiation of CISC and specific criteria for stopping CISC, as well as following subjects overall satisfaction with their therapy.

B.5 Justification for using a PVR >200 ml with symptoms as threshold for initiating clean intermittent catheterization

We are using the same post void residual criteria as in RUBI and in the two other randomized placebo controlled studies using 200 units as well as the recent dose response trial,^{39,40,41,58} In RUBI, 40% of the cohort was diagnosed with impaired bladder emptying, 75% of the them were only diagnosed because of routine PVR checks at 4 weeks and only 14% were symptomatic. In the dose response trial, 28.8% of subjects injected with 200 units of Botox A[®] had a documented post treatment PVR of >200 ml. However, a stated limitation was that a PVR > 200 ml was recorded as an adverse event regardless of symptoms or need for intervention. Furthermore, no subjects discontinued treatment due to a treatment related adverse event.⁵⁸ Two studies evaluated upper urinary tract (kidney) function with serum creatinine measurements and renal ultrasound after Botox A[®] injections and found no abnormalities even in the patients with partial urinary retention^{50,52} Additionally, PVR volumes of > 30 ml had a positive association with recurrent urinary tract infections (UTI). The incidence of

recurrent UTI's remained high with increasing PVRs, but does not surpass the incidence detected at 30-50 ml PVR.⁵⁹

B.6 Justification for stratification by age less than or greater than 65

Multiple factors have been considered when evaluating associations for success after incontinence surgery, such as parity, medical comorbidities, body mass index, previous pelvic surgery, and age. Although older women are reported to have significant improvement in quality of life after incontinence surgery, compared to younger women, some studies have reported that they are less responsive and more likely to recur. In a retrospective cohort study evaluating combined POP and SUI surgery, women > 65 years were at increased odds for SUI treatment failure than their younger cohort.⁶⁰ A randomized study (tension-free vaginal tape v. transobturator tape) reported that age was an independent risk factor associated with recurrent SUI.⁶¹ There are several publications that also suggest age may be associated with response to therapy for refractory OAB. Older refractory urge incontinent women were found to have a statistically significant difference in long term cure or "dry" rates (37% versus 65% in younger women; $p < 0.05$), when treated with InterStim therapy.²⁹ A large Medicare database study reported an overall low response rate (40%) to the InterStim test stimulation in their population of patients >65 years of age and that age >79 is an independent risk factor for poor response²⁸. In a retrospective cohort study of InterStim patients, mean follow up of 48 months, an elderly cohort (>70 years) had a lower rate of maintaining functional use of their implant, 65% (11/17) compared to 85% (153/165), in the younger cohort, $p = 0.018$.⁶² There are no studies comparing age groups and response to Botox A[®], but one study evaluating the efficacy of injecting 200 units Botox A[®] for refractory urinary urgency in elderly men and women reported a >50% improvement in the mean number of voids/day and pad usage in 16/21 (76%) with a mean time to deterioration of 7 months, no patients experienced urinary retention.⁶³ Therefore, if a particular intervention was found to be more effective in the older populations, this would help lower the health burdens and health care costs of OAB. The results of a prevalence- based model to examine economic costs of OAB in the United States found that not only does the economic burden of OAB

appear to be much higher than previous estimates, the annual per capita costs for women are higher than for men at ages >65 years. In addition, per capita costs increase in both groups for 65-74 year olds and increases substantially for those >75 years.⁶⁴

A recent cost- effectiveness study reported that over a two-year time period, botulinum A toxin was cost effective compared to sacral neuromodulation for the treatment of refractory urge incontinence.⁶⁵ However, if Botox A[®] was more expensive or less effective for controlling IDO symptoms, injected less frequently, resulting in longer periods of incontinence between injections (ie: decreased efficacy), or if society was willing to pay \$150,000 for increased effectiveness (instead of the \$100,000 used for the study calculations) the results would shift in favor of the SNS treatment. The study concluded that more information is needed regarding willingness to pay, long-term efficacy and adverse events. This would allow for more accurate assessments of cost-effectiveness over longer periods of time.

A well- powered, randomized trial in patients with refractory urge urinary incontinence that directly compares InterStim[®] and Botox A[®] efficacy, side effects, complications and cost-effectiveness is needed.

B.7 Translational Component

The etiology of OAB is not well understood. Several hypotheses have been advanced to explain the etiology of OAB, including changes to the central, spinal cord or peripheral nervous system, alterations in the properties of the detrusor myocytes, and more recently, dysregulation of the bladder afferent activity leading to an altered signaling within the bladder efferent pathway. It is very likely that the true cause of OAB may be different in different individuals and may include several and possibly other mechanisms that are yet to be described. The concept of "neurogenic inflammation" has recently been described suggesting that inflammation might be involved in the pathophysiology of neuronal events resulting in OAB. Several neuropeptides (nerve growth factor, substance P, and tachykinins) are thought to be causative for the symptoms of OAB.⁶⁶ ROSETTA provides an opportunity to genetically characterize a unique patient population that has experienced suboptimal improvement and/or poor tolerance with current pharmacologic

therapy. The study also provides the opportunity to characterize biomarkers and analyze DNA in blood. All women in this study are extensively phenotyped by history, validated instruments (quantifying severity and bother), physical examination, and urodynamics. In addition, response to two therapeutic modalities is assessed with the same scrutiny.

The aim of this translational component is to provide the blood specimens along with the phenotypic information for future biomarker and DNA analysis. Specific and detailed research protocols related to the analysis of these data will be aimed at understanding the association of genetic variation, inflammatory mediators, growth factors and other biomarkers in the plasma of women participating in this study. These protocols will be encouraged and undergo peer review, either within the PFDN or via separate funding mechanisms.

C. STUDY SCHEMA

This study is a randomized, open-label, active-control clinical trial of sacral neuromodulation therapy with InterStim[®] v. therapy with intradetrusor botulinum toxin A for women with refractory moderate to severe urge urinary incontinence, without neurologic disease. Three hundred and eighty (380) subjects will be randomized. The primary outcome is measured over 6 months. Subjects will be followed up to 2 years.

Subjects will be screened to assess eligibility criteria and baseline number of daily urge urinary incontinence episodes. Candidates will be approached for enrollment in a manner consistent with local IRB requirements and will be consented and enrolled into the study with verbal and written consent. A minimum of a 3-week washout period is required for any subject currently on anticholinergic therapy prior to randomization. Eligible subjects will complete baseline assessments, be randomized and be scheduled for either a first stage lead placement (FSLP) InterStim[®] or Botox A[®] injection visit.

The criterion for an initial clinical response to InterStim[®] therapy will be defined as a $\geq 50\%$ improvement in the mean number of UUIE/day on a minimum 3 day bladder diary. For subjects randomized to InterStim[®], this

diary will be completed during the testing period, which is a duration, of at least 7 days up to 14 days following the first stage lead placement (FSLP). Subjects with a $\geq 50\%$ improvement mean number of UUIE/day will be eligible to proceed with implantation of the implantable pulse generator (IPG). Subjects will then be followed monthly to determine the response to therapy.

Similarly, subjects who received a Botox A[®] injection will be assessed for a clinical response, at one month from injection, using the same clinical criterion ($\geq 50\%$ improvement in the mean number of UUIE/day on a 3 day bladder diary completed prior to the 1 month visit). Those subjects that experience a clinical response, at one month, will be eligible for a repeat Botox A[®] injection after 6 months, if they experience degradation of clinical effect, using the PGSC.

All randomized subjects will continue to participate in all study follow-up visits and calls regardless of whether or not they receive either study intervention or had a poor clinical response (non responders) and subsequently use other therapy such as anticholinergic medication. Those subjects that received either InterStim[®] or Botox[®] therapy and were "responders" will also be followed per protocol and use of any additional supplemental therapy such as anticholinergic medication are not allowed or encouraged and will be considered a protocol deviation.

C.1 FSLP (testing period) InterStim[®]

The test stimulation period will occur during the next 7 days to 14 days following FSLP using the tined lead placement technique for testing. This time period will vary with each subject according to operating room availability. The site staff will be the primary contact to assist subjects with troubleshooting and changing programs during the FSLP testing period and with any InterStim[®] concerns until the end of the study. However, the study team can use Medtronic technical assistance for troubleshooting problems throughout the entire study, if needed.

During the testing period, subjects will complete a bladder diary on each day. The 3 days on the bladder diary that represent optimized therapy will

be used to calculate degree of improvement. Those with a $\geq 50\%$ improvement in the number of UUIE/day, as assessed by the mean UUIE/day over a minimum of 3 days of bladder diary recordings, relative to baseline, are eligible to undergo implantation of the implantable pulse generator (IPG). Verification of continued correct lead placement will be made by confirming vaginal/perineal or rectal sensation of the stimulation. Those assessed as having a technical problem with their device as the cause for not responding may undergo a second attempt at lead placement. Those having appropriate lead placement and a $< 50\%$ improvement in #UUIE/day will be considered non responders but will continue to be followed monthly until the 6 month primary outcome.

At the discretion of their physician, they may receive therapy, other than Botox A[®], for their UUI. After completion of the 6 month visit, the subjects can seek Botox A[®] therapy off study protocol while continuing study follow up.

C.2 First injection with Botulinum A Toxin

Subjects randomized to Botox A[®] injections will receive 200 units of Botox A[®] injection into the submucosa of the bladder, sparing the bladder trigone. A 3 day bladder diary will be completed before their one month follow up visit, and if a subject has a $< 50\%$ improvement in UUIE/day assessed by the mean UUIE/day on their 3 days of bladder diary recordings, they will be considered non responders but will continue to be followed monthly until the 6 month primary outcome. At the discretion of their physician, they may receive therapy, other than InterStim[®], for their UUI. After completion of the 6 month visit, the subjects can seek InterStim[®] therapy off study protocol while continuing study follow up.

C.3 Post procedural follow-up

Post procedural follow-up visits are scheduled relative to final placement or removal of device for InterStim[®] subjects and relative to first injection for Botox A[®] subjects. During the first 6 months, monthly contacts with either visits or calls will occur. Along with adverse events, subject's symptoms will be assessed with a 3 day bladder diary and the Patient Global Symptom Control rating scale (PGSC). All study subjects may have additional visits to

address adverse events. Additionally, InterStim[®] subjects may have additional visits scheduled for generator reprogramming if PGSC is 1 or 2, or occurrence of pain or decreased efficacy (<50% reduction in UUIE/day from baseline) or surgical revision if reprogramming is unsuccessful or infection. (See K. for reprogramming principles). Furthermore, Botox A[®] subjects who are initial clinical responders ($\geq 50\%$ improvement in UUIE/day after initial injection) may be assessed for a reinjection visit on or after the 4 month visit if the PGSC rating is 1 or 2 (See L. for criteria for reinjection).

Adverse events or low PGSC scores for all subjects should be evaluated and every attempt at resolution should be made within the following 4 week period.

Between 6 and 24 months, subjects will continue to be followed and assessed for reinjections, reprogrammings and surgical revision. For Botox A[®] subjects who are initial responders, if the PGSC score is 1 or 2 and all inclusion and exclusion criteria are met (except inclusion items 2,5 and 8), the subject will be offered a repeat injection. Intervals for Botox A[®] reinjections will be offered after 6 months from the initial injection and may occur at a minimum of 4 months apart (see L. for criteria for reinjection). For InterStim[®] subjects, reprogramming of InterStim will be performed if PGSC is 1 or 2 or occurrence of pain or decreased efficacy (<50% reduction in UUIE/day from baseline) or surgical revision if reprogramming is unsuccessful or infection (see K. for reprogramming principles).

