C O N F I D E N T I A L

Pelvic Floor Disorders Network

NeurOmodulaTion for Accidental Bowel LEakage

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Confidentiality Statement

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ABBREVIATIONS

ABL	Accidental Bowel Leakage
ABLE	Accidental Bowel Leakage Evaluation
AE	Adverse Event
BM	Bowel Movement
BMI	Body Mass Index
CAPABLe	Controlling Anal incontinence by Performing Anal Exercises with Biofeedback or Loperamide Trial
CNS	Central Nervous System
CONFIDeNT	CONtrol of Faecal Incontinence using Distal NeuromodulaTion Trial
CRF	Case Report Form
DCC	Data Coordinating Center
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
FI	Fecal Incontinence
FIE	Fecal Incontinence Episode
FIQL	Fecal Incontinence Quality of Life Scale
FUI	Fecal Urgency Incontinence
HHS	Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
ICI	International Consultation on Incontinence
ICS	International Continence Society
MID	Minimal Important Difference
NICHD	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
NOTABLe	NeurOmodulaTion for Accidental Bowel Leakage Trial
OAB	Overactive Bladder
OrBIT	Overactive Bladder Innovative Therapy Trial
PAC-SYM	Patient Assessment of Constipation-Symptom Questionnaire
PFDI-20	Pelvic Floor Distress Inventory Questionnaire – Short Form 20
PFDN	Pelvic Floor Disorders Network
PFIQ-7	Pelvic Floor Impact Questionnaire
PGI-I	Patient Global Impression of Improvement
PGSC	Patient Global Symptom Control Rating
PISQ-IR	Pelvic Organ Prolapse/Incontinence Sexual Questionnaire – IUGA Revised
PMT	Pelvic Muscle Training
PTNS	Percutaneous Tibial Nerve Stimulation
QOL	Quality of Life
RCT	Randomized Controlled Trial

ReFINE	Refractory Fecal IncoNtinencE Trial
SAE	Serious Adverse Event
SANS	Stoller Afferent Nerve Stimulator
SAP	Statistical Analysis Plan
SF-12	12-Item Short Form Health Survey
SNS	Sacral Nerve Stimulation
STEP	Sustained Therapeutic Effects of Percutaneous Tibial Nerve Stimulation Study
TENS	Transcutaneous Electrical Nerve Stimulator
tTNS	Transcutaneous Tibial Nerve Stimulation
USPSTF	US Preventative Services Task Force
UI	Urinary Incontinence
UUI	Urgency Urinary Incontinence

1 STUDY AIMS

The overarching goal of this randomized clinical trial is to determine if percutaneous tibial nerve stimulation (PTNS) is more effective than sham PTNS for the treatment of fecal incontinence (FI) in women.

1.1 Primary Aim: To determine whether the change from baseline in St. Mark's (Vaizey) score in women with symptomatic accidental bowel leakage (ABL) undergoing PTNS differs from sham after 12 weeks of stimulation.

Hypothesis: This study will test the null hypothesis that change from baseline in St. Mark's (Vaizey) score after 12 weeks of stimulation is not significantly different in women with symptomatic ABL receiving PTNS treatments compared to women receiving sham PTNS treatments.

1.2 Secondary Aims:

1. **<u>Part I.</u> To compare changes from baseline in self-reported functional outcomes after 12 weekly stimulation sessions in both PTNS and sham groups. Outcomes include:**
    a. Measures of symptom severity documented on a 14-day bowel diary including ABL episodes, fecal urgency, and number of defecation(s)/day.
    b. Condition-specific quality of life (QOL); global impression of improvement; co-existent bowel, bladder, and prolapse symptoms; adaptation measures; sexual function; and change in ongoing interventions for ABL described at baseline.
2. **<u>Part II.</u> Durability of Effect:** To determine whether symptom relief amongst study "responders" can be sustained for one year with maintenance treatments. A 4-point reduction from baseline in the St. Mark's score will be considered clinically significant and will be used to define an eligible treatment response for entry into Part II.
    a. To determine whether either a fixed schedule or a subject driven (PRN) schedule of treatments in "responders" of Part I is effective in maintaining symptom control at one year from start of treatments.

    This aim will estimate the percent of women assigned to each treatment schedule who maintain symptom control (defined as a 4-point reduction from baseline in the St. Mark's score) at one year from start of PTNS treatments.
    b. To determine whether the durability of symptom reduction acquired in Part I is sustained for up to 9 months after starting a maintenance strategy (comparison of Part I and Part II outcomes).
    c. To determine if the Fixed and the PRN schedule of treatments in Part II are feasible to implement, and are associated with different costs and participant satisfaction.

3. 6-Month Follow-Up of Symptom Control, Improvement, and QOL After Final PTNS Session Amendment to Protocol (see appendix 1)

OBJECTIVES AND PURPOSE

a. To establish a 6-month follow-up phase after the final PTNS session to determine the duration of effect of treatment. Follow-up will be discontinued when subjects report PGSC of ≤2 or report initiating NEW treatment for ABL that is prescribed by a health provider.

Primary Hypothesis

The likelihood of return of ABL symptoms increases over time after the last PTNS session is completed.

Secondary hypothesis:

Patient characteristics are associated with recurrence of ABL symptoms after ≥6 months of PTNS treatments.

4. Impact of completing a bowel diary and receiving education on fecal incontinence (FI) (NIDDK pamphlet) on symptom severity:

a. To determine the impact of education and completing a bowel diary on FI symptom severity as measured by a change from baseline in the St. Mark's score and change in weekly fecal incontinence episodes (FIEs) (Week 1 vs. Week 4) during the Run-In Phase.

b. To compare modalities of the bowel diary (phone app vs. paper) on their impact on FI symptom severity as measured by change from the baseline St. Mark's score and change in mean FIEs/week recorded in Week 1 and Week 4 of the Run-In Phase.

5. Ability of the PFDN ABL phone app diary to detect change: To determine if the changes from baseline in FIEs recorded on the PFDN ABL phone app diary correlate with changes from baseline in other measures of FI symptom severity including the St. Mark's score after 12 weeks of stimulation.

6. Determine association between St. Mark's score and both fat and fiber intake alone and in combination

a. The overall goal is to determine if accidental bowel leakage severity is associated with dietary intake. Dietary intake will be determined using the Dietary Screener self-administered questionnaire which captures both dietary fats and fiber (68). The association between St. Mark's score and lower dietary fat intake and higher fiber intake will be assessed.

1.3 Exploratory Aims

1. **Safety:** To describe and compare adverse events in PTNS and sham groups.
2. **Treatment compliance:**

a. To describe adherence to the treatment protocol in the PTNS group of Part I (defined as attendance at 10 of 12 scheduled treatment sessions) and to compare it to that of the sham group.
b. To describe treatment adherence in the fixed schedule group of Part II.

3. **Willingness to continue maintenance PTNS therapy amongst responders:** To determine their willingness to continue PTNS therapy for maintenance of symptom suppression in Part II.
4. **Validity of the sham:** To determine whether participants were aware of their assigned intervention in Part I.
5. **Predictors of response:** To identify clinical characteristics associated with treatment success at the end of Part I and Part II. Characteristics to be studied include, but are not limited to, age, Baseline body mass index (BMI), Baseline ABL (severity), Baseline St. Mark's (Vaizey) score, Baseline stool consistency, presence or absence of anal sphincter squeeze at baseline, and adherence to treatment schedule.
6. **Rate of UTIs:** To identify if there is a difference in the rate of UTIs treated with antibiotics between the PTNS and sham groups.

N.B. The term "accidental bowel leakage" is frequently used in this document. This descriptive term was preferred by women who participated in PFDN-sponsored focus groups convened to develop the Accidental Bowel Leakage Evaluation (ABLE), a new condition specific measure of fecal incontinence symptom severity and bother. The term "fecal incontinence" is also used in recognition of the historic and internationally recognized diagnostic term for the symptoms under investigation.

2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Disease/Condition Background

2.1.1 Accidental Bowel Leakage: Description and Epidemiology

Accidental bowel leakage (ABL), aka fecal or anal incontinence, is a common debilitating condition experienced by millions of women. Unfortunately, there has been little emphasis on identification and treatment of this condition. With new findings confirming the high prevalence of the disorder and new treatment options available, there is a move toward educating the public about this under-recognized problem. In 2011 the National Institutes of Health (NIH)/National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) launched a "Bowel Awareness Campaign" aimed at raising public awareness, preventing the condition and improving quality of life in those suffering with ABL (1). Despite this new focus on ABL, understanding the prevalence, etiology, and best treatment approaches to ABL is still in its infancy.

Prevalence estimates for ABL range widely depending on the definition used (solid, liquid, and/or gas) and the population studied. Reported rates range from 2% to 20% in

community dwelling populations and 46% in nursing home settings (2-6). Recent studies have demonstrated that up to 40% of women with ABL have severe negative impact on QOL and among women with urinary incontinence (UI), the additional presence of ABL significantly worsens QOL over the impact of UI alone (7, 8). Although there are limited data on the negative impact of ABL, overall it is likely underestimated given limited public awareness about the condition and available treatment options. Most women suffer in silence with reports of fewer than 30% of women with ABL seeking care for their condition (8-10).

The underlying etiology of ABL is likely multifactorial with no one common underlying preventable condition. However, ABL has been most strongly associated with conditions resulting in diarrhea (i.e., irritable bowel syndrome, inflammatory bowel disease) (5, 11, 12). While diarrhea is common in those with ABL, constipation is also a condition that can result in overflow ABL (13). In addition to bowel disorders, conditions associated with neuromuscular compromise of the anal sphincter complex such as UI, stroke, diabetes, pulmonary disease, and vaginal delivery have been implicated in the presence of ABL (5, 11, 12). Though not fully understood, the pathophysiology of ABL is likely related to disruption of one or more of the neuromuscular functions of the sphincter. Therapeutic options have been limited due in part to the incomplete characterization and understanding of this complex condition.

2.1.2 Current Treatment for Disease

Despite growing evidence surrounding the enormous impact of ABL on society, there are few evidence-based therapies available. As most ABL is associated with abnormal stool consistency, first-line therapies commonly instituted in clinical practice are aimed at altering stool consistency (dietary modification with fiber and constipating agents) and increasing pelvic muscle strength (pelvic floor exercise with or without biofeedback) (14). Those who fail these interventions have historically been left with few options. Until recently, surgery in the form of sphincteroplasty or artificial sphincter were the only available procedures for treatment of ABL with insufficient data on optimal surgical options (15). These surgical procedures for ABL are associated with high morbidity and poor long-term outcomes (16-19). New minimally invasive procedures are currently emerging with very little long-term safety and efficacy results. Anal bulking injections and radiofrequency treatment of the anal sphincter have shown some promise with short-term success rates of nearly 50%, but no comparative or long-term data are available (20, 21). In 2011, sacral neuromodulation with the Interstim (Medtronic, Minneapolis, MN) device was approved for the treatment of FI with promising short-term results (22), but long-term success rates have been less encouraging with variable results from 42% to 86% at 3 to 5 years (20, 23). Revisions for this device are common and costs for implantation are substantial. Thus, demand for a minimally invasive and cost-effective therapy remains.

2.1.3 Percutaneous Posterior Tibial Nerve Stimulation

The tibial nerve contains both afferent and efferent fibers originating from L4-S3. Percutaneous electrical stimulation of the tibial nerve (PTNS) appears to facilitate peripheral neuromodulation similarly to sacral neuromodulation stimulation (SNS). It has emerged as a viable, minimally invasive, low risk, and relatively low cost option for management of urgency urinary incontinence (UUI). The site of stimulation in PTNS, posterior and superior to the medial malleolus (inner ankle), is an acupuncture point ('sanyinjiao' or 'spleen-6') in traditional Chinese acupuncture where therapy is directed to reduce pelvic symptoms including bladder dysfunction, pelvic pain, FI, and impotence (24). It was first described as a therapeutic modality for UUI and overactive bladder (OAB) by McGuire et al. in 1983 (25) using a transcutaneous electrode and subsequently modified by Stoller who reported on a percutaneous needle approach (26). As with the Interstim device, peripheral neuromodulation was also found to have a positive impact on ABL. Since 2003, investigators have explored PTNS as a modality for treatment of ABL.

2.1.3.1 Mechanism of Action of Peripheral Neuromodulation

The mechanism of action of peripheral neuromodulation is uncertain but is thought to be similar to that of SNS. The posterior tibial nerve contains mixed sensory-motor nerve fibers that originate from L4 through S3 nerve roots which contain the peripheral nerves involved in the sensory and motor control of the pelvic floor and viscera. The majority of mechanistic studies on neuromodulation have focused on bladder function in the cat model by Tai et al. They postulate that electrical stimulation of the tibial nerve, sufficient to generate an action potential on somatic afferent nerves, triggers the release of multiple neurotransmitters in the central nervous system (CNS) that modulate pelvic visceral function (28). They have demonstrated that tibial nerve stimulation induces a persistent post-stimulation inhibitory effect on bladder activity which differs from SNS in that induced bladder changes only continued while the SNS stimulator is turned on (28, 29). Similarly, for bowel function, tibial nerve stimulation is thought to alter the local somato-visceral reflexes leading to changes in colonic motility and anal sphincter activity and may also modulate afferent sphincter information (50, 51). Clinical trials of percutaneous and transcutaneous tibial nerve stimulation have not consistently documented anorectal physiologic changes (30, 31, 32). The duration of effect on bowel activity in humans has not been determined.

2.1.4 Tibial Nerve Stimulation Techniques

Tibial nerve stimulation is usually delivered unilaterally; dominance of the left or right tibial nerve has not been reported. There is no published data supporting the superiority of bilateral stimulation though Stoller described placing needles bilaterally and proceeded with stimulation on the side that demonstrated the most pronounced response during the test stimulation (33). The transcutaneous method delivers energy from a transcutaneous electrical nerve stimulator (TENS) to two surface electrodes which are placed either directly over the tibial nerve just above the medial malleolus or on the bottom of the foot where

peripheral branches of the tibial nerve, the lateral and medial plantar nerves are stimulated (34). The first prospective cohort study of transcutaneous stimulation of plantar nerves for humans with OAB is underway. The percutaneous approach entails insertion of a 36-gauge needle electrode at a 60 degree angle approximately 5 cm or 3 finger breadths cephalad to the medial malleolus and posterior to the tibia. A portable electrical stimulator delivers an adjustable current in the range of 0.5-9 mA. When described in the literature, the generators commonly are set for a pulse frequency of 20 Hz with a goal of creating a motor and/or sensory response in the foot.

Effective stimulation parameters are highly variable between subjects. Differences in pulse width, voltage/current, biphasic/uniphasic pattern are not known to be therapeutically relevant in facilitating effective peripheral neuromodulation (personal communication Changfeng Tai, William C. Degroat). What is important is that a sensory/motor threshold is reached with the combination of stimulus parameters. As long as the stimulus induces a tingling sensation on the bottom of the foot and/or toe twitching, the effect of nerve stimulation is the same (i.e., generating action potential on the nerve). The optimal stimulation intensity has not been established. In the early manuscripts on PTNS for both UI and FI investigators administered the maximum tolerated stimulation during the treatment session. In contrast, Cogentix (formerly Uroplasty) recommends sub-threshold stimulation intensity in the Urgent PC IFU for treatment of UUI. The rationale for this recommendation is not elucidated.

2.2 Summary of Previous Studies

2.2.1 Summary of Previous Studies on PTNS for UUI

Over 20 cohorts, 5 randomized controlled trials (RCTs), 5 systemic reviews, and 1 Cochrane meta-analysis have been published on PTNS for urinary frequency, urgency, and UUI (35). The efficacy of PTNS is similar to anticholinergic medications (36, 37). Two RCTs show that PTNS is better than validated sham for the treatment of refractory OAB (38, 39) and efficacy in responders was sustained with maintenance treatments to 12, 24, and 36 months (40, 41, 42). The weekly treatment schedule, though demanding, appears to be acceptable with a study drop-out rate of 14% vs. 16% for anti-cholinergic drugs (36, 37).

Initial Treatment Schedule for UUI

The optimum duration and frequency of the treatment for PTNS has not been determined. For UUI, one study suggested that it may not be the frequency but the total number of treatments that is associated with response. Finazzi Agro found that 12 weekly sessions compared to 3 times a week sessions resulted in equivalent outcomes with a quicker improvement noted in the group receiving 3 times a week sessions (39). However, likely due to patient burden, most studies for urinary symptoms continue use the protocol described by Stoller (i.e., 12 weekly 30-minute treatment sessions).

Maintenance Treatment Schedule for UUI

Discontinuation of PTNS treatments amongst "responders" for OAB bladder symptoms results in return of symptoms in a relatively short period of time (6 weeks) (43). Attempts have been made to determine objective criteria for maintenance plans. The Sustained Therapeutic Effects of Percutaneous Tibial Nerve Stimulation (STEP) trial used a tapering protocol of 5 treatments over 14 weeks to help patients and their physicians understand the effect of PTNS on urinary symptoms in an individual patient. They then used this information to develop a maintenance plan of gradually lengthening intervals between treatments. This resulted in a median of 1.1 treatments per month between 6 to 36 months (41, 42). Several implantable devices are under development for chronic ambulatory peripheral neuromodulation therapy. The principal advantage of these units would be reprieve from office-based treatment sessions.