A subject will continue to be followed for the entire 24-month period if they were randomized to study therapy even if they were considered non responders (i.e. did not receive the InterStim device or had a <50% improvement in #UUIE/day on a 3 day bladder diary after Botox therapy). These subjects will continue to be followed even if they received off-protocol treatment for urge urinary incontinence such as any anticholinergics or supervised behavioral interventions prior to 6 months. In addition, subjects will continue to be followed if they were randomized to study therapy, did not respond, and after 6 months underwent other therapy which they were not randomized to in this study.

All attempts will be made to maintain subjects in the study, however, if a subject withdraws from study participation the reason for withdrawal will be documented (e.g. complications, patient request including withdrawal of consent, physician request, moved away from area.)

C.4 Assessments

Subjects will be seen in person at baseline, within the first 2 weeks following injection or FSLP as well as at 1 month, 3 months, 6 months, 12 months and 24 months following injection or final device implantation or removal.

At baseline a medical and surgical history, physical exam, urodynamic assessment (if prior result not available), Functional Comorbidity Index, serum creatinine (if prior result not available), urine dip and PVR will be performed, as well as the Timed "Up and Go" assessment in subjects 65 years or older⁶⁷. This assessment measures the overall time to complete a series of functionally important tasks. This performance-based measure of functional mobility can distinguish between older adults who are mostly independent and those needing some help in everyday activities.

Subsequent urine dip and PVR assessments will be obtained for Botox A[®] subjects at 2 weeks, 1 month, 3 months, 6 months, 12 months and 24 months. Baseline, 6, 12, and 24 month assessments will also include a 3-day bladder diary for incontinence episodes, Overactive Bladder Questionnaire Short Form (OABq-SF), Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire Short Form and Revised Form (PISQ-12, R), Vaizey bowel questionnaire, Incontinence Impact Questionnaire (IIQ-SF), Urinary Distress Inventory (UDI-SF), Sandvik Incontinence Severity Index, Life-Space Assessment Questionnaire, and the Health Utilities Index Mark 3 (HUI-3).⁶⁸ In addition, subjects will complete the Patient Global Symptom Control Rating (PGSC), Overactive Bladder Satisfaction of Treatment Questionnaire (OAB-SATq), Patient Global Impression of Improvement, (PGI-I) at 6, 12, and 24 months.

Subjects will also complete a 3-day bladder diary, OABq-SF and PGSC every month for the first 6 months, then every 6 months for next 18 months. Subjects will complete an additional bladder diary during the test stimulation

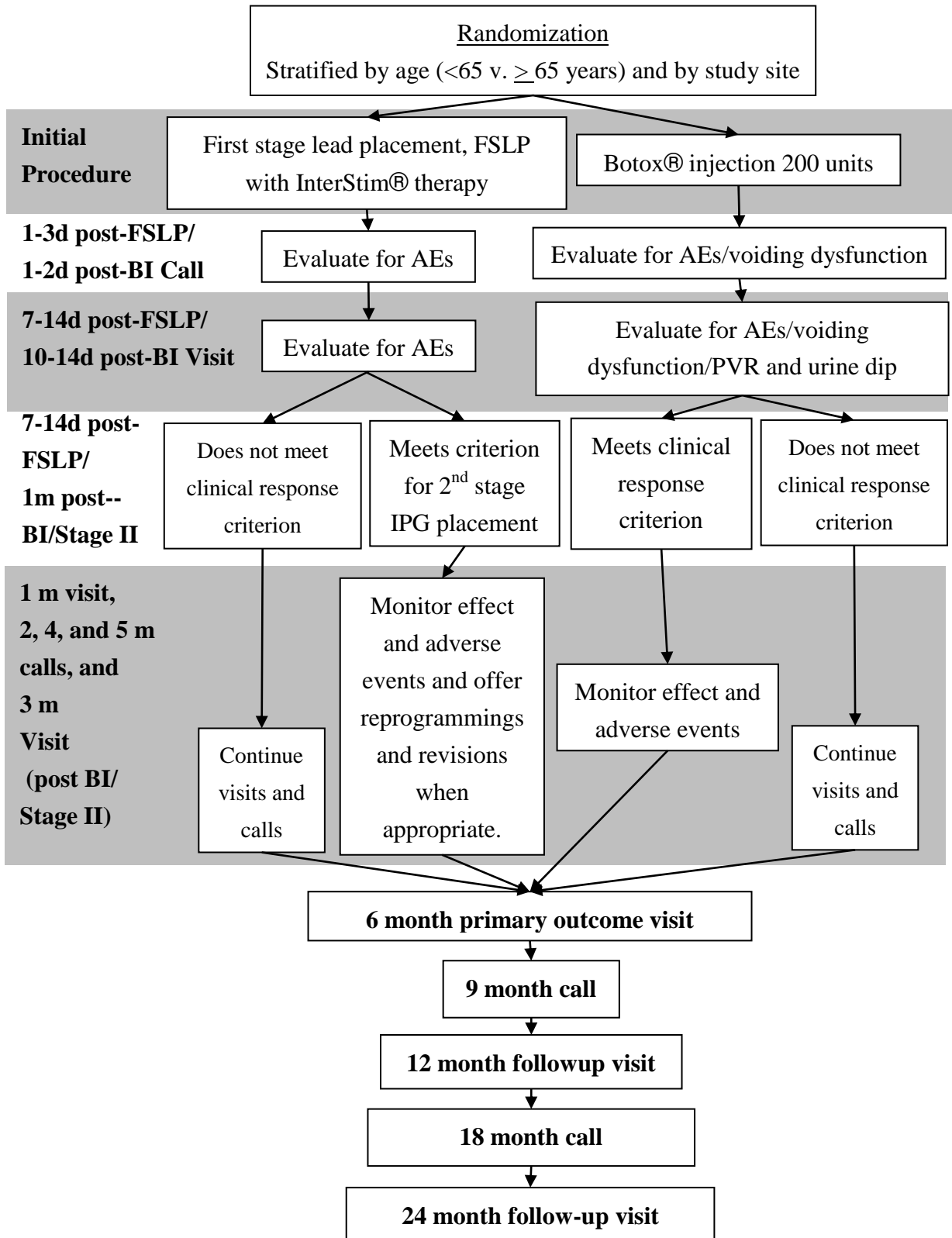
period, a duration of 7 days or more, up to 14 days, immediately following FSLP (for InterStim[®] subjects) or for 3 days prior to the one month visit (for Botox A[®] subjects) post- intervention to assess early response. At the 1 and 6 month visit, the InterStim[®] group will also complete a questionnaire assessing their understanding of the patient ICON programmer. Additionally, at every in person visit InterStim[®] subjects will have data obtained from their ICON programmer.

Voiding assessments (for Botox A[®] subjects) and collection of AEs and concomitant medications will occur at all calls and visits.

Throughout the study, subject data may be collected by any of three methods: during a research office visit, during a telephone call from the research staff and/or during a telephone interview by the QOL Center.

C.5 Study Design Diagram

Randomized, open-label, active-control, parallel-group study assessing InterStim® and Botox A®



D. STUDY POPULATION

Subjects will be women aged 21 or older who do not have neurologic disease and present with refractory urge urinary incontinence that have persistent symptoms despite trying at least two anticholinergic therapies (or unable to tolerate medication or contraindication to medication) and undergoing at least one more conservative treatment. All subjects will provide written informed consent before any research data collection takes place. An estimated total sample size of 380 randomized women (190 per randomized treatment group) is planned.

The ROSETTA protocol will adhere to the CONSORT guidelines for performing and reporting randomized controlled clinical trials. Women who are eligible but decline enrollment will be characterized in a manner consistent with the CONSORT requirements.

E. INCLUSION AND EXCLUSION CRITERIA

E.1 Inclusion criteria

To participate in the study, subjects must meet all of the following criteria:

1. Non-pregnant adult female at least 21 years old, with no plans to become pregnant during the course of the trial) and if of child-bearing potential, with a negative pregnancy test, and if sexually active, must be using medically acceptable contraception.
2. ≥ 6 urge urinary incontinence episodes on a 3-day baseline bladder diary, with these urge incontinence episodes representing greater than 50% of the total incontinent episodes recorded.
3. Willing and able to complete all study related items and interviews.
4. Refractory urinary urge urinary incontinence: defined as
 - a. Persistent symptoms despite at least one or more conservative treatments (e.g. supervised behavioral therapy, supervised physical therapy); and
 - b. Persistent symptoms despite the use of a minimum of two anticholinergics, or unable to tolerate medication due to side effects, or has a contraindication to taking anticholinergic medication.

5. Currently not on an anticholinergic or antimuscarinic medication (e.g. oxybutynin, tolterodine, and/or fesoterodine) or be willing to stop medication for 3 weeks prior to completing baseline bladder diary and expected to remain off medications through duration of study.
6. Demonstrates ability (or have caregiver demonstrate ability) to perform clean intermittent self-catheterization.
7. Grossly neurologically normal on exam and no gross systemic neurologic conditions believed to affect urinary function.
8. Urodynamic assessment within the previous 18 months prior to enrollment or done after enrollment, prior to randomization.

E.2 Exclusion Criteria

Subjects with any of the following criteria will be excluded from the study:

1. Neurologic diseases such as multiple sclerosis, Parkinson Disease, CVA within 6 months prior to enrollment, myasthenia gravis, Charcot-Marie-Tooth disease, clinically significant peripheral neuropathy, and complete spinal cord injury.
2. Untreated urinary tract infection (UTI).
3. Any prior use of either study therapy for treatment of urinary urge incontinence (Botox A[®] or Interstim[®]).
4. Current participation in any other conflicting interventional research study, deemed by the site PI would interfere with the ROSETTA study.
5. PVR >150 ml on 2 occasions within 6 months prior to enrollment (If the PVR value was obtained by ultrasound and was ≥ 150 ml, the PVR will be confirmed by catheterization which will be the gold standard)
6. Subjects with knowledge of planned MRIs or diathermy except those allowable per Medtronic guidelines.
7. Current or prior bladder malignancy.
8. Surgically altered detrusor muscle, such as augmentation cystoplasty.
9. Subjects taking aminoglycosides.
10. Currently pregnant or lactating.
11. Subjects who are on ambulatory anticoagulant therapy, including aspirin, who are unable to discontinue treatment for 24 hours prior to bladder injection and staged InterStim[®] procedure.

12. Serum creatinine level greater than twice the upper limit of normal within the previous year prior to enrollment.
13. Surgical treatment for stress incontinence (sling, Burch or urethral injection) or pelvic organ prolapse recommended or planned at enrollment by study investigator(s).
14. Prior stress incontinence or prolapsed surgery within the last 6 months prior to enrollment.
15. Allergy to lidocaine or bupivacaine.
16. Prior pelvic radiation.
17. Uninvestigated hematuria.
18. Greater than or equal to Stage III vaginal prolapse.
19. Known allergy to Botox A[®].
20. Use of a vaginal pessary

F. SUBJECT SCREENING

As with all PFDN protocols, this study will have to be tailored to fit each site and their specific resources or needs. Subjects will be identified as candidates by their physician.

The Coordinator (research coordinator or nurse) will screen subjects before enrollment, obtain informed consent, record all baseline physical examination items, randomize the subject, schedule the intervention, schedule and collect data at 1, 3, 6, 12, and 24 month follow-up visits as well as follow up phone calls.

The PI at each participating site will provide a written plan to the Protocol Committee Chair, the DCC PI, and the NICHD Program Scientist, describing how the ROSETTA protocol will be performed at their sites.