2.2.2 Summary of Previous Studies on PTNS for ABL

Early published studies of PTNS for ABL show promising effects, though they are limited by lack of controls, small sample sizes, poorly defined populations, variable neuromodulatory protocols, and differing definitions of success and outcome measures. A systematic review published in 2013 by Horrocks et al. (44) summarized the findings of 12 studies in English reporting on 375 patients (range 10-88) treated for FI of various etiologies. There were 6 studies of PTNS, 5 of transcutaneous tibial nerve stimulation (tTNS), with one RCT comparing both modalities. The PTNS studies reported on 30-minute stimulation sessions with varying treatment intervals: weekly (4 studies), twice weekly (2 studies), and every other day for 4 weeks (1 study). Mean follow-up was 5 months (range 1.5-22). Studies using the outcome of ≥50% reduction of FIEs/week using bowel diaries reported response rates from 63-82% (30, 31, 32, 45). One study reported 59% treatment success at one year (32). Two RCTs of PTNS vs. sham have been conducted with conflicting results. George et al. conducted a small (N=30) three-arm RCT of percutaneous vs. transcutaneous vs. sham stimulation and reported superior efficacy in the PTNS group which was sustained over a 6-month follow-up period (30). In 2015, the CONtrol of Faecal Incontinence Using Distal NeuromodulaTion (CONFIDeNT) trial, a double-blind, multicenter pragmatic, parallel-group RCT of PTNS vs. sham electrical stimulation reported no group difference in the primary outcome of ≥50% reduction in weekly FIE (38% in PTNS arm and 31% in the sham arm; [OR 1.283, 95% CI 0.722 to 2.281; p=0.396]) (61). The PTNS arm reported significantly greater decrease in total weekly FIE compared to sham (difference in means -2.3, 95% CI -4.2 to-0.3; p=0.02), as well as reduction in weekly urgency associated FIEs (-1.5, 95% CI -2.7 to -0.2; p=0.02). The improvement in the patient-centered outcomes was significantly greater in the PTNS arm than in the sham arm. The proportion of patients who were able to reduce their loperamide use was higher in the PTNS arm than in the sham arm (29% vs. 11%); however, this difference was found not to be significant (p=0.06).

The generalizability of the CONFIDeNT trial findings is suspect as the study population was recruited from regional and tertiary colon and rectal surgery programs and likely do not reflect the typical community dwelling women who experience FI. The primary indication for referral to the centers was not reported. Notably, the median (IQR) days per week subjects experienced "mostly liquid stool" at baseline was 3.5 days (1.9-5.3) and 2.9 (1.4-4.5) days at end of treatment; this was despite the study exclusion criterion of chronic bowel conditions such as inflammatory bowel disease leading to chronic uncontrolled diarrhea (62). In personal communications with the primary author, Charles Knowles, a substantial proportion of subjects reported obstructed defecation symptoms (evacuatory difficulty, straining, digitation, sense of blockage).

Percutaneous vs. Transcutaneous Stimulation Technique

In one of the few RCTs of tibial nerve stimulation for FI, PTNS resulted in greater treatment success than tTNS and a tTNS sham (9/11, 82% for PTNS; 5/11, 45% for tTNS; and 1/8, 12.5% for tTNS sham) (30). This lack of therapeutic effect from tTNS was confirmed by Leroi who conducted a tTNS vs. inactive tTNS sham study. The interventions were delivered twice daily at home for 3 months. Neither arm demonstrated a statistically significant difference in the median decrease in FI and urgency episodes or QOL scores (46). A potential explanation for lack of effect of tTNS is that the tibial nerve is too deep (4 cm) at the medial malleolus, a distance too far for effective stimulation from the surface electrode.

Because of the poorer efficacy of the tTNS in these trials, and the absence of data supporting therapeutic efficacy of plantar nerve transcutaneous stimulation, the NOTABLe trial will study the percutaneous tibial nerve stimulation technique.

2.3 Treatment Schedule for Fecal Incontinence

Initial Treatment Schedule for FI

As summarized above (2.2.2), studies of PTNS for FI have offered 12-14 sessions at intervals of weekly, twice weekly, and every other day (Table 1). No data support the superiority of a specific regimen. To date, the widest experience for this treatment modality is with the Stoller method developed for UUI (12 weekly treatments of 30 minutes each). The treatment interval for Part I of the NOTABLe trial will be weekly x 12 treatments of 30 minute duration.

Maintenance Treatment Schedule for FI

In the case of FI, most studies offered a slowly tapering schedule to responders with an option for patient driven "top-up" treatments. Only one study defined "responder" (at least 50% improvement in weekly FIEs) (30). The most common tapering protocol includes one session every 2 weeks, followed by one session every 3 weeks, and one session in a month.

This again likely reflects empiric adoption of results from the STEP trial for UUI (41, 42). How long the residual therapeutic effect on ABL lasts is unclear, as is whether long-term symptom control is influenced by when maintenance treatments are administered (with symptom recurrence or prior to symptom recurrence). Hotouras et al. published "long-term" results of a regimen that included 12 sessions in 3 months, followed by a "wean" of q 2 weeks x 2 followed by recommendations to seek "'top-up" therapy every 6 months or sooner if symptoms returned. The "top-up" regimen was 2 treatments one week apart. Of an initially enrolled cohort of 150 subjects, 115 met criteria for the analysis (minimum of 12 months follow-up after 12 treatments). Symptom improvement from baseline remained significant though it diminished significantly from the end of the 12 weekly treatments. The mean interval for "top-up" treatments was 12 months instead of the recommended 6 months per protocol. Authors concluded that "top-up" treatments should be given more frequently though conceded that optimal frequency was not known (47).

2.4 Validated PTNS Sham

A validated PTNS sham technique has been developed and has been used in RCTs studying PTNS for OAB (36, 38, 52). The sham intervention uses a Streitberger retractable placebo acupuncture needle, as well as surface electrodes and a (TENS) unit (53). In addition to the skin poke (but not puncture), the sham employs stimulation from a TENS unit that simulates a PTNS sensory effect without delivering a therapeutic effect. A validation study of the sham found that only 33% of subjects correctly identified the sham; women were more likely to identify the sham than men (40% v. 27%) (52).

2.5 Known and Potential Risks and Benefits of PTNS and Sham Treatment

Safety Profile and Adverse Events of PTNS

No serious adverse events (SAEs) have been reported in any of the studies of PTNS for either urinary symptoms or FI (54).

Mild or moderate side effects reported in a UUI population included swelling, bruising or slight bleeding at the needle insertion site, worsening of incontinence, headache, hematuria, inability to tolerate stimulation, leg cramps, vasovagal response to needle placement, minor bleeding or a temporary painful/numb feeling at insertion site or under the sole of the foot, and tingling in the leg (36, 38, 39, 43, 55). Long-term follow-up of 115 subjects receiving a minimum of 15 PTNS treatments for FI symptoms found all patients tolerated the treatment well without any SAEs. Slight bleeding at the site of needle insertion occurred in 14 (12%) subjects; 3 (2.6%) subjects experienced transient tingling in the foot that resolved within a few hours (47). Per FDA guidance document, there is a risk of skin irritation and burns beneath the surface electrodes with the use of powered muscle stimulators (63).

The FDA guidance document recommends caution when using a pulse generator (both percutaneously and transcutaneously) in patients with suspected or diagnosed cardiac rhythm abnormalities though there are no published reports of cardiac-related adverse events (AEs). Use of an electrical stimulator is contraindicated for patients with pacemakers or implantable defibrillators. Repeated use of needle electrodes is relatively contraindicated in those prone to excessive bleeding, in the setting of neuropathy that may impact the effect of PTNS or pelvic floor function, and if the skin in the area of use is inflamed, infected, or otherwise compromised. The safety of electrical stimulation has not been established in pregnancy therefore it is contraindicated in those pregnant or planning to become pregnant while using a stimulator (63).

Stimulation sessions will be conducted under direct supervision of a member of the research team to address the caution advised by the FDA with use of an electrical stimulator in patients with suspected or diagnosed heart problems or epilepsy. Staff will be instructed to terminate sessions and to seek urgent physician assessment in response to report of cardiac symptoms (chest pain, shortness of breath), report of feeling poorly or seizure activity.

Safety Profile and Adverse Events of Sham Intervention

There are no reports of AEs from use of the retractable Streitberger sham acupuncture needle. It is designed to not puncture the skin. Per the FDA guidance document for powered muscle stimulators, there is also a risk of minor, transient burning, itching sensation or skin irritation beneath the surface electrode when used with activation of the TENS unit. Like PTNS, use of the TENS unit is contraindicated in subjects with pacemakers or implantable defibrillators, and the surface electrode should not be placed on broken skin or areas of numbness as it may also cause skin irritation due to the inability to feel currents until they are too high (63).

2.6 Adverse Event Collection and Reporting

Definitions

Adverse Events

Adverse events (AEs) can be directly observed by research personnel, reported spontaneously by the research participant, or reported in reply to open-ended questions (ICH).

Adverse event means any untoward medical occurrence associated with a clinical study in humans, whether or not considered study-related. An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g. an abnormal

laboratory finding), symptom, or disease temporally associated with study intervention, and does not imply any judgment about causality.

An *adverse device effect (ADE)* is an event related to the use of an investigation medical device. This category includes any AE resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. Furthermore, it includes any event that is a result of a user error or intentional misuse (21 CFR 812.3).

A device *malfunction* is defined (21 CRF 803.3(n)) as a failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed (21 CRF 801.4).