F.1 Urodynamic Assessment

A multi- channel cystometrogram (CMG) will have been performed in the 18 months prior to enrollment or done after enrollment, prior to randomization as part of the usual care in the evaluation if the subject is to meet eligibility.

The CMG results can be accepted from another facility if it meets the criteria outlined below. If the following criteria are NOT met, the CMG will be repeated by the investigator at baseline:

- a) The actual CMG tracing (not just the report summary) must be available.
- b) The report must state: fill rate
- c) The tracing must have evidence that the catheters were zeroed to atmosphere prior to beginning the study
- d) The following events must be marked on the tracing: volume at first urge, volume at strong urge, volume at capacity
- e) The CMG tracing must be of sufficient quality to determine the presence or absence of detrusor overactivity (DO) or detrusor overactivity incontinence (DOI), volume at first detrusor contraction if it occurred, and max Pdet.

Demonstration of DO or DOI will be recorded and the appropriate research variables will be abstracted.

Diagnosis of Detrusor Overactivity: During the cystometrogram, DO will be defined as the presence of involuntary detrusor contractions during the filling phase which may be spontaneous or provoked. Further, the following patterns of DO will be determined based on the ICS Terminology:

- *Phasic detrusor overactivity* will be defined as a characteristic wave form that may or may not lead to urinary incontinence and will include measurement of max Pdet.
- *Terminal detrusor overactivity:* single, involuntary detrusor contraction, occurring at cystometric capacity, that cannot be suppressed and results in incontinence usually associated with voiding
- *Detrusor overactivity incontinence* will be defined as incontinence due to an involuntary detrusor contraction.

G. BASELINE VISIT

At the baseline visit (prior to conducting any study procedures required or collecting any data required for screening or baseline assessments), the study will be explained and an IRB-approval written consent will be obtained. Subjects will be enrolled with both verbal and written consent.

Human subjects' protection will follow local and national regulations at all times.

A minimum of a 3-week washout period is required for any subject still on anticholinergic therapy prior to completion of their baseline bladder diary.

At the baseline visit, the bladder diary will be reviewed to ensure that entries are clear and interpretable. If the first baseline bladder diary is not acceptable or has not been completed, the subject will be allowed one more attempt to complete the bladder diary. If the second baseline bladder diary is not acceptable, the subject is not eligible for the trial.

Additional baseline assessments include:

- A directed history examination as assessed by the Functional Comorbidity Index and physical examination including height and weight will be completed.
- A blood specimen will be obtained to determine serum creatinine level if not documented within the previous 12 months.
- A blood specimen will be obtained for the biomarker and DNA biorespository. It may be obtained at the same time as the baseline serum creatinine.
- A catheterized or ultrasound measure of the post-void volume will be obtained. If a PVR is 150 mL or greater on two occasions with a void over 150 ml, the patient will not be eligible for participation. If the PVR value was obtained by ultrasound and was ≥ 150 mL, the PVR will be confirmed by catheterization which will be the gold standard. Eligible subjects will be instructed on clean intermittent self catheterization (CISC) and the subject or an immediately available and identified person will need to demonstrate the ability to perform CISC to be eligible to participate in this study.
- In all subjects, a urine dip will be performed either of a clean catch or catheterized sample. Subjects with symptomatic urinary tract infection will be treated clinically and may be enrolled in the study after complete resolution of the urinary tract infection. Eligible subjects ≥ 65 years old will have the Timed "Up and Go" Test completed by the Coordinator.

- Self-administered OABq-SF provided by the Coordinator.
- The PISQ-12/R, IIQ-SF, UDI-SF, Sandvik, Vaizey, Life-Space Assessment and HUI-3 will be scheduled and completed by phone by the Quality of Life Interviewing Center prior to study treatment.
- UDS data sheet (for urodynamic assessment completed up to 18 months prior to enrollment or done after enrollment, prior to randomization.)

The baseline phase may comprise multiple visits in order to complete all baseline assessments.

H. RANDOMIZATION

If all inclusion/exclusion criteria are met, procedure visit will ensue after randomization. At some sites, both interventions will be done by one person; at others, each will be done by different people. Randomization is to be completed such that the subject will receive the randomized initial treatment (first Botox injection or FSLP) within three months of enrolling/consenting into the study

In order to assure between-group comparability *age* (<65 v. ≥65 years) will be stratified.

Within each stratum (including site), subjects will then be randomized to InterStim® or botulinum A toxin injection (200 units). The Coordinator will be provided the randomization assignment from the Data Coordinating Center (DCC), based on the subject's stratification factor. The Coordinator will provide the randomization assignment to the surgeon.

Stratified randomization (1:1 InterStim®: Botox A®) will be performed using permuted blocks, with a block size that is known only to the DCC. No more than 25% of randomized subjects will be enrolled at any single study center.

I. Appointment Scheduling:

After the randomization, the Coordinator will schedule the Botox A[®] injection visit or first stage lead placement (FSLP) depending on group assignment and coordinate the scheduling of the first post procedural visit (7-14 days following FSLP in person visit with Physician for InterStim[®] and 10-14 days following injection in person visit with Physician for Botox[®]) as well as the second InterStim[®] surgery (8-18 days following FSLP).

If the bladder diary obtained during the next 7-14 day period following FSLP documents a $\geq 50\%$ improvement in their incontinent episodes compared to their baseline bladder diary, the subject will be offered to proceed to Stage II IPG placement at the second InterStim[®] surgery; otherwise, the device will be removed at this surgery.

The Coordinator is responsible for sending the bladder diary, PGSC and OABq to the subjects prior to each outcome assessment and also responsible for the return of the completed forms. The Coordinator will also record adverse events, concomitant medications and UDI-SF.

J. PROCEDURES

The FSLP or Botox A[®] injection is to be completed within three months of enrolling/consenting into the study. If more than three months pass between enrolling/consenting into the study and injection/FSLP, then study eligibility should be reconfirmed prior to proceeding and the baseline urine dip and 3-day diary must be repeated (even if after randomization).

J.1 InterStim[®] Surgery

Surgeons at each site will be designated an InterStim[®] device implanter if they have performed a total of 10 procedures and are performing InterStim[®] implants routinely in their practice.

All surgeons performing InterStim[®] surgery will be required to view a short instructional video demonstrating optimal techniques and detailing a standardized placement of the lead. An optional online video detailing the principles of neuromodulation will also be offered as supplemental education.

At least one person will be designated the programming expert at each site and must have attended the advanced programming course conducted by Medtronic or completed the online training Medtronic DVDs entitled InterStim[®] Therapy for Urinary Control Programming Basics and N'Vision Clinician Programmer (Model 8840) Emulators and viewed a short video on the basics of troubleshooting neuromodulation. This Clinician Programmer is able to interrogate and program signals to the neurostimulator and receive status information from the neurostimulator.

J.1.1 First stage lead placement (FSLP) InterStim[®]

Before surgery, a confirming urine pregnancy test will be performed in all premenopausal women. A urine dip to rule out infection will also be performed. If the urine dip is positive (1+ or greater leukocytes or nitrates), subjects will be treated for the urinary tract infection prior to surgery.

The surgical site will be marked in the pre op surgical unit. Prior to operation, antibiotics of either Ancef 1 gm or Clindamycin if allergic to Penicillin will be given. The subject will be given monitored anesthesia care (MAC) and local anesthesia with 1% bupivacaine. C-arm fluoroscopy will be used to identify boney landmarks.

Spinal needles will be placed in both S3 foramen. Both sides will be stimulated and the side with the best response as determined by the surgeon will undergo lead placement into that S3 foramen. The tined Lead Model 3093 will be used. Lead length will be at the discretion of the surgeon.

Intraoperative sensory and motor responses (type and intensity), as well as the stimulation parameters and electrodes used to elicit them, will be recorded. Responses must be documented at an amplitude <5 on at least 2 of the 4 electrodes. Therefore, the lead should be positioned close enough to the nerve to require very low amplitude for an appropriate S3 sensory response (without the stimulation being uncomfortable) or an appropriate S3 motor response. The lead tunneling and wire connections will be completed and side of future generator placement will be determined by the surgeon.

The incisions will be closed in a subcuticular fashion, covered with Steri-

strips™, dressed with gauze and covered with a medium-sized transparent film dressing (Tegaderm™). A large Tegaderm™ is then placed over the entire sacral area, overlying the individual dressings. PA and lateral Xray confirmation will be obtained at the end of the surgery and the films submitted to the hospital electronic radiologic system. Sensory responses, stimulus parameters, and electrode selections will be reassessed and documented again in the recovery room.

A member of surgical team will determine the external stimulator settings and two electrode combinations will be determined and documented. Sensation type and intensity will be documented on these two electrode combination. A member of the study team will review bladder diary instructions and how to use the external stimulator. Each subject will complete a bladder diary during their testing period. Subjects will report UUIE/day on each testing day. During the testing period, the subjects will be contacted by phone by a member of the study team and a switch to the other electrode combination may be made by the subject as determined by the subject's response.

The Coordinator will record peri-procedural events and complications. Success of the FSLP will be assessed during the testing period (next 7-14 days) by the study coordinator/physician. Ciprofloxacin 500mg bid will be given for the length of the testing period; if subject is allergic to Ciprofloxacin, doxyclyne 100mg bid or Keflex 500mg bid will be given for the same duration.

J.1.2 Day 3 (±2 days) telephone follow-up post FSLP

All subjects will receive a phone call, to assess urinary incontinence and any adverse experiences (i.e., wound healing, appropriate stimulation).

J.1.3 FSLP testing period (7-14 day period following FSLP)

The test stimulation period will occur over a 7-14 day period immediately following FSLP using the tined lead placement technique for testing. Subjects will report UUIE/day on each testing day. All subjects will receive a phone call on Day 3 (±2 days) after lead placement to assess urinary incontinence and any side effects ie, wound healing, appropriate stimulation. During this

call, the subject will be assessed if changes in amplitude and/or electrode combination need to be made by the participant at home, as determined by subject's response. The 3 consecutive days on the bladder diary that represent optimized therapy will be used to calculate degree of improvement. All subjects will be scheduled a first post procedure visit with the Coordinator and Physician 7-14 days after FSLP. The MD will determine if FSLP was successful using the 3 day bladder diary and plans will be made for 2nd stage (IPG) or removal of lead for InterStim[®] subjects. Those with a \geq 50% improvement in the number of UUIE/day, as assessed by the mean UUIE/day over the consecutive 3 days of bladder diary recordings representing optimized therapy, relative to baseline, are eligible to undergo implantation of the implantable pulse generator (IPG).

Verification of continued correct lead placement will be made by confirming vaginal/perineal or rectal sensation of the stimulation. Those assessed as having a technical problem with their device as the cause for not responding may undergo a second attempt at lead placement. In this scenario, subjects will repeat the Day 3 telephone follow-up and FSLP testing period for the second FSLP attempt. The second FSLP must be initiated no longer than one month since the initiation of the first FSLP. If more than three months pass between enrolling into the study and injection/FSLP, then study eligibility should be reconfirmed prior to proceeding and the baseline urine dip and 3-day diary must be repeated (even if after randomization).

Those having appropriate lead placement and a $<$ 50% improvement in #UUIE/day will be considered non responders but will continue to be followed monthly until the 6 month primary outcome. At the discretion of their physician, they may receive therapy, other than Botox A[®] for their UUI. After completion of the 6 month visit, the subjects can seek Botox A[®] therapy off study protocol while continuing study follow up.