Serious Adverse Events

Serious is defined as an adverse event or suspected adverse reaction that the sponsor or investigator views as resulting in the following outcomes:

a.) Death

b.) Serious injury

Serious injury (21 CRF Part 803.3(bb)(1)), is an injury or illness that:

i. is life threatening (occurrence places the participant at immediate risk of death; it does not include an AE had it occurred in a more severe form might have caused death);

ii. results in permanent (irreversible impairment or damage) impairment of a body function or permanent damage to a body structure; or

iii. necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

c.) Unanticipated adverse device effect

Unanticipated adverse device effect (UADE) is defined as "any **serious** adverse effect on health or safety or any life-threatening problem or death **caused by, or associated with, a device**, if that effect, problem, or death:

i. was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application); or

ii. any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects" (21 CFR 812.3(s).)(64)(65).

d.) Requires or prolongs inpatient hospitalization

e.) Is a congenital anomaly/birth defect in a fetus and/or newborn

f.) Is another medically important condition – based upon appropriate medical judgement, may jeopardize subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition

Collecting and Reporting Requirements

Reporting requirements will be the same for any device used in the trial, whether it is the treatment/diagnostic device or placebo. All untoward events experienced by study participants will be reported as AEs, beginning at the time of the first stimulation session and ending with the completion of study follow-up or sooner if the participant withdraws or is withdrawn from the study. This includes:

- Adverse Events
  - Any untoward event experienced by the study participant
  - Adverse device effects (defined above)
- Serious Adverse Events
  - Any untoward event experienced by the study participant that meets the *serious* definition above
  - Unanticipated adverse device effects
  - Serious injuries

Serious adverse events will be reported to the sponsor, Medical Safety Monitor, and DSMB. If the SAE is determined to be related and unanticipated (unexpected), the SAE will be reported to the FDA (if under IDE), and all participating sites. The participating sites will be responsible for reporting the SAE to their respective IRBs per their IRB policies.

Pre-existing events or illnesses that do not worsen during a study period are not considered an AE. If a baseline condition subsides and then reappears, it must be recorded as an AE if it is unexpected and related. Furthermore, the failure of an investigational product to provide treatment benefit for fecal incontinence (failure of efficacy) which is captured by other study forms does not constitute an AE.

Determining Relatedness

Per ICH, only an investigator who has medical expertise should make the determination of relatedness. In 2005, the Council for International Organizations of Medical Sciences (CIOMS VI) working group recommended a binary causality assessment of Related or Not Related (Management of Safety Information from Clinical Trials, Report of CIOMS Working

Group VI). For the purposes of this study, the investigator will assign a relationship of related or not related in lieu of assigning degrees of relatedness or unrelatedness such as possibly related, probably related, and definitely related. Events will be categorized as related if they are possibly, probably, or definitely related in the opinion of the investigator. This is an attempt to provide more meaningful data and lessen the burden on site staff.

Determining Expectedness

The AEs listed in the investigator's brochure, protocol, informed consent, and device label will be considered expected (ICH E6 1994.) If, however, the specificity or severity of the event is not consistent with the descriptions those documents, the investigator should consider that event unexpected. The investigator or designee should include an explanation of how the AE diverges from the expected specificity or severity in the comments section of the AE log. For example, if an increase in transaminase is included in the investigator's brochure and hepatic necrosis is seen in study participants, hepatic necrosis should be considered an unexpected AE because the specificity is not consistent with the investigator's brochure. In addition, if the investigator feels that the occurrence of a serious *expected* AE represents a clinically important increase in the expected rate of occurrence, then he/she should record this on the AE log and provide an explanation of the divergence in the comments section (FDA Guidance for Clinical Investigators, Sponsors, and IRBs AE Reporting to IRBs Improving Human Subject Protection, January 2009).

Based on literature reviews, the expected AEs are listed below:

PTNS Intervention	**Sham Intervention**
*Mild to moderate pain in the site of the needle puncture	*Minor transient burning around needle or beneath the surface electrode placement site
Skin irritation and burns at the surface electrode site	Itching sensation around needle or beneath the surface electrode placement site
Swelling of the foot at the site of needle insertion	Bruising around needle or beneath the surface electrode placement site
Bruising at the needle site	Altered sensation in the toe of the foot receiving stimulation
Headache	Bleeding around needle or beneath the surface electrode placement site
Hematuria	Pain around needle or beneath the surface electrode placement site

PTNS Intervention	Sham Intervention
Inability to tolerate stimulation	Skin irritation around needle or beneath the surface electrode placement site
Leg cramps	
Vasovagal response to needle placement	
*Minor bleeding at the needle insertion site	
Temporary painful, numb, or tingling feeling at needle insertion site, the sole of the foot, or the toes on the foot receiving stimulation	
Tingling in the leg	

*If the severity of the AE is greater than what is considered expected, the AE would be recorded as unexpected.

Reporting Timeframes

Each clinical investigator is responsible for reporting SAEs to the IRB at their institution per local IRB requirements, and to the DCC (Data Coordinating Center) within 24 hours of when the clinical site is notified of the event. This time frame is consistent with industry standards (ICH). The DCC will in turn report the SAE to the sponsor, MSM, and DSMB. If the SAE is determined to be related and unanticipated, the DCC will report the SAE to the FDA (if under IDE), and other participating site investigators within 10 working days (812.46(b), 812.150(b)(1). The other participating site investigators will be responsible for reporting those SAEs to their respective IRBs once the summary report is received from the DCC.

The DCC summarizes all SAEs and AEs by randomization group for the DSMB at each DSMB meeting. In addition, the DSMB report contains accrual and dropout rates. The DSMB will summarize their findings to the sponsor with a recommendation to continue or to modify or terminate the trial.

2.7 Protocol Violations

Protocol violations that *affect the safety or rights* of the participants will be reported to the local site's IRB within 5 working days (ICH E3.) (66) Examples of protocol violations:

a. Failure to obtain valid informed consent
b. Not following inclusion/exclusion criteria
c. Loss of laptop computer that contained private and identifiable information about study participants

2.8 Translational Research Component: Blood Collection for Biomarkers

Given the prevalence of accidental bowel leakage, the lack of emphasis on identification and treatment of the condition, and its likely multifactorial etiology, there is interest in identifying and testing biomarkers which may help in developing more effective treatments. The PFDN has a well-established biorepository at the University of Texas – Southwestern in Dallas Texas.

The primary aim of this translational component is to collect blood samples from study participants with accidental bowel leakage to enable future studies to characterize biomarkers and analyze DNA in blood. All NOTABLe participants are extensively phenotyped by history and validated instruments measuring symptom severity.

Whole blood will be collected from participants and processed at the sites to obtain plasma and serum. Whole blood, plasma, and serum will be shipped to and stored at the biorepository for future biomarker and DNA analyses. Specific and detailed research protocols related to analyses of these data will target understanding the association of genetic variation, inflammatory mediators, growth factors, and other biomarkers. These protocols will be encouraged and undergo peer review, either within the PFDN or via separate funding mechanisms.

2.9 Ethical Concerns, Limitations, and Informed Consent

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Pelvic Floor Disorders Network (PFDN) plans to make data generated by PFDN studies available to external researchers in accordance with NIH data sharing policies. Data to be shared include clinical datasets of variables collected via the electronic data capture system, and analysis datasets containing derived variables that would enable a researcher to reproduce published study results. The data will be de-identified to protect study participant confidentiality. PFDN Data Coordinating Center (DCC) statisticians will implement a series of steps to de-identify study datasets in order to minimize the risk of researchers identifying any individuals in the data. This process will be consistent with Health Insurance Portability and Accountability Act (HIPAA), Health and Human Services (HHS) policies for protection of human research subjects, and related requirements for protecting participant confidentiality. The PFDN Steering Committee will have the opportunity to review and approve each request for the Network's data prior to release of the data. This data sharing plan has been included in the informed consent for participants in NOTABLe.

Furthermore, the NIH affords protections to participants of federally funded research projects such as this study, in accordance with subsection 301(d) of the Public Health

Service Act. The study will be issued a Certificate of Confidentiality which prohibits disclosure of any information or biospecimen that contains identifiable, sensitive information about the research participant. Disclosure is only permitted when required by Federal, State, or local laws; necessary for medical treatment and with the consent of the study participant; made for the purposes of other scientific research that is in compliance with applicable Federal regulations governing the protection of human subjects in research; or the research participant consents to a disclosure. This NIH policy has been included in the informed consent for participants in NOTABLe.

2.10 Rationale for Study

The placebo effect of PTNS for the treatment of ABL has not been determined in community dwelling women who experience FI in the absence of chronic bowel diseases, such as inflammatory bowel disease associated with chronic uncontrolled diarrhea, limiting the ability to draw conclusions surrounding the effectiveness of this therapy for ABL. The pragmatic trial design of the CONFIDeNT trial, though oriented toward generalizability, was premature for a pivotal study of an emerging treatment in the absence of knowledge on mechanism of action and in recognition of the heterogeneous pathophysiology of FI. In CONFIDeNT, the subjective inclusion criterion of investigator's judgment that the patient had FI sufficiently severe to warrant intervention limits reproducibility and introduces numerous concerns for recruitment biases. The target population from which subjects were enrolled (regional and tertiary care colon and rectal surgery centers) was a poor match for the relatively low cost, minimal risk treatment of PTNS. When used for the indication of OAB symptoms, PTNS is offered to patients who fail to achieve adequate symptom reduction after behavioral modification, pelvic muscle training (PMT), and pharmaceuticals. Similarly, if proven efficacious, we envision that PTNS would be a secondary intervention for FI after failed medical management (diet, PMT, constipating agents, etc.) and before more costly and invasive sacral nerve stimulation or bowel surgery.