J.1.4 InterStim[®] Second Stage surgery (IPG) (8-18 days following FSLP)

Subjects $<$ 50% improvement during the testing period or who do not desire placement of the implantable pulse generator (IPG) will undergo MAC and local anesthesia and removal of lead and connecting wires.

Subjects meeting criteria for and desiring placement of generator will undergo MAC and local anesthesia and placement of either Neurostimulator Model 3023 (InterStim[®]) or Neurostimulator Model 3058 (Interstim II generator) as determined by the surgeon. However, if the subject has been requiring an amplitude setting of ≥ 5 during the testing period, then the Neurostimulator Model 3023 must be used. Subjects will be given their InterStim[®] iCon patient programmer (Model 3037) programmed with 4 different settings.

The Coordinator will record peri-procedural events and complications. Pre op antibiotics will again be given and post op oral antibiotics (the same as given after FSLP) will be prescribed for one week

J.2 Botox A[®] Injection and Post-procedure Follow-up

J.2.1 Botox A[®] Injection

All physicians administering injections will be required to view a short instructional video demonstrating optimal techniques and detailing sites of drug injection in a standardized manner. In addition, physicians at each site must have previously performed a total of 10 injection procedures (either intradetrusor muscle or intraurethral).

The Coordinator will ensure that the subject has been instructed regarding the proper technique for clean intermittent self catheterization (CISC) and will confirm that the subject or designated care-taker is able to perform the task.

Within one week prior to injection, a confirming urine pregnancy test will be performed in all premenopausal women. A urine dip to rule out infection will also be performed. If the urine dip is positive (1+ or greater leukocytes or nitrites) the participant will be treated for a urinary tract infection and rescheduled within 2 weeks for another Botox A[®] injection visit.

The bladder will be catheterized and 50 ml of 2% lidocaine placed in the bladder and 10 ml of 2% lidocaine jelly in the urethra. The subject will be

asked to lie on their left and right lateral decubitus for several minutes at a time to ensure diffuse anesthetic effect on the bladder. Cystoscopic surveillance of the bladder will be used to confirm normality.

Cystoscopy will be performed with a 12 or 30-degree lens and rigid scope. A 22 gauge disposable needle, which is passed through the cystoscopic channel and secured via a luer lock screw, will be used. Approximately 100-200 ml of total fluid will be instilled during cystoscopy to allow adequate visualization of the entire bladder urothelium. Botulinum toxin A will be prepared by dissolving 200 units of botulinum toxin A into 10 ml of injectable saline. Indigo carmine or methylene blue 0.1 ml will be added to each syringe of botulinum toxin A. The treating physician will inject a total of 10 ml of the Botox A[®] into approximately 15 to 20 different detrusor muscle sites under direct visualization. Injections will be spread out to equally cover the posterior bladder wall and dome, but spare the bladder trigone and ureteral orifices. The anterior bladder dome will not be injected secondary to technical difficulties associated with injecting this area cystoscopically

All physicians administering injections will be required to view a short instructional video demonstrating optimal techniques and detailing sites of drug injection in a standardized manner.

The Coordinator will record peri-procedural events and complications. The instilled fluid will be left in the bladder after the injections are complete. The subject will remain in a post-procedure area until a spontaneous void occurs. The patient must have a spontaneous void before going home. All subjects will receive a single dose of Ciprofloxacin 500mg orally immediately after injection and subjects will take Ciprofloxacin 500mg orally for 3 days post injection. If the patient is allergic to Ciprofloxacin, another clinically appropriate antibiotic will be prescribed by the investigator

J.2.2 Day 3 (± 2 days) telephone follow-up post Botox A[®] injection

All subjects will receive a phone call on Day 3 (± 2 days) after injection to assess voiding function and any adverse experiences.

Clean intermittent self catheterization (CISC) will be instituted if PVR volume >300 ml regardless of symptoms OR PVR>200 ml **plus** the symptom of incomplete bladder emptying associated with degree of bother being “moderately” or “severely”, as collected with the following voiding assessment questions from the UDI-SF:

<u>Are you experiencing difficulty emptying your bladder?</u>		<input type="checkbox"/> No <input type="checkbox"/> Yes	
<u>If yes, how much does this bother you?</u>			
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4
Not at All	Mildly	Moderately	Severely

Macrochantin 50mg po qhs will be administered for the duration of CISC. If the patient is allergic to Macrochantin, Bactrim DS 1 po qhs will be prescribed. If the patient is allergic to both Macrochantin and Bactrim, another appropriate antibiotic will be prescribed and recorded.

J.2.3 Botox A® Post-procedure Follow-up (10-14 days after injection)

All subjects will be scheduled for a first post procedure visit 10-14 days with coordinator after Botox A® injection. Urine dip and PVR will be obtained, and question about difficulty emptying bladder and adverse experiences will be asked during the visit. Subjects will also complete a 3 day bladder diary prior to this visit (see above for criteria for initiating CISC).

If subjects require CISC, the coordinator will contact them weekly by phone to assess their voiding function and to determine if they can discontinue CISC.

Criteria to Discontinue CISC: PVR \leq 200 ml regardless of symptoms of incomplete emptying or \leq 300 ml without symptoms of incomplete bladder emptying associated with “moderate” or “quite a bit” of bother on the UDI-SF question (described above).

K. Regular InterStim® Effectiveness Assessment and Reprogramming Principles

After InterStim[®] implantation, subjects will be assessed regularly. An algorithm (Appendices 1-3) will be provided as a guide for investigators for trouble shooting adverse events or decreased efficacy concerns. If PGSC scores are 1-2 with InterStim[®] technically correct as assessed by the MD, subjects will be offered removal and alternative therapy off study protocol. Nonetheless, these subjects will be followed even after removal of Interstim[®] or receiving alternative therapy. If PGSC scores are 1-2 with technical problems deemed amenable to treatment or pain or decreased efficacy (<50% reduction in UIIE/day) occurs, reprogramming will be attempted. If reprogramming is unsuccessful or infection occurs, subjects will be offered a surgical revision. There will be only one InterStim[®] surgical revision allowed for any reason (technical, pain, infection, lead migration) within the first 6 months. Any subject who has a surgical revision will receive a phone call 3 days (+/- 2) after that revision.

Reprogramming Principles:

1. Device interrogation should start with checking stimulation pattern of the 4 unipolar electrode combinations, then fine-tune with bipolar combinations
2. If a "good" stimulation pattern is found with electrode mapping, program it and leave it. If stimulation is still not in the correct area, continue with more advanced electrode combinations
3. Fine-tune with pulse width and rate adjustments
4. If unable to achieve a "good" stimulation pattern with reprogramming, obtain plain film /lateral view to visualize lead placement in comparison with original implant film.
5. Take electrical impedance measurements: in general, they should be between 400 and 1500 ohms. If not, and lead points show > 4000 ohms, suggests open circuit (lead microfracture, loose connection) whereas < 50 ohms suggests short circuit (overtightened screw (now uncommon)). If abnormal impedance is in one or two leads only, one can program "around" them.

L. Criteria for Botox A[®] Reinjection

Subjects determined at the 1 month visit to have a clinical response after their initial injection, may receive additional injections between 6 months and 24 months after initial injection for subjects that are considered responders to the initial injection. Eligibility for repeat injections will be based on a PGSC score of 1-2 and who continue to meet study inclusion/exclusion criteria (except inclusion items 2, 5 and 8). A maximum of 2 additional injections will be allowed during the entire 2 year period (total of 3 injections). No injections will be given at an interval less than 4 months and subject will have a post injection phone call at 3 days (+/- 2) following injection.

Subjects who are eligible for a repeat injection, but after their initial Botox A[®] injection met the criteria **AND** performed CISC for > 6 weeks, will be dose reduced to receive 100 Units of Botox A[®]. All other subjects eligible for a repeat injection will receive 200 Units Botox A[®].

Subjects eligible for a 3rd (final injection) and who were dose reduced for their 2nd injection will have the option to receive either 100 Units or 200 Units. Rationale for their decision will be collected. If any subject required CISC for > 6 weeks after their 2nd injection, they will be dose reduced to 100 Units if they meet eligibility for a 3rd injection.

M. OUTCOME VISITS

Subjects will be instructed not to start any new treatments for UUI (such as pelvic muscle exercises or taking medications) while enrolled in the study before speaking with the coordinator and physician.

All outcome visits in this section are relative to the first injection for treated Botox A[®] subjects and final implantation/removal of the device for treated InterStim[®] subjects. For randomized subject that are not treated, the outcome visits are relative to the date the final determination to not treat is made.

M.1 Post procedural visit 2: 1-month in-person visit

One week prior to the visit, the site coordinator will provide the subject a telephone reminder to complete 3-day bladder diary. The 1 month (\pm 10 days) in-person visit will be with the MD and Coordinator.

For subjects randomized to Botox A[®], if a subject has a < 50% improvement in UUIE/day assessed by the mean UUIE/day on their 3 days of bladder diary recordings, they will be considered non responders but will continue to be followed monthly until the 6 month primary outcome. At the discretion of their physician, they may receive therapy, other than InterStim[®], for their UUI. After completion of the 6 month visit, the subjects can seek InterStim[®] therapy off study protocol while continuing study follow up.

Additional visit assessments include:

- Assess for adverse events.
- Urine dip for infection and PVR (Botox A[®] arm only). For criteria for CISC and discontinuing CISC see J.2.2.-J.2.3.
- Voiding assessment (Botox A[®] arm only).
- Review 3-day bladder diary.
- Have subject complete PGSC and OABq-SF questionnaire.
- For subjects randomized to InterStim[®], reprogramming of InterStim[®] device if deemed necessary by MD (pain, <50% reduction in UUIE/day from baseline, PGSC 1-2) and documentation of reasoning and parameter changes (See K. for reprogramming principles).
- Parameters of the subject InterStim[®] programmer will be recorded.
- InterStim[®] subjects will complete Icon programmer questionnaire.

M.2 Post procedural visit 3: 3-month in-person visit

One week prior to the visit, the site coordinator will provide the subject a telephone reminder to complete 3-day bladder diary. The 3 month (\pm 10 days) in-person visit will be with the MD and Coordinator.

Additional visit assessments include:

- Assess for adverse events.
- Check urine dip and PVR (Botox A[®] arm only). See J.2.2.-J.2.3. for criteria for initiating or discontinuing CISC.

- Voiding assessment (Botox A[®] arm only).
- Review 3-day bladder diary.
- Have subject complete PGSC and OABq-SF questionnaire.
- For subjects randomized to InterStim[®], reprogramming of InterStim[®] device if deemed necessary by MD (pain, <50% reduction in UIIE/day from baseline or PGSC 1-2 score) and documentation of reasoning and parameter changes (See K. for reprogramming principles).
- Parameters of the subject Interstim[®] programmer will be recorded.

M.3 Post procedural visits: 6, 12, and 24-month in-person visit

One week prior to the visit, the site coordinator will provide the subject a telephone reminder to complete 3-day bladder diary. The 6, 12 and 24 month in-person visit will be with the MD and Coordinator (\pm 10 days for 6 month and \pm 4 weeks for 12 and 24 months).