A PTNS proof of effectiveness trial should be conducted on women recruited from primary care and centers of women's health. The severity of symptoms and etiology of bowel dysfunction in this population are likely better matched to this intervention.

The validated PTNS sham affords the opportunity to definitively assess the efficacy and safety of PTNS in the treatment of ABL. Moreover, the durability of treatment effect and optimal schedule of maintenance treatments for sustained symptom control beyond 12 weeks has not been established. Information acquired from NOTABLe is essential for the subsequent design of comparative effectiveness and cost effectiveness studies of this modality to other treatment options such as sacral neuromodulation, anal bulking agents, or radiofrequency therapies in the future.

The PFDN is committed to enhancing knowledge on the comparative effectiveness of therapies for ABL. Its research portfolio includes investigations of primary treatments for ABL (Controlling Anal Incontinence by Performing Anal Exercises with Biofeedback or Loperamide [CAPABLe]) and a concept in development for comparison of central and peripheral neuromodulation techniques in women with refractory ABL. Results of the NOTABLe trial will inform on the design of this latter study.

2.10.1 Rationale for Primary Outcome for this Study

Though most studies of neuromodulation for FI report on changes in bowel diary parameters such as FIEs, fecal urgency, number of bowel movements, and pads used per day, these discrete measures inadequately reflected the patient's perspective of her symptom severity and bother and the reliability of these diaries can be variable. The commonly reported measure of the percent of subjects who achieve 50% reduction in FIEs similarly fails to capture the patient-centered outcome.

Diary data have limitations due to retrospective accrual of data and reliance on subject compliance; additionally, a clinically relevant reduction in incontinent episodes has not been established. The St. Mark's (Vaizey) score was selected as the primary outcome in the PFDN CAPABLe trial after an extensive review of outcome measures for FI (56). Amongst the available instruments, it most closely meets the recommendations for outcome measures as outlined by the NIH State of the Science Consensus Conference on prevention of incontinence in 2008 which recommended that 5 outcome features be reported: frequency, severity, volume, bother to patient, and desire for treatment (57). It has been validated and an improvement of 5 points from baseline is considered clinically important (58). In addition to the aforementioned strengths of the St. Mark's (Vaizey) score, maintaining internal consistency within the PFDN portfolio of studies of ABL will enable future comparisons between study populations.

<u>The primary outcome will be the change from baseline in the severity of FI symptoms as measured by the St. Mark's (Vaizey) score.</u>

St. Mark's (Vaizey) Score

	*Never**	*Rarely**	*Sometimes**	*Weekly**	*Daily**
Incontinence for solid stool	*0*	*1*	*2*	*3*	*4*
Incontinence for liquid stool	*0*	*1*	*2*	*3*	*4*
Incontinence for gas	*0*	*1*	*2*	*3*	*4*
Alteration in lifestyle	*0*	*1*	*2*	*3*	*4*

	No	*Yes*
Need to wear a pad or plug	*0*	*2*
Taking constipating medicines	*0*	*2*
Lack of ability to defer defecation for 15 minutes	*0*	*4*

Never: no episodes in the past four weeks
Rarely: 1 episode in the past four weeks
Sometimes: > 1 episode in the past four weeks but < 1 a week
Weekly: 1 or more episodes a week but < 1 a day
Daily: 1 or more episodes a day
(Scoring: add points from each row; minimum score = 0 = perfect continence; maximum score = 24 = totally incontinent)

A recognized shortcoming of selecting the St. Mark's (Vaizey) questionnaire is that it is reported in only one manuscript on PTNS for FI. George et al. reported a mean St. Mark's (Vaizey) score improvement from 19 (3) at baseline to 12.7 (2.1) after 12 sessions (Δ 6.3 points) in 11 women randomized to active PTNS (30). To address this limitation, we have selected several secondary outcome measures including the bowel diary and the Rockwood FIQL to enable us to draw comparisons with outcomes reported in the literature.

Rational for Extending Study Follow-up 6 months After Final PTNS Treatment (see appendix 1)

The long-term need for PTNS maintenance treatment for FI in a "responder" population has not been determined, nor has the interval of time to symptom relapse. This information has been somewhat characterized in the OAB population. Van der Pal et al, reported return of urinary symptoms after a relatively short treatment pause (6 weeks) in a group of PTNS "responders" who had received treatments for a mean of 13 (1-36) months (van der Pal, 2006). In the *Sustained Therapeutic Effects of Percutaneous Tibial Nerve Stimulation (STEP) trial,* 45 subjects with OAB maintained their symptom control with a mean of 1.3(0.7) and a median of 1.2 (0.3-4.3) treatments per month between 6 and 24 months after initiating PTNS (Peters, 2013). Because the goal was maintenance of symptom control, the intervals likely reflect the time to early recurrence of symptoms.

The PFDN has an opportunity to determine the duration of symptom control in women who have experienced ≥6 months of PTNS for ABL using the established study specific ePRO platform in REDCap.

Collection of a limited subset of ePRO measures after final PTNS session will enable us to determine:

1. The percent of subjects who report loss of symptom control at 6, 10, 14, 18, 22 and 26 weeks after their last PTNS session. Loss of symptom control will be characterized with several outcome measures including:
    a. % of subjects who no longer meet the definition of responder (4-point reduction from baseline St. Mark's score)
    b. % of subjects with PGSC score of ≤2, ≤3
        i. My current treatment is giving me adequate control of my ABL (1-5: strongly disagree – Strongly Agree)
    c. change over time in PGI-I
        i. What best describes how your ABL is now, compared to how it was before you began study treatment? (1-7: very much better to very much worse)
2. The severity of symptom recurrence over the 6-month period after the final PTNS session:
    a. Change over time in St. Mark's Score, and other condition specific QoL measures (FIQL)
3. The impact of discontinuing PTNS on adaptive behaviors for ABL (comparison to Visit 26)

2.10.2 Rationale for the Exclusion Criteria

Our study population will be restricted to women expected to respond to neuromodulation. Prior experience with PTNS therapy may lead to unmasking of subjects. All recognized contraindications to PTNS or TENS will be considered exclusions.

Rationale for mandating bowel diary collection through the PFDN Bowel Diary Phone App:

Eligible subjects who do not allow downloading of the PFDN Bowel Diary App on their smartphones will be excluded from the study. The protocol committee believes that the quantity and quality of the data recorded by phone app will be different from that of a paper diary. Additionally, though the study has budgeted to lend a smartphone to those who do not own one, it will not provide "second" phones for the sole purpose of documenting bowel events. We are concerned that the participant is less likely to carry two phones with her throughout the study. As such, she will likely record in a manner different from those participants who carry a single phone.

Subjects will be free of the following conditions by self-report (or urine pregnancy test):

a. CNS compromise: Though the mechanism of action of PTNS has not been determined, it is believed to modulate neural pathways through neural circuitry in the central nervous system. Women with clinically significant peripheral neuropathy or CNS disorders known to impact anal continence (i.e., stroke, spinal cord injury), as well as those who are cognitively impaired will be excluded.
b. History of uncontrolled chronic diarrhea: There is no data to support the efficacy of PTNS for the treatment of chronic diarrhea (usual or most common stool type over the preceding 3 months of 7 on the Bristol Stool Form Scale) due to various etiologies including infection, malabsorption, dietary intolerance, autoimmune, or inflammatory bowel disease.
c. History of severe constipation (usual or most common stool type over the preceding 3 months) reported as 1 on the Bristol Stool Form Scale as chronic constipation has been associated with FI and paradoxical or overflow diarrhea (encopresis) which are beyond the scope of the intended study population.
d. History of anorectal malformations (congenital, acquired, inclusive of full thickness rectal prolapse or cloaca): Congenital malformations of the anus and rectum are uncommon and are often addressed with surgery in infancy. The etiology of ABL in this population is not representative of the general population.
e. History of bowel resection for any indication (excluding polyp removal at colonoscopy): Subjects are expected to have stable colonic function during the trial period. Therefore, women with a history of bowel resection surgery regardless of indication and anal bulking agent injection or radiofrequency sclerosing procedures to the rectum within 6 months will be ineligible as both recovery and/or dissipating effectiveness from these interventions may influence the stability ABL symptoms.
f. Pregnant or planning to become pregnant during the course of the study (1 year): The risks of PTNS to a fetus are unknown; therefore, all sexually active participants capable of becoming pregnant will be required to use reliable contraception (sterilization, hormonal contraception, barrier methods, IUD are acceptable). For participants of child-bearing potential, a urine pregnancy test will be performed and must be negative at Visit 2 prior to the randomization visit.

2.10.3 Rationale for the Inclusion Criteria

PTNS is an experimental treatment modality for FI. Superior effectiveness over a validated sham has not been established; therefore, it is not currently considered a first line treatment for ABL. **Our study population will be limited to subjects with refractory ABL symptoms who have failed to achieve satisfactory symptom control from 2 first-line treatments for ABL: supervised pelvic muscle training (PMT) and constipating medication.** This failure of response may be due to lack of response to PMT or intolerance, unwillingness or contraindication to use of constipating medications. In this study, supervised PMT must

be conducted by a health provider experienced with treating ABL (minimum 2 treatment sessions).

Study Eligibility:

Eligible participants will report a minimum score of 12 on the St. Mark's (Vaizey) Questionnaire. This eligibility threshold will provide a study population with severity of symptoms that have the potential to achieve a response within our stated effect size of 4.0. George et al reported baseline St. Mark's (Vaizey) scores of 16-19 (SD 3-3.9) in their study population that met inclusion criteria of ≥ 2 FIEs per week.

Rationale for Run-In Phase:

The unintended interventional effect of journaling bladder and bowel function in a diary is well established in UI and FI studies. Significant symptom improvement in the "sham" arms of RCTs that collected diary data to document bowel movements and FI range from (12.5% to 31%) (30, 61). *In the PFDN CAPABLe study, 32 women assigned to receive placebo drug and the NIDDK educational pamphlet had baseline St. Mark's scores of 12 or higher. Of the 28 with 12 week assessments, 16 (57%) had St. Mark's scores lower than 12*. The aim of the 4-week Run-In Phase is to identify and exclude enrolled women who report symptom improvement such that their symptoms are below the eligibility threshold of 12 points on the St. Mark's scale after being given verbal and written information on causes and treatments for FI (https://www.niddk.nih.gov/health-information/digestive-diseases/bowel-control-problems-fecal-incontinence) and after completing two 7-day bowel diaries in Weeks 1 and 4. The rationale for a 28-day duration of the Run-In Phase is based upon the stem of the St. Mark's scale which is "In the past 4 weeks, ...". The protocol committee selected Weeks 1 and 4 for diary completion in that 4-week window to capture any short-term and long-term impact on behavior as a result of journaling. The Run-In Phase will also identify enrolled subjects who are unable to or are unwilling to complete a bowel diary. Subjects who do not provide data from ≥ 10 of 14 days and with minimum of 3 consecutive days per week will be considered ineligible for randomization.

Rationale for Permitting Continuation of Baseline Compensation Strategies for ABL:

Study subjects will be permitted to continue compensatory measures for ABL that they declare at baseline. They will NOT be permitted to increase their constipating Rx but will be permitted to reduce or discontinue them. After the Run-In Phase, they would be advised not to alter other interventions such as supplementary fiber, daily Kegel exercises, and bowel regimen routines. The primary and secondary outcome measures will record use of these strategies throughout the trial. This decision is based upon the expectation that PTNS will be one component of a multimodal management strategy for FI. It is expected that randomization will equally assign users of supplementary interventions. The eligibility criteria will select a significantly symptomatic study population, despite their compensatory regimen. Investigators anticipate that eligible subjects will be reluctant to stop constipating agents if they perceive benefit and are tolerated. Moreover, due to the bothersome nature

of ABL, subjects may choose not to report continued use of constipating medication. This would compromise the interpretability of the results. Randomization will balance the percent of women who use constipating agents in each group. Behavioral interventions such as dietary modification (high fiber diet or fiber supplements), scheduled bowel movements (BMs), and pelvic muscle strengthening cannot be readily "washed out".

Rationale for Continuing Stimulation Sessions Despite Absence of Reported Sensory or Motor Response

In clinical practice, there are instances when multiple attempts at needle repositioning or placement does not lead to an expected sensory or motor effect on the foot. The frequency and clinical impact of these "failed" attempts have not been described. In this study, participants who do not report the expected sensory or motor effects of PTNS will not be excluded from receiving their assigned stimulation sessions. Their study outcomes will be analyzed in an ITT analysis as well as in subpopulation analyses.

2.11 Significance and Innovation

Because PTNS is relatively inexpensive, well-tolerated, and minimally invasive, it has attracted support as a treatment option for debilitating symptoms of ABL despite the absence of established effectiveness. There is an urgent need to compare its effectiveness to a validated sham before widespread adoption. Additionally, this study provides an opportunity to contribute data supporting an optimal symptom suppression schedule of treatments with a 1-year endpoint.

The PFDN is creating and assessing a smartphone bowel diary app for this protocol. This is an innovative tool for the fecal incontinence research community. The app is designed to address the established limitations of paper diaries by date and time stamping entries thus enhancing the veracity of data and eliminating the potential for back-filling and front-filling of forms. Additionally, we will send push notifications as reminders twice daily. A supplementary study will assess the performance, acceptability, test-retest reliability and internal consistency of the PFDN phone app bowel diary.

The PFDN has committed to contributing to an evidence-based approach to treatment of ABL. In addition to having completed a protocol comparing primary treatments for ABL (*CAPABLe*), it is developing a comparative effectiveness trial of two second-line treatments for Refractory Fecal IncoNtinencE (*ReFINE)* trial. The *ReFINE* RCT will compare the effectiveness of two neuromodulation techniques: SNS (Interstim) and PTNS in women. If PTNS is shown to be effective compared to sham, then knowing the sham effect of PTNS for treatment of ABL and generating data on the expected durability of effect in a maintenance treatment schedule will facilitate development of the *ReFINE* study. Though use of the

validated PTNS sham has been done before for OAB, this is the first study to contribute insight into use of PTNS for long-term control of ABL.

3 STUDY OBJECTIVES AND PURPOSE

The overarching goal of this randomized clinical trial is to determine if PTNS is more effective than sham PTNS for the treatment of FI in women after 12 weeks of treatment and 1 year after initiating treatment.

3.1 Prescreening

Waivers of informed consent and HIPAA authorization will be sought for *recruitment purposes* only. Such waivers will allow study staff to identify potential candidates for this study using the methods described below. The minimum amount of protected health information (PHI) necessary to determine possible eligibility will be accessed. PHI will be obtained by authorized members of the study team and will not be disclosed. Any list of subjects generated under the recruitment methods listed below will be kept on a secure, password-protected study drive with access limited to the study team, and will not be removed from the individual site premises.

Prescreening may occur via phone or in-person in clinic. The potential participant will be asked or administered the following items:

a. Willingness and ability to attend weekly intervention sessions for 12 weeks
b. Willingness to have a bowel diary phone app downloaded to her personal smartphone
c. St. Mark's questionnaire
d. Bristol Stool questionnaire

If the potential participant does not meet the prescreening assessment, she will be thanked for her time and her responses will not be retained. If the potential participant meets the prescreening assessment, she will be invited to learn more about the study. If the participant completed the St. Mark's Questionnaire and Bristol Stool Questionnaire prescreening via *phone*, then these assessments must be repeated via REDCap after signing consent. If the person met eligibility during the phone pre-screen and subsequently did not meet eligibility with the repeat of those measures in REDCap, then the participant cannot be enrolled in the study. If the participant completed the St. Mark's Questionnaire and Bristol Stool Questionnaire *in-person on paper*, the participant's answers from the paper can be retained and transcribed into REDCap after signing consent. The St. Mark's score will be calculated by the data management system.

3.2 Study Design

This is a two-part trial with a Run-In Phase prior to randomization.

The purpose of the Run-In Phase is to identify and exclude from randomization women whose FI symptoms improve to the point that they are below the eligibility threshold of 12 points on the St. Mark's scale after receiving education on FI and completing two 7-day bowel diaries. The Run-In Phase is a 4-week period during which participants will complete bowel diaries (either on paper or by phone app) in Weeks 1 and 4. Women who have a St. Mark's score ≥ 12 after the Run-In will move on to Part I of the study.