Additional visit assessments include:

- Assess for adverse events.
- Check urine dip and PVR (Botox A[®] arm only). See J.2.2.-J.2.3. for criteria for initiating or discontinuing CISC.
- Voiding assessment (Botox A[®] arm only).
- Review 3-day bladder diary
- Have subject complete PGSC and OABq-SF questionnaire.
- If the PGSC is 1 or 2 and the subject desires another Botox A[®] injection, the study coordinator will arrange a visit to have PVR checked and Botox injection repeated if criteria met (See K. for reinjection criteria) and subjects will be assessed if the next injection will be dose reduced. If the PGSC is 1 or 2 and subject does not desire another Botox A[®] injection, they will continue to be followed.
- Reprogramming of InterStim[®] device if deemed necessary by MD (injection, pain, <50% reduction in UIIE/day from baseline or PGSC score of 1 or 2) and documentation of reasoning and parameter changes (See K. for reprogramming principles).
- For InterStim[®] subjects completion of ICONIC patient programmer questionnaire (6 months only)

- The Central Quality of Life Interview Center will contact the subject by phone and administer the OAB-SATq, Vaizey, IIQ-SF, UDI-SF and PISQ-12/R, PGII, Sandvik, Life-Space Assessment, and HUI-3.

M.4 Post procedural phone calls: 2, 4, 5, 9, and 18 months

The Coordinator will telephone subjects at each specified month (± 10 days calls prior to 6 months and ± 4 weeks for subsequent calls) to have them complete the PGSC and OABq-SF questionnaires, 3 day bladder diary, adverse events form and voiding assessment (Botox A[®] arm only).

For Interstim[®] subjects, if PGSC is 1 or 2 and/or the subject has pain or decreased efficacy (<50% reduction in UUIE/day from baseline), the Coordinator will arrange a visit for reprogramming (See K. for reprogramming principles).

Return visits to address adverse events or low PGSC scores will be scheduled within the following 4 weeks.

N. TIMELINE OF VISITS/CALLS AND MEASURES

N.1 Through Primary 6 Month Outcome

	Baseline/ screening	Inject /FSLP [^]	3d call [‡]	2wk visit [‡]	Implantation [‡]	1m visit [†]	2m call [†]	3m visit [†]	4m call [†]	5m call [†]	6m visit [†]
Window			3±2d	7-14d (Interstim) /10-14d (Botox)	8-18d (Interstim)	30±10d	61±10d	91±10d	122±10d	152±10d	183±10d
Consent	X										
Biomarker/DNA collection	X										
Hx/PE	X										
Timed Up and Go	X										
Urodynamic assessment	X										
Serum creatinine	X										
Preg test~		X									
Urine dip~	X	X*		X*		X*		X*			X*
PVR	X			X*		X*		X*			X*
Adv Events/voiding assessment		X	X/X*	X/X*	X**	X/X*	X/X*	X/X*	X/X*	X/X*	X/X*
Bladder diary #	X			X		X	X	X	X	X	X
PGSC and OABq-SF	X (only OABq)					X	X	X	X	X	X
Icon Programmer/ Device data**						X**		X**			X**
Iconic Questionnaire **						X**					X**
IIQ-SF, UDI-SF, PISQ- 12/R, Vaizey, Sandvik, Life-Space Assessment, HUI-3	X										X
PGII and OAB-SATq											X
ConMeds	X	X	X	X	X	X	X	X	X	X	X

[^] <2 months (61 days after completion baseline/screening phase)

[‡] Relative to first injection or FSLP for those treated, to final decision to not treat for those not treated

[†] Relative to first injection or final implantation/removal of device, to final decision to not treat for those not treated

*Botox subjects only

**InterStim subjects only

~Also at before any subsequent reinjection or revision of surgery

Typically obtained during week prior to visit/call

N.2 Long-Term Follow-up

	9m call [†]	12m visit [†]	18m call [†]	24m visit [†]
Window	274±28d	365±28d	548±28d	730±28d
Consent				
Hx/PE				
Timed Up and Go				
Urodynamic assessment				
Serum creatinine				
Preg test~				
Urine dip~		X*		X*
PVR		X*		X*
Adv Events/voiding assessment	X/X*	X/X*	X/X*	X/X*
Bladder diary #	X	X	X	X
PGSC and OABq-SF	X	X	X	X
Icon Programmer/ Device data**		X**		X**
Iconic Questionnaire **				
IIQ-SF, UDI-SF, PISQ-12/R, Vaizey, Sandvik, Life-Space Assessment, HUI-3		X		X
PGII and OAB-SATq		X		X
ConMeds	X	X	x	X

~ <2 months (61 days after completion baseline/screening phase)

‡ Relative to first injection or FSLP for those treated, to final decision to not treat for those not treated

† Relative to first injection or final implantation/removal of device, to final decision to not treat for those not treated

*Botox subjects only

**InterStim subjects only

~ Also at before any subsequent reinjection or revision of surgery

Typically obtained during week prior to visit/call

O. OUTCOME MEASURES

O.1 Primary Outcome Measure

The primary outcome is the change from baseline in mean number of UIIE over the first 6 month visit period (1, 2, 3 4, 5 and 6 month assessments); and is measured using 3-day bladder diaries administered monthly for the first 6 month visit period.

O.2 Comparative Secondary Outcome Measures

1. Proportion of subjects who report adequate improvement of their bladder function with the Patient Global Impression of Improvement Questionnaire (PGI-I) at 6, 12, and 24 month visits.
2. Change from baseline to 6, 12 and 24 month visits in the Overactive Bladder Questionnaire Short Form (OABq-SF).
3. Change from baseline to 6, 12 and 24 month visits in urinary frequency and nocturia as measured by the 3 day bladder diary and severity of urge incontinence symptoms as measured by the Sandvik questionnaire.
4. The proportion of subjects satisfied with their treatment as measured by the Overactive Bladder Satisfaction of Treatment questionnaire (OAB-SATq) at 6, 12 and 24 month visits.
5. Changes from baseline to 6, 12 and 24 month visits in quality of life measures as measured by the Urinary Distress Inventory Short Form (UDI-SF), Incontinence Impact Questionnaire Short Form (IIQ-SF), Pelvic Organ Prolapse/Urinary Incontinence/Sexual Function Questionnaire Short Form and Revised Form (PISQ-12/R), St Mark's (Vaizey) questionnaire for bowel incontinence, and the Health Utilities Index Mark 3 (HUI-3).
6. The cost of InterStim[®] therapy and Botox A[®] therapy as determined by utilization of medical resources for use in cost-effectiveness analysis.

O.3 Secondary Descriptive Measures for Interstim ® Therapy and Botox ® Therapy

1. Proportion of subjects and reasons for required additional Botox A[®] injections recorded during follow-up visits

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2. The proportion of subjects with voiding dysfunction/partial urinary retention requiring catheterization (PVR>300 ml or PVR>200 ml and symptoms of incomplete voiding).
3. The proportion of subjects with infection, pain or lead migration of the InterStim[®] device recorded during follow-up visits
4. The proportion of subjects and reason for reprogramming of InterStim[®] device
5. The proportion of subjects and reason for early surgical revisions of InterStim[®] device
6. Poor initial clinical response as defined by <50% improvement in average UIIE/day compared to baseline at the Day 7-14 visit for InterStim[®] and Month 1 visit for Botox A[®]
7. Poor response at each follow-up visits defined by <50% improvement in average UIIE/day at each visit compared to baseline
8. Occurrence of adverse events for InterStim[®] of infection, pain, decreased efficacy, need for surgical revision and for Botox A[®] of need for CISC or UTI

P. SAMPLE SIZE

Data from past studies are insufficient to provide robust estimates of the effects of Botox A[®] or InterStim[®] in patient populations similar to that proposed in our study; furthermore available studies vary in terms of the time points analyzed (from 1 month to 3 months for the Botox A[®] studies and 6 months to 5 years for the InterStim[®] studies), the endpoint used (urge incontinence episodes per day or total incontinence episodes per day), and population studied (e.g., refractory UUI, refractory DOI, refractory OAB, urge/frequency). Thus, a conservative approach was taken to sample size calculations for this study that utilizes a modest treatment effect size and that does not incorporate the additional information obtained from utilization of the longitudinal measurements for the primary analyses.

The table below provides a high-level summary of the studies that serve as the basis for sample size calculations.

Study	Population	N	Endpoint*	Time Point	Change* *	SD
BOTOX						
Brubaker ⁴⁰	Refractory UUI	25	UIE	1 mo	-4.81	4.99
Sahai ³⁹	Refractory UUI	<34	UIE	3 mo	-3.50	1.01
Flynn ⁴¹	Refractory DOI	15	IE	6 wk	-4.5	3.4
INTERSTIM						
Schmidt ¹⁴	Refractory UUI	34	IE	6 mo	-7.1	8.05
Siegel ¹⁵	Refractory UUI	41	IE	3 yr	-6.6	8.93
Van Kerrebroeck ¹⁶	Refractory UI, urge/frequency & retention	57-71	IE	5 yr	-5.7	7.14
Bosch ⁸³	Refractory UUI & OAB	45	IE	6 mo	-5.8	NA

*Endpoint is the Change from Baseline to Time Point in UIE = Urge Incontinence Episodes per day or in IE = Incontinence Episodes per day.

**All changes are mean changes from baseline, except for the Bosch study which provided changes in median values.

The change from baseline for InterStim[®] ranges from approximately -6.0 to -7.0 IE/day, while the change from baseline in Botox A[®] ranges from approximately -3.5 to -5.0 incontinence episodes/day (assuming that the change in UUIE/day is similar to the total change in IE/day). The estimate of variability ranges, conservatively, from 5.0 to 9.0. The combination of these treatment effects results in treatment differences ranging from -1.0 to -3.5. The table below provides the total sample size required to achieve adequate power to compare botulinum toxin A and InterStim[®] therapy with respect to the primary endpoint, the change from baseline in the mean number of UUIE per day over the 6-month period. Urge incontinence episodes are measured prospectively using 3-day voiding diaries administered approximately every 4 weeks during the study. Subjects are required to have at least 6 UUIE on a baseline 3-day bladder diary. The sample sizes are based on a 2-sided type I error rate of 5%, 80% power and a 10% loss-to-follow-up rate. The EAST 5.1 software package was used.

Total Sample Size for Various Treatment Differences and SD Estimates, Assuming Two-Sided Type I error of 5%, 80% power and 10% LFU.

Treatment Difference	SD=5.0	SD=6.0	SD=7.0	SD=8.0	SD=9.0
-3.5	72	103	140	183	232
-3.0	97	140	190	248	315
-2.5	140	202	274	357	453
-2.0	218	316	428	558	707
-1.5	338	558	760	993	1256
-1.0	873	1256	1709	2233	2826

A sample size of 316 subjects (158 per treatment group) provides at least 80% power to detect an absolute difference of -2.0 urinary UUIE per day between the two treatments (considered to be the minimal clinically important difference for this outcome measures), assuming a common SD of 6.0 and two-sided type I error rate of 5% and 10% loss to follow-up . Further adjusting the sample size to allow for a 20% initial non responder rate for each treatment group, the number to be enrolled and randomized will be **380** subjects (190 per treatment group).

If the trial fails to detect a significant difference between botulinum toxin A and InterStim[®] therapy, interval estimates of the difference in change from baseline in the number of urge incontinence episodes between the two groups will be generated to compare, in a descriptive manner the effectiveness of botulinum toxin A and InterStim[®] therapy. The following table shows the probability that these analyses will provide evidence of noninferiority between the treatment arms, assuming the SD of change from baseline is 6.0, for different assumptions regarding the noninferiority margins and true treatment differences.

Since two randomized studies showed no placebo effect in the refractory groups^{39,40}, we assume the change from baseline for Placebo is 0 urge urinary incontinence episodes/day. By further assuming the change from baseline for InterStim[®] is approximately -6.0 to -7.0 incontinence episodes/day, we propose that the descriptive non-inferiority margin be established at -1.0; at that level, the effect size of the less effective treatment would be at least 83% to 86% the effect size of the more effective treatment compared to placebo.

Probability for confidence intervals indicating non-inferiority of Treatment A compared to Treatment B for n=316 and SD=6.0, where Δ is the assumed true difference between Treatment A and Treatment B.

Non-inferiority Margin	$\Delta=-1.0$	$\Delta=-0.5$	$\Delta=0$	$\Delta=0.5$	$\Delta=1.0$
-2.0	0.29	0.56	0.8	0.94	0.99
-1.5	0.10	0.29	0.56	0.8	0.94
-1.0	n/a	0.10	0.29	0.56	0.8
-0.5	n/a	n/a	0.10	0.29	0.56

P.1 INTERIM ANALYSIS

No formal interim analysis of efficacy is planned.

Q. STATISTICAL DESIGN

Q.1 Statistical Analysis

Prior to analysis, the two groups will be compared with respect to demographic and baseline variables (e.g., age, race, BMI, quality of life status). If a significant difference is found in any variable, the models described below will be fitted both with and without the variables that differ at baseline.

Q.1.1 Analysis of Primary Outcome

For InterStim[®], sustained improvement in baseline incontinence parameters has been documented at 3-5 year follow-up. In contrast, the therapeutic effectiveness of a single Botox A[®] injection diminishes over time, thus it requires reinjection to sustain the effect. Previous studies^{36,37,49} showed that after each injection, the urodynamic parameters improve significantly. Because the therapeutic effectiveness fluctuates for the Botox A[®] treatment scheme but is sustained over long term for InterStim[®], the preferred comparison of the two treatments requires a measure of the accumulated effectiveness over time.

The primary outcome measure, change from baseline in mean number of UUIE per day over the initial 6-month period (i.e., change from baseline to average number of UUIE per day across months 1, 2, 3, 4, 5 and 6) provides a cumulative measure. To test for differences in this cumulative

measure, a longitudinal approach incorporating all time points (including baseline) will be employed. Specifically, the outcome will be analyzed using a mixed effect model for repeated measures with time (treated as a categorical variable), treatment group, treatment by time, site, and age stratum (<65 v. \geq 65 years) as fixed covariates. Under the model, estimates will be generated for each time and treatment group combination, and the primary hypothesis will test whether the difference between the average number of UIIE per day across months 1 through 6 and the baseline number of episodes for the InterStim® arm differs from that same difference for the Botox A arm. The primary analysis set will use a modified intent-to-treat approach, which includes subjects who are randomized, treated, and have a baseline and at least one follow-up observation of UIIE. For purposes of the primary analysis, any missing observations will be treated as missing at random. We will also use both parametric mixed models and longitudinal semi-parametric regression model (SPMM, Zhang et al, 1998) to explore and compare differences in the trajectory of urinary incontinent episodes over time in the two arms.

Missing data: Standard procedures will be used to ensure that data are as complete and accurate as possible. As noted in other sections of the protocol, the study is designed to obtain as much follow-up data as possible on all randomized subjects, including those that initially fail to achieve 50% improvement and those who implement off-protocol therapies. In analyses, a full accounting will be made for all data items. Generally, missing data will initially be treated as randomly missing (either missing at random (MAR) or missing completely at random (MCAR) as appropriate for the analytic approach) with no data imputation. General strategies for developing sensitivity analyses that examine the robustness of this approach are outlined below; more details on these sensitivity analyses will be specified in the Statistical Analysis Plan (SAP).

In this study, we anticipate that missing data will be generated in three primary ways. First, a small fraction of subjects may withdraw consent or be lost to follow-up and will not have any measurements after their withdrawal. Second, subjects may fail to provide data at a specific

follow-up time due to unforeseen circumstances (e.g. travel or an unplanned surgical procedure) that do not allow them to provide assessments within the allowable window. The missing data from the first set of subjects will follow a monotonic pattern while those from the second will follow an intermittent pattern. For both groups, the missing data may fall across the missingness spectrum from MCAR to missing not at random (MNAR). The third category involves subjects that select to use “off-protocol therapy” prior to the end of the follow-up period, but continue to supply follow-up data. While the data from these subjects are not technically missing, they do create issues in inference that are often addressed using missing data approaches

We will use two general strategies for assessing the sensitivity of both primary and secondary analyses to MAR and MCAR assumptions. First, for individuals that withdraw from the study or have missing visits, we will collect information on the reasons for those missed visits. That information, coupled with data collected from earlier visits will be used to develop comparisons of the two treatment arms using pattern mixture models. For the second approach, we will use multiple imputation based on a model conditional on baseline covariates, treatment group, and all previous measures. Since we expect the trajectories of the two treatment groups to be quite different from each other, separate imputation models will be used for the two groups. The Botox A[®] model should also include whether and when the subject has received Botox A[®] reinjection, and InterStim[®] model should include whether the device has been revised or removed.

For those who switch to the alternative treatment arm therapy or implement off-protocol therapies, we will examine the sensitivity of the intention to treat analyses in two ways. First, in the various modeling approaches, we will modify the models to incorporate a time-varying treatment parameter that can be used to examine the effect of as received treatment. Second, we censor all measurements after they receive alternative treatment, and then impute all censored measurements based on information collected from those who do not switch. We require initial failures not to switch to alternative therapy prior

to the 6 month visit, so we anticipate that we should have at least one measurement available that is not influenced by alternative treatment. Additional details for these sensitivity analyses will be provided in the SAP.

Q.1.2 Analysis of Secondary Outcomes

There are three categories of secondary outcomes: continuous outcomes such as change from baseline in OABq-SF, IIQ, UDI, Vaizey, PISQ-12/R, and HUI-3 scales; dichotomous outcomes such as the proportion of subjects who report adequate improvement of their bladder function ("very much better" and "much better" on the PGI-I), who report satisfaction on the OAB-SATq, and with voiding dysfunction/partial urinary retention requiring catheterization; and utilization of medical resources for cost-effectiveness analysis.

Continuous secondary outcomes will be compared between treatment groups using the same primary methods as described for the primary outcome. For dichotomous secondary outcomes, logistic regression will be used with treatment group and stratification factors included as covariates. Statistical significance for the secondary outcomes will be set at 5%. No adjustment will be made for multiplicity.

The cost-effectiveness analysis will be conducted from a payer perspective and will be expressed as incremental cost required to produce one additional unit of quality-adjusted life year (QALY). Data on each subject's use of medical and non-medical resources related to urologic or gynecologic conditions will be collected during the 24 month follow up period. Direct and indirect costs of the treatment of urinary incontinence with Botox A® injections and SNS and women's preference for incontinence health states for improvement in urge urinary incontinence will be estimated.

We plan to capture incremental health care resource use related to study interventions and complications and other incontinence management (such as anti-cholinergics, pelvic floor rehabilitation). Costs will be estimated using the resource costing method where medical service use

from each study case report form is monetized by multiplying the number of units of each medical service by the average unit cost of this service in dollars. This method allows a consistent capture of resource use when costs are incurred across multiple health systems or payers. Detailed case report forms, that include the number of procedures performed (e.g. SNS, Botox injections, reprogramming or surgical revision for SNS and reinjection for Botox) and clinical events (e.g. UTI, admission for pyelonephritis) will be completed by the study coordinator at the 1, 3, 6, 12 and 24 month visits. Data from physician visits, will be collected. Cost for each medical service use will be assigned based on national Medicare reimbursement rates, as indicated in the following table.

Resource utilization data collection (at 1, 4, 6, 12, and 24 month visits) and price data source, by utilization category

Service	Price Weight
Physician visit	Medicare reimbursement
SNS implantation or surgical revision	Medicare reimbursement
Botox injection (cystoscopy, Botox)	Medicare reimbursement Retail cost of Botox (or Medicare reimbursement if available)
Self-catheterizations	Retail cost
Anticholinergic medications	National retail cost of Oxybutynin
Pelvic PT sessions	Medicare reimbursement

The HUI-3 algorithm will be used to calculate each subject’s utility index at baseline and various follow up time points based on her responses to the HUI-3 questionnaire. We will use the self-assessment, interviewer (telephone) administered version of the HUI-3 questionnaire to be administered during the baseline, 6, 12 and 24 month phone interviews. This is a 40-item questionnaire but should only take respondents 3 minutes to complete (because of embedded skip patterns). This instrument has been previously used in women with urinary incontinence (Subak et al, 2008). These data will be used to compare change in QALYs between the two treatment groups. We are choosing to use a general scale to calculate change in utilities (rather than condition-specific) to allow for comparison of cost-effectiveness results with other interventions and diseases. Because the follow up period for subjects spans two years, costs and QALYs in the second year of follow up will be discounted using a 3% discount rate.

Differential mean costs and differential mean QALYs between the two treatment groups will be estimated using multiple regression analysis. Specifically, a generalized linear model with appropriate link function (e.g., log-link) and response probability distribution (e.g., gamma distribution) will be used to analyze costs due to the potential skewness and heteroscedasticity of medical expenditure data, while an ordinary least squares regression will be used for analyzing QALY data. The models will account for treatment group, study site and stratification factors, as well as other characteristics of the subjects that are found to differ significantly between the botulinum toxin A and the InterStim[®] groups. When estimating QALYs, we will also adjust for subjects' baseline utility scores to account for potential imbalance in baseline utility between the two treatment groups.⁶⁹

We will calculate the incremental cost-effectiveness ratio (ICER), which is the differential mean costs divided by the differential mean QALYs between the two groups, to assess the additional costs associated with each additional QALY gained. Our base case analysis will be conducted based on subjects with complete data. Sensitivity analysis will be conducted to include subjects with incomplete data using the multiple imputation method.⁷⁰ Non-parametric bootstrapping resampling technique will be used to derive the 95% confidence interval for the ICER.⁷¹ In addition, cost-effectiveness acceptability curve (CEAC) will be generated to illustrate the likelihood that one treatment is more cost-effective than the other with various ceiling cost-effectiveness ratios.

In the case that a statistically significant difference in changes in utilities (as measured by HUI-3) between the treatment groups is not detected, we plan to conduct supplemental analyses using alternative outcome measures, such as incremental cost per UUI episode, incremental cost per UUI HRQOL, or incremental cost per satisfaction.

The cost-effectiveness evaluations will be conducted as within-trial comparisons. A decision analytic model will also be developed from trial data to evaluate the trajectory of the cost-effectiveness ratio over a

lifetime; assuming an average life expectancy, given the average age of participants at the time of the intervention.

Q.2 Subject Withdraws, Loss to Follow up and Completion of Study

If a subject withdraws consent for study participation, the subject will complete end of study data collection and will be transferred to their primary physician for continued care of their OAB symptoms.

Upon completion of the study at 2 years (or after withdrawal of consent after receiving therapy), subjects and/ or their insurance providers will be responsible for any future costs to manage their InterStim[®] device and for potential further Botox A[®] injection therapy.

If a subject takes off-protocol treatment for urge urinary incontinence for any reason (no or poor response to either study therapy) or discontinues study treatment (e.g. does not have final InterStim[®] device implantation or repeat injections or has device removed), the subject will remain on study follow-up. If the subjects are receiving off-protocol therapy at the time of data collection, the specific therapy and duration of such therapy will be recorded. No subject will be transferred to clinical care until any urinary retention has resolved.