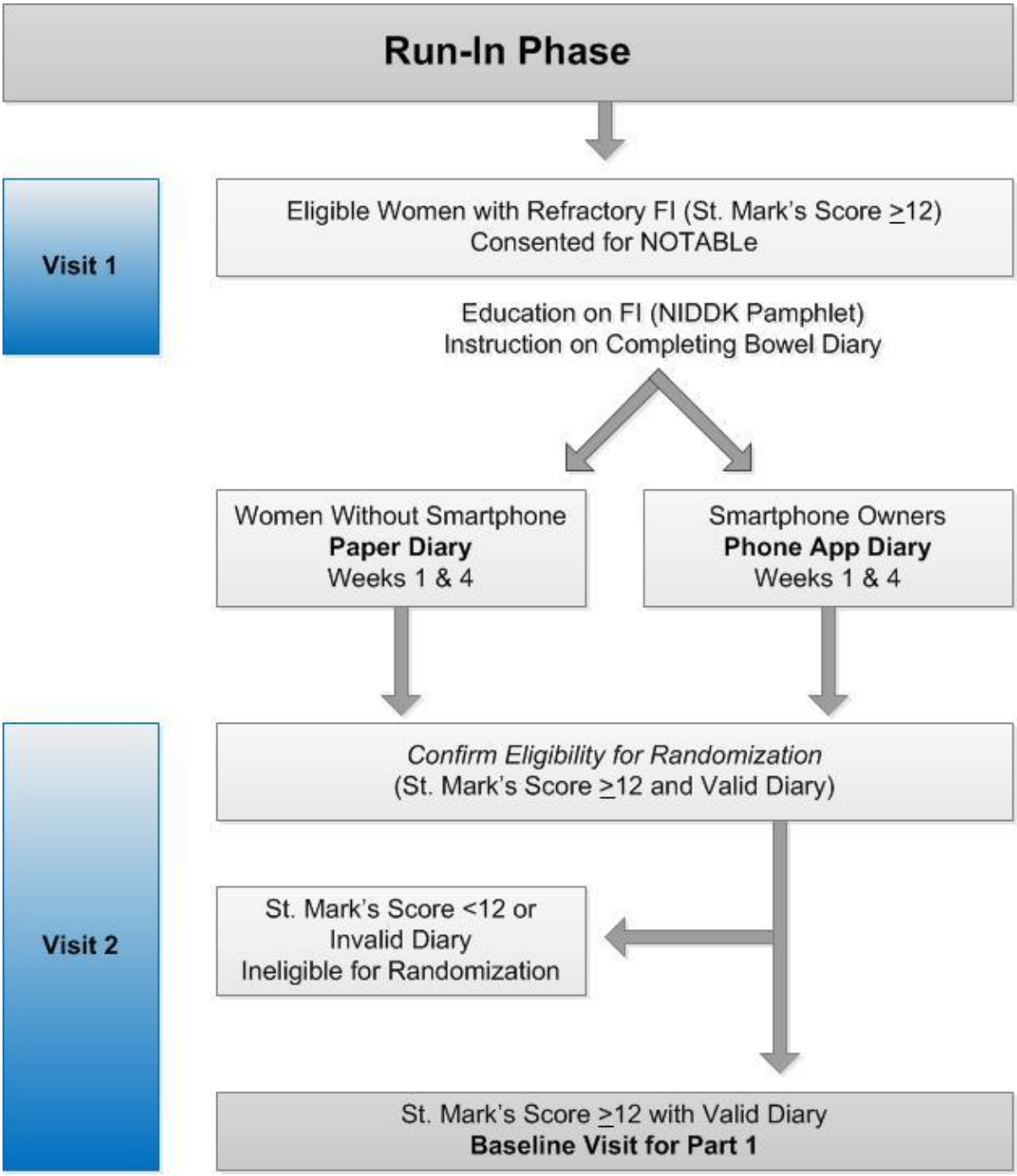
Part I is a randomized, single-masked controlled trial comparing the effectiveness of PTNS to a validated sham in women with refractory FI using a 2:1 assignment. Its purpose is to evaluate the impact of PTNS above sham for treatment of ABL symptoms. The primary outcome, change from baseline in the St. Mark's (Vaizey) score, will be measured over time (after 12 weeks of stimulation). A change of 4 points will be considered clinically significant. Randomization will be by randomly permuted blocks, stratified by site and by type of diary completed in the Run-In Phase (paper or phone app). The analysis of Part I outcomes will occur when the Part I sample size is reached and those participants have completed 12 weeks of stimulation.

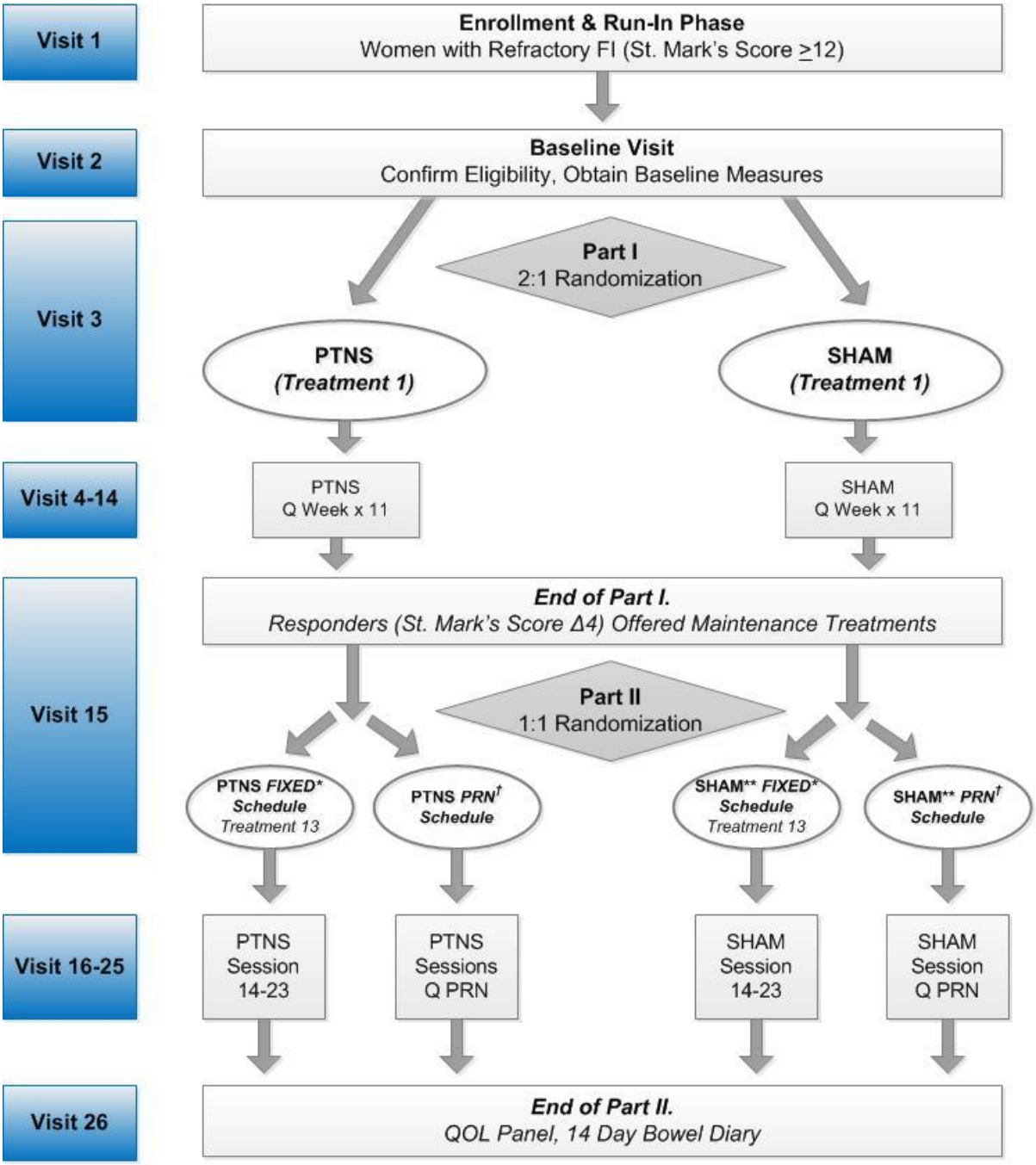
Part II is a trial of two maintenance strategies amongst participants who are treatment responders, where treatment response is defined as an improvement from baseline in St. Mark's score of ≥ 4 points after 12 weeks of stimulation. Eligible participants will be randomized using a 1:1 assignment to either a fixed schedule of treatments or a patient symptom driven (PRN) treatment schedule. The purpose of Part II is to evaluate:

a. The percent of women assigned to each treatment schedule who maintain symptom control (defined as a 4-point reduction from baseline in the St. Mark's score) at one year from start of treatment.
b. Whether the fixed and the PRN schedule of treatments in Part II are feasible to implement, and are associated with different costs and/or participant satisfaction

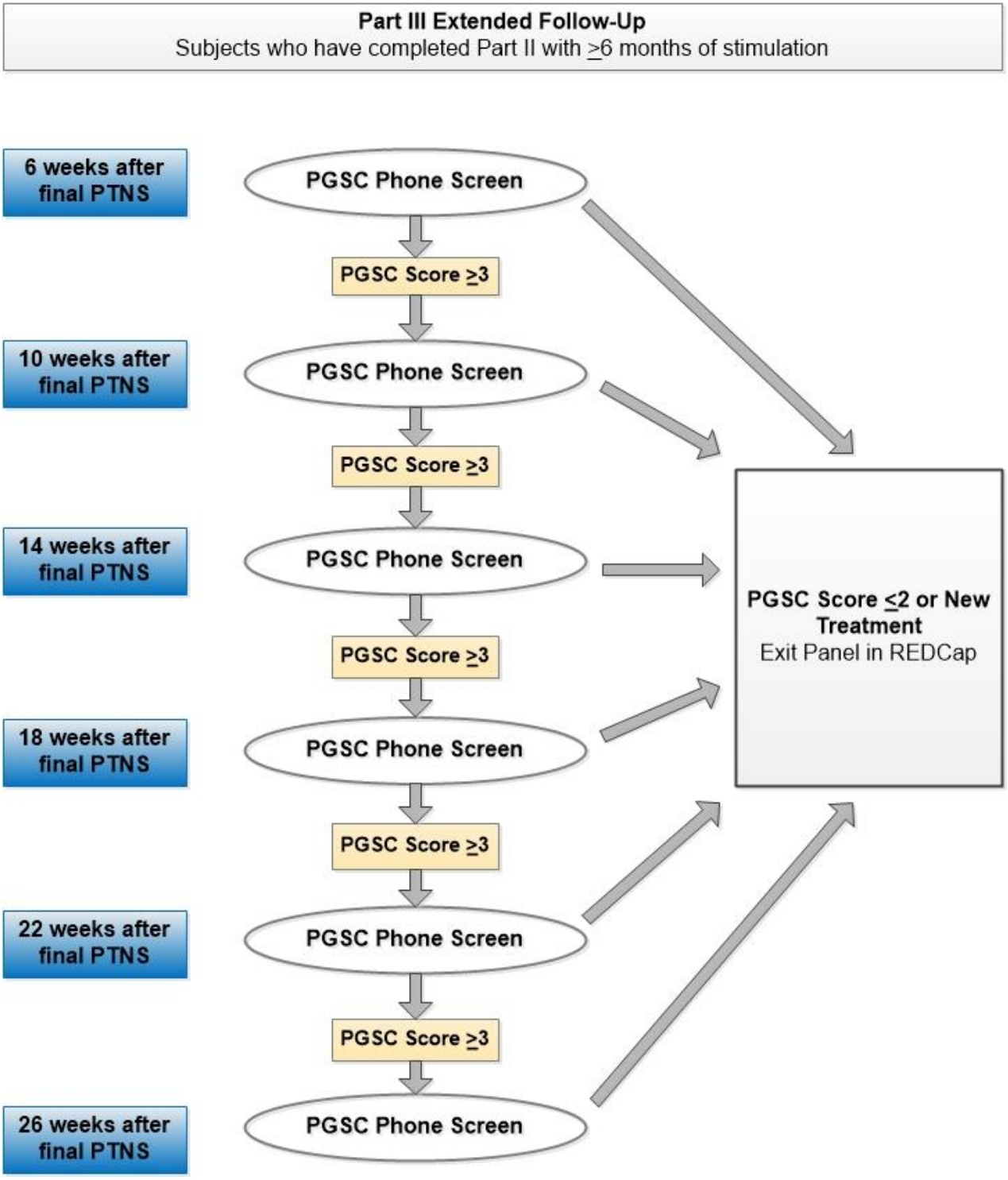
Randomization to Part II maintenance strategy will be by randomly permuted blocks. In order to maintain masking prior to the analysis of Part I data, Part I participants who respond to either PTNS or sham treatment will be eligible to begin Part II. Participants responding to sham in Part I will continue to receive sham treatments in Part II. Part II randomization will not be stratified by site but will be stratified by PTNS/sham group to assure that randomization of the PTNS group is balanced between the two maintenance groups. Only women receiving PTNS treatment will be included in Part II analyses.

The extension will follow women for up to an additional 6-months after the final PTNS session. In the absence of published data to indicate the duration of PTNS effect, the Protocol Committee proposes up to a 6-month observation period at 4-week intervals after visit 26: 6 weeks, 10 weeks, 14 weeks, 18 weeks, 22 weeks and 26 weeks after final PTNS session. Currently, the PRN group provides a PGSC score to the coordinators by phone in lieu of attending study visits. If their score does not trigger an in-person treatment visit, the subjects are emailed a secure online link to the NOTABLe REDCap database where they enter responses to the ePRO panel. This ePRO mechanism will be used in the follow-up phase to collect the abbreviated panel of outcome measures. All NOTABLe subjects randomized to Part II and with total of ≥6 months of PTNS treatment (≥6 months from randomization into Part I) will be eligible for inclusion. Any NOTABLe subjects with total of <6 months of PTNS sessions (those exiting Part II early) will be excluded from the 6-month extended follow-up. Subjects will be withdrawn from follow-up when they report PGSC of ≤2 or initiate NEW treatment for ABL that is prescribed by a health provider such as pessary (for ABL), Diphenoxylate/Atropine (Lomotil), sacral neuromodulation, or anal/colonic surgery. Resumption of baseline compensatory strategies such as Imodium, fiber supplements, pelvic muscle strengthening exercises are not considered NEW treatment for ABL during this observation period. If Part I analysis does not demonstrate that PTNS is superior to sham for the treatment of FI, then the NOTABLe study will be halted, and participants involved in Part II will be notified that the study is ending and maintenance treatments will not continue. If the analysis of Part I data supports the use of PTNS for FI, treatment of sham participants in Part II will be discontinued and additional participants will be recruited in order to reach the Part II sample size. These participants will complete the Run-In Phase and, if eligible after the Run-In Phase, they will receive PTNS treatments as specified in Part I. Women who are PTNS responders after 12 weeks of stimulation will be eligible for randomization to Part II. Women who previously completed Part I of the study in the sham group may be re-enrolled in this part of the study if they meet eligibility criteria. These women will be randomized in the sham group stratum of Part II, but their data will be included in Part II analysis as PTNS responders. A figure illustrating the study design inclusive of the Run-In Phase is depicted on the next two pages.


Run-In Phase
Visit 1
Eligible Women with Refractory FI (St. Mark's Score ≥12)
Consented for NOTABLe
Education on FI (NIDDK Pamphlet)
Instruction on Completing Bowel Diary
Women Without Smartphone
Paper Diary
Weeks 1 & 4
Smartphone Owners
Phone App Diary
Weeks 1 & 4
Visit 2
Confirm Eligibility for Randomization
(St. Mark's Score ≥12 and Valid Diary)
St. Mark's Score <12 or
Invalid Diary
Ineligible for Randomization
St. Mark's Score ≥12 with Valid Diary
Baseline Visit for Part 1



* FIXED Schedule: Q 14d x 2; Q 21d x2; Q 28d x 7 (11 sessions in Phase II)
† PRN Schedule projected to be Q 1.1-1.3 per month (up to 12 sessions in Phase II)
**Sham sessions will be discontinued if PTNS demonstrates superiority to Sham



Study Endpoints

Primary Endpoint:

a. Part I. Two weeks after completion of 12 weekly treatment sessions
b. Part II. 1 year from first treatment

A ≥ 4-point reduction from baseline in each subject's St. Mark's (Vaizey) score will be considered clinically significant and will be used to define treatment response for entry into Part II.

3.3 Outcome Measures

Primary Outcome Measures:

a. Part I. Change from baseline in St. Mark's (Vaizey) score after 12 weeks of stimulation
b. Part II. Percent of responders at one year

Secondary Outcome Measures were selected with a priority to minimize redundancy within the instruments and subject burden. Additionally, the selected measures will enable comparison of study findings to other published studies of PTNS for FI. They include measures of symptom severity, QOL, common co-existent bowel and bladder symptoms, global impression of improvement, and behavior adaptations for pelvic floor disorders.

Secondary/ Exploratory Aims	Measure	Outcome
PTNS and sham group differences through 13 weeks in		
Self-reported Symptom Severity, Bother, and Functional Outcomes	14-day bowel diary	Change from baseline in: episodes of FI, fecal urgency, defecation
	ABLE	Change from baseline in score
Condition-specific QOL	FIQL, Modified Manchester Questionnaire with FSFI	Change from baseline in scores
Other Bowel, Bladder, and Prolapse Symptoms	PFDI-20, PFIQ-7, PAC-SYM	Change from baseline in scores
Sexual Function	PISQ-IR	Change from baseline in score
Adaptive Behaviors	Fecal Incontinence Adaptation Index	Change from baseline in score
Use of Supplementary Treatments for ABL	St. Mark's (Vaizey) question 3b	Self-reported use of constipating Rx over time
Patient Global Impression of Improvement (PGI-I) and Patient Global Symptom Control (PGSC)	PGI-I modified for bowel function, PGSC Rating (modified for ABL)	PGI-I and PGSC scores over time
General Health Survey	SF-12	Change from baseline
Safety/Adverse Events	SAE/AE reports	AEs and SAEs reported
Other Secondary/Exploratory Measures		
PTNS Treatment Adherence and Feasibility of Treatment Schedule	Session attendance. Session completion (30 min stimulation)	% who attend 10 of 12 scheduled PTNS treatments in Part I and 9 of 11 sessions in Part II (Fixed schedule)

Impact of absence of sensory or motor response to PTNS stimulation on self-reported Symptom Severity, Bother, and Functional Outcomes	Stimulation response [yes / no]	Change from baseline in primary and secondary outcome scores
Validity of the Sham (Part I)	Query on treatment assignment	% correctly identifying their treatment assignment
Effectiveness of PTNS Maintenance Schedules	St. Mark's (Vaizey) score and other functional outcome measures in Part I	Change from baseline in St. Mark's (Vaizey) scores through 1 year; changes in other functional outcome measures through 1 year
Rate of UTIs treated with antibiotics	