R. ETHICAL CONCERNS AND INFORMED CONSENT

R.1 Ethical Concerns

This study is significant because the subjects in this study have persistent, bothersome, symptoms of urge incontinence and have failed or been unable to tolerate multiple standard therapies, including anticholinergic therapy. InterStim[®] therapy is currently the only well recognized therapy for refractory urinary urge incontinence for which 9,500 implants were performed in the US in 2009. The use of intra-detrusor botulinum toxin A injections for the treatment of refractory urge incontinence has reported demonstrated short term efficacy and safety. Despite the drug not being currently FDA- approved, it is being used off-label by many US urologists and urogynecologists for urge incontinence.

Our randomization will be comparing InterStim[®], a staged procedure requiring two operating room visits, monitored anesthesia care, and radiation exposure, to Botox A[®] therapy, an office cystoscopic procedure with intradetrusor injections. Since these procedures are quite dissimilar with regards to time commitment, complexity of techniques, and adverse events, consideration for patient acceptability or preferences will be made. Data regarding health state utilities for urge urinary incontinence (UII) are very limited. A computer elicitation tool to assess UII patient preferences for different treatment options for UII has been developed.⁷² Preferences are assessed using the visual analog scale (VAS) and time trade-off techniques (TTO), which were interviewer-administered. Preliminary results show that, as expected, median VAS scores were lower than TTO scores. However, although the treatment options are vastly different, patient preferences were surprisingly similar using both scoring systems. The median VAS for InterStim[®] without AE was 0.71 v. Botox A[®] without AE = 0.67, with AEs InterStim[®] 0.41 v. Botox A[®] with AE 0.33. The results of this pilot study suggest that randomization of similar patients to InterStim[®] v. Botox A[®] therapy will impose no perceived inequality to what patients will accept. Subjects will undergo this same tool for our utility assessment of the therapy before randomization.

Additionally, adverse events of botulinum neurotoxin A include the potential for clean intermittent self-catheterization. A recent study investigating the hypothesis that the need for CISC is outweighed by the efficacy of the therapy, reported that there was no significant differences in QOL scores before and after Botox A[®] injections in women performing CISC and those who did not.⁷³

Both therapies will have initial failures. Continuing to follow the failures will be important statistically under the ITT principle, and we believe that encouraging them to remain until the 6 month primary endpoint, prior to seeking alternative therapy, is justified in this study setting. This population includes individuals who have had symptoms of OAB for many years; a retrospective study describing a refractory OAB population

reported that those seeking InterStim[®] therapy had symptoms for a mean of 116 months (range 9-600).¹⁹

R.2 Informed Consent

Patients will be examined for clinical care prior to recruitment into the study. Patients who are candidates for study participation will be approached for enrollment. Written informed consent will be obtained at that time in accordance with Institutional Review Board Guidelines. A common template for informed consent will be used by all centers, with modifications allowed to meet the necessary requirements of their respective institutional human subjects committees. The informed consent will list risks specific to each procedure as listed in R3. After Botox A[®] injections, there is a low to medium risk of a lower urinary tract infection which can be successfully treated with an oral antibiotic. After an InterStim device has been implanted, there is a low to moderate risk of pain related to the device or lead movement requiring an office visit to reprogram the device. There is a low risk that a reprogramming does not resolve the problem and a subsequent outpatient surgical procedure is required to revise the device.

R.3 Risks/Benefits

	InterStim[®]	Botulinum toxin A
Risk of incomplete bladder emptying that could require catheterization	Very low	Low to medium
Risk of infection from therapy	Low	Low to medium
Compliance – short term	Excellent	Excellent (injectable)
Compliance – long term	Moderate	Unknown
Cost	High	Medium-high
Invasiveness	Medium-high (2 visits to OR, MAC, small incisions, little pain)	Medium (office based, with local anesthesia, no incision, little to no pain)
Issues with prolonged therapy	Possible mild to moderate: Pain (lead or generator site) Lead migration Stimulation pain	No known risks from prolonged therapy exist.
Adequate symptom control	Moderate -high effect	Moderate effect

R.4 DATA SAFETY MONITORING BOARD

The National Institutes of Health have set up a Data Safety Monitoring Board (DSMB) to oversee this study. Members of the DSMB are independent of the study investigators and represent Urology, Urogynecology, and Biostatistics, as well as having a lay member. The DSMB will meet every three months or more frequently if requested by the Chair, either in person or by teleconference. This protocol will be approved by the DSMB prior to initiation of recruitment.

R.5 SIDE EFFECTS/SAFETY

Multi-center clinical studies of InterStim[®] Therapy began in the United States in December 1993. The FDA requires that the placement of the Interstim device, lead and implantable pulse generator, is tracked by the manufacturer so that they can expeditiously remove potentially dangerous or defective devices from the market and/or notify patients of significant device problems. To date there have been no reported serious adverse events requiring device recall. The most common complications from this therapy can include pain, infection, transient electrical shock, lead migration, and constipation. These complications are generally resolvable. An absolute contraindication to the therapy is shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy anywhere on the body. Energy from diathermy can be transferred through the implanted system, and cause tissue damage and result in severe injury or death. Diathermy can also damage parts of the neurostimulation system. This can result in loss of therapy from the neurostimulation system, and may require additional surgery to remove or replace parts of implanted device. Injury or damage can occur during diathermy treatment whether the neurostimulation system is turned "on" or "off." The system may be affected by or adversely affect cardiac pacemakers or therapies, cardioverter defibrillators, electrocautery, external defibrillators, ultrasonic equipment, radiation therapy, theft detectors and screening devices. No life threatening or irreversible adverse events have been reported, although in a retrospective review spanning 11 years, 53% of patients experienced a mild to moderate

reportable event.¹⁹ The majority the events did not affect continued use of the therapy.

A relative contraindication is a body magnetic resonance imaging (MRI). However, in a survey of active implanters⁷⁴, 51% of the 106 respondents have had patients who required an MRI after implantation and over 40% had experience with patients undergoing an MRI while the device was in place. No consequences were reported in 97.4% of patients. The effect of magnetic resonance imagers on implanted neurostimulators was evaluated in a study.⁷⁵ The neurostimulators were mounted on a support and placed in the imagers. The effect of the static magnetic field produced very weak forces on the Medtronic Irel neurostimulator and the programmed stimulus parameters were unchanged. However, the device was heated when the magnetic fields were at the isocenter. Clinically, there are anecdotal reports of MRIs being performed on patients with InterStim[®] implants. A small case series of 8 MRI examinations at 1.5 Tesla were conducted on six patients. All MRIs were performed outside the pelvic area. Patients were monitored before, throughout, and after the MRI procedure. The results were promising as no patients had unpleasant sensations requiring stopping the examination, no change in bladder function occurred afterwards and all devices functioned properly. Currently, it is thought that if the implantable device does not enter the magnet bore no significant interaction occurs.⁷⁶ In addition, there is a decrease in temperature in leads when the region to be imaged is located 30 cm or farther from the center of the lead.⁷⁷

A recent comprehensive review identified 44 original research studies that reported on 16 different conditions treated with multiple treatments with Botox A[®]. The conditions treated with Botox A[®] were varied and included such disorders such as achalasia, blepharospasm, cervical dystonia, cerebral palsy, esophageal spasm, hemifacial spasm, laryngeal dystonia, oromandibular dystonia, strabismus in addition to detrusor overactivity. Botox A[®] has been FDA approved since 1989 for only some of the conditions it is currently been used for. According to the American Society of Plastic Surgery, 4.6 million cosmetic botulinum toxin A injections were administered in 2007, primarily for cosmetic indications.

This figure was up from 787,000 in 2000.

<http://www.plasticsurgery.org/media/statistics/index.cfm>

Despite the increasing popularity of Botox A[®] for the treatment of neurologic disorders, its efficacy as a potent neurotoxin remains an important clinical consideration in its use. Known side effects of treatment listed in the package insert include: nausea, vomiting, dry mouth, and respiratory muscle weakness or paresis. Cases of fatal cardiovascular compromise (including myocardial infarction or arrhythmia) or spontaneous death due to major debility are also cited in the drug package insert.

The FDA recently released an Early Communication about an Ongoing Safety Review: botulinum toxin A and botulinum toxin A Cosmetic (Botulinum toxin Type A) and Myobloc (Botulinum toxin Type B). http://www.fda.gov/cder/drug/early_comm/botulinium_toxins.htm. They reported on an investigation of 12 deaths or complications in patients that received botulinum toxin A injections. There were no deaths or intubations in adult patients. All such serious adverse events were in children and at doses of botulinum toxin A ranging from 100U-700U.

While no adult patients have reportedly required either intubation or death, in an attempt to maximize patient safety, subjects will receive verbal and written instructions to identify the signs and symptoms of systemic effects after receiving an injection of a botulinum toxin injection. Subjects will be told that they should receive medical attention if they have worsening or unexpected difficulty swallowing or talking, trouble breathing or muscle weakness and that these symptoms can occur days to weeks after injection.

Several authors have documented distal effects of botulinum toxin A therapy due to drug migration from treatment sites. Girlanda demonstrated mild abnormalities in cardiovascular reflexes and electromyographic tracings of muscles distant from the site of botulinum toxin A injection, the extensor digitorum communis muscle of the hand.⁷⁸ These mild changes in distant muscle activity suggest a small migrational

effect of botulinum toxin therapy from the original site of treatment. Boyd reported transient urinary incontinence in two twin boys treated with Dysport® for mild spastic diplegia.⁷⁹ The new onset incontinence was thought to be secondary to botulinum toxin A therapy and transient in nature, spontaneously resolving after 3 weeks. Botox A® is commercially available in the United Kingdom as Dysport. Although Botox A® and Dysport are the same serotype, they have different doses, efficacy, and side-effect profiles.⁸⁰ Some studies using Dysport have shown side effects thought to be caused by migration of Dysport from the detrusor. In a study that evaluated both Dysport and Botox A®, of the 22 patients who received Dysport, four observed transient muscle weakness in the trunk or extremities for up to 2 months. Two patients were injected with 750 units of Dysport and 2 patients were injected with 1000 units of Dysport. The authors felt that the muscle weakness was caused by systemic dispersion of Dysport.³⁶ Wyndaele reported two cases of muscle weakness lasting 3 months with Botox A®.⁸¹ Current formulations of Botox A® contain less protein content per unit of toxin, thereby providing less immunogenic potential. Resistance to the toxin has been thought to be the reason for patients who had a prior response to Botox fail further injections. Pistolesi et al. described a patient with NDO who developed resistance to Botox A® after repeated injections but had a favorable response to BTX-B.⁸² A case report described antibodies against Botox A® as the cause for failure after only the first detrusor injection.⁸³ Resistance to the toxin is also related to technique. Higher doses and shorter intervals between injections may contribute to the development of resistance. More recently, repeat injections were reported in refractory IDO patients.⁵⁷ Eleven patients underwent a second Botox A® injection of 200 units and nine patients received up to 4 injections. Repeat injections appeared to be equally efficacious and safe as the first injection, showing improvement in OAB symptoms, urodynamic parameters and QOL. In addition, there was no change in PVR between injections. The median time between injections 1 and 2 and 2 and 3 was 377 and 378 days.

Special precautions should be taken in patients with known neurologic disease when being treated with botulinum toxin A therapy. Patients with impaired neurotransmission (i.e. Myasthenia Gravis, Charcot-Marie-Tooth

disease) are at high risk to experience detrimental effects from distal botulinum toxin A effects and should be treated with caution, for safety, patients with impaired neurotransmission will be excluded from this trial.

R.6 ADVERSE EVENTS REPORTING

Adverse events will be reported in a manner consistent with the requirements outlined in the NICHD Clinical Research Policy Guidance Document. That document specifies that adverse events be reported to the Office for Human Research Protections (OHRP), and to the FDA, if FDA-regulated products such as a device, drug, or biologic are used. Consistent with that policy, adverse events will be reported in a manner consistent with OHRP and FDA regulations.

R.6.1 Definitions

An adverse event (AE) is any occurrence or worsening of an undesirable or unintended sign (including an abnormal laboratory finding), symptom, or disease that is temporally associated with the use of a study product whether considered related to the medicinal product or not.

A serious adverse event (SAE) or reaction is defined as “any adverse event occurring at any dose that suggests a significant hazard, contraindication, side effect, or precaution.” This includes but is not limited to any of the following events:

1. Death: A death that occurs during the study or that comes to the attention of the investigator during the protocol-defined follow-up after the completion of therapy must be reported whether it is considered treatment related or not.
2. A life-threatening event: A life-threatening event is any adverse therapy experience that, in the view of the investigator, places the participant at immediate risk of death from the reaction as it occurred.
3. Inpatient hospitalization or prolongation of existing hospitalization.
4. Persistent or significant disability/incapacity.
5. Congenital anomaly or birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

An AE is considered “unexpected” for purposes of the IND sponsor reporting to health authorities when the nature (specificity) or severity of the AE is not consistent with applicable product information, such as safety information provided in the package insert or the investigator’s brochure. Adverse events that are determined to be at least partially caused by the procedures involved in the research would be considered “related to participation” in the research.

The OHRP considers adverse events that are unexpected, related, or possibly related to participation in research, and *serious* to be the most important subset of adverse events representing unanticipated problems because such events always suggest that the research places subjects or others at a *greater risk* of physical or psychological harm than was previously known or recognized. Such events routinely warrant consideration of substantive changes in the research protocol or informed consent process or other corrective actions in order to protect the safety, welfare, or rights of subjects.

R.6.2 Collection and Recording of Adverse Events

At each clinic visit or follow-up telephone call, subjects will be asked to recall any adverse events since the time of their last contact (either via phone call with the coordinator or clinic visit). Coordinators will record this information using the appropriate case report forms and report the data through the study data management systems.

Serious adverse events will be promptly reported to the clinical center IRB as per local IRB guidelines, the data coordinating center, the NIH

Project Scientist and the Data and Safety Monitoring Board as required by PFDN serious adverse event reporting procedures.

Particular attention will be focused on collection of adverse sequelae associated with the initial treatment activities, and subjects receiving either Botulinum toxin A or InterStim[®] therapy will be asked to report selected adverse events immediately to the study coordinator or physician. For Botulinum toxin A subjects will be instructed to report the following adverse events immediately if they are encountered:.

Medication related adverse events. This includes but is not limited to difficulty breathing, speaking, or swallowing:

Procedure related adverse events. This includes voiding dysfunction, need for catheter use, urinary tract pain, bleeding, fever, or cystitis.

For InterStim[®] therapy subjects will be instructed to report the following adverse events immediately if they are encountered:

Device related adverse events. This includes those attributable to any part of the InterStim system (tined lead, neurostimulator or extension), including but not limited to: pain, infection, or transient electrical shock.

Procedure related adverse events. This includes any adverse event attributable to any procedure required to implant, modify, or explants any part of the Interstim[®] system

R.7 CONCOMITANT MEDICATIONS

Concomitant medications will be captured at baseline and through the completion of study follow-up at 24 months.

S. PROTOCOL COSTS

Study related visits, as outlined in the protocol, will be research costs. The botulinum A toxin and botulinum A toxin injection procedures, not considered standard clinical practice, will be considered research costs. The costs of the InterStim[®] device will be considered part of clinical costs

and be billed to the subjects' insurance company or covered by the study. Implantation procedures will be considered part of clinical costs, and be billed to the subject's insurance company, as this is a current therapeutic procedure rather than experimental. Some charges for the InterStim surgery may be billed to the study. However, portions of the bill not paid by the insurance company or study will be the subject's responsibility. . The study or hospital will cover the cost of the InterStim[®] device and implantation procedures in subjects who are not insured and randomized to that arm. Subsequent costs for evaluation and treatment of urinary incontinence after completion of the 2 year follow up period will be considered part of clinical costs.

Subjects may receive up to \$500 over the two year study period to partially cover their personal time and expenses related to study participation.

This will be provided as follows:

- \$50 following completion of baseline visit bladder diary and QOL
- \$30 following completion of 1 month bladder diary and visit
- \$30 following completion of 2 month bladder diary
- \$30 following completion of 3 month visit and bladder diary
- \$30 following completion of 4 month bladder diary
- \$30 following completion of 5 month bladder diary
- \$100 following completion of 6 month visit, bladder diary and QOL
- \$25 following completion of 9 month bladder diary
- \$50 after 1 year visit, bladder diary and QOL
- \$25 following completion of 18 month bladder diary
- \$100 after 2 year visit, bladder diary and QOL

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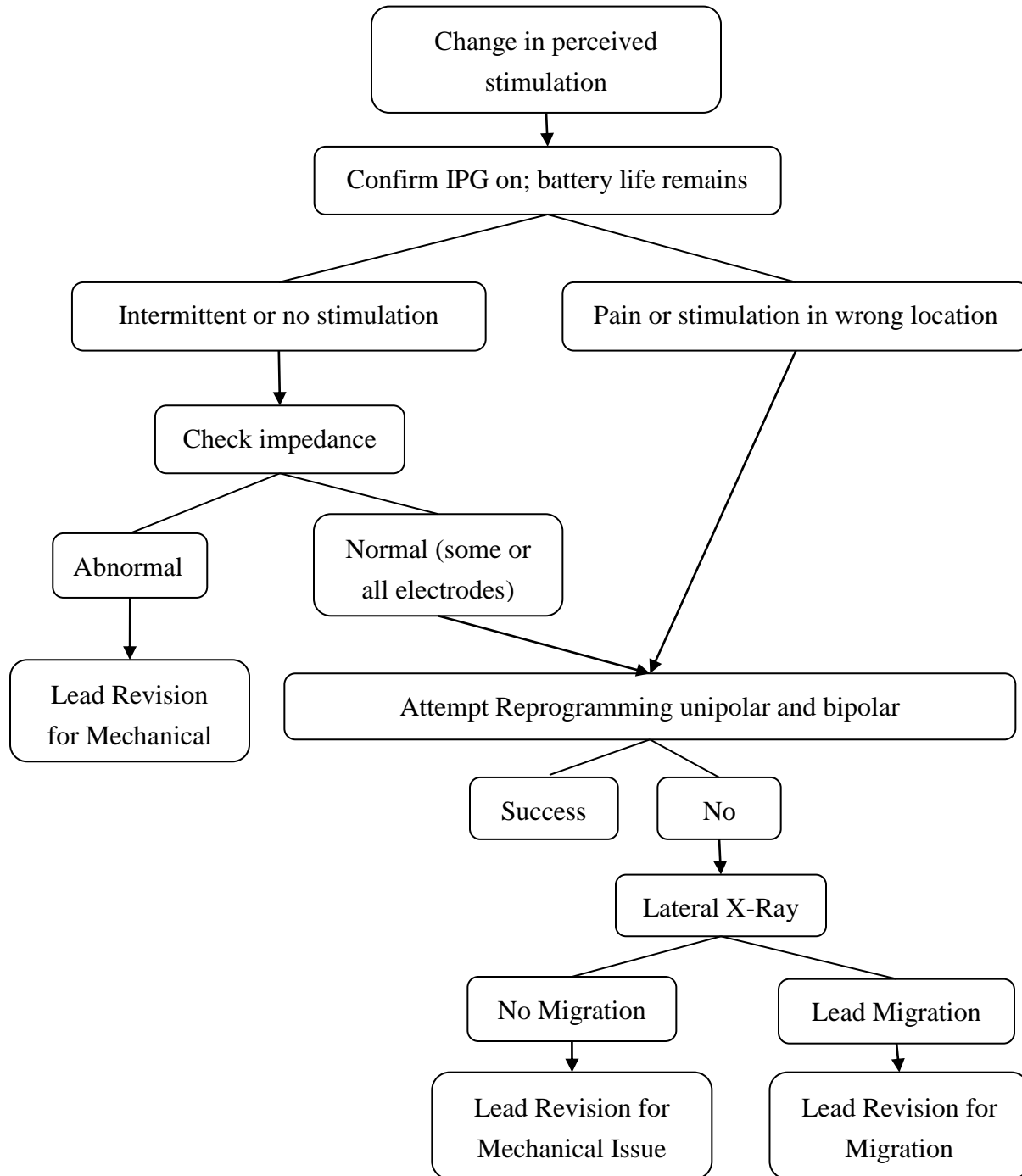
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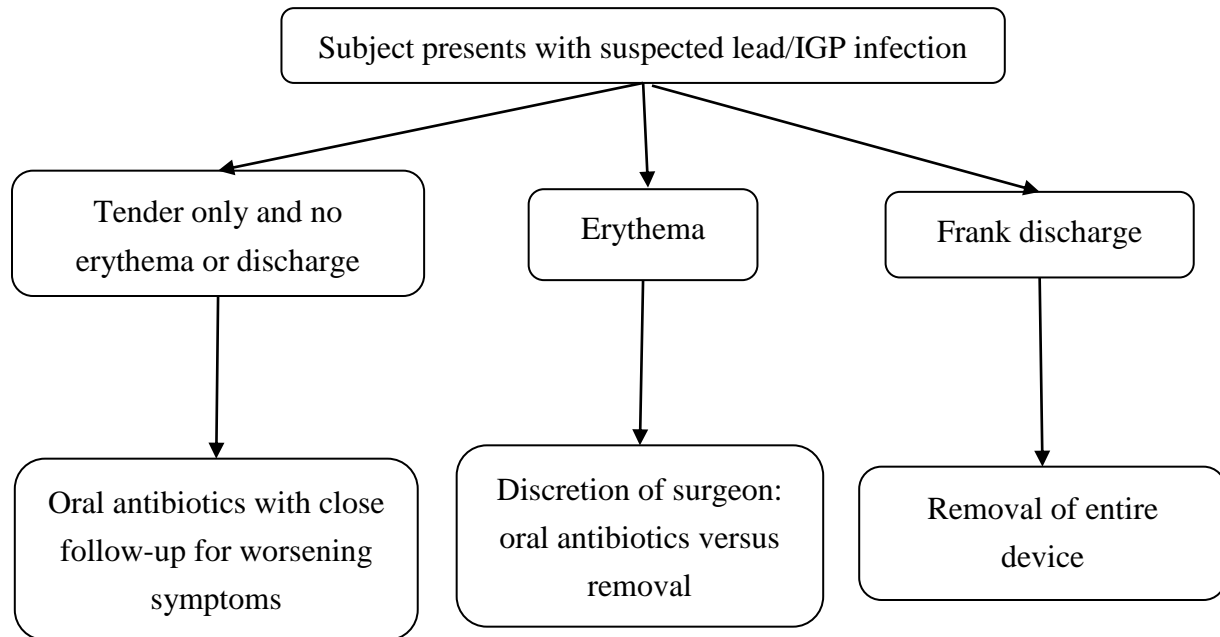
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U. APPENDICES

Appendix 1. Diagnostic Algorithm for Abnormal or No Stimulation Perception (includes sites of wrong or abnormal stimulation, i.e. non S3 nerve distribution sites/pain, foot, etc.)



Appendix 2. Evaluation for IPG/Lead Infection



Appendix 3. IPG Discomfort

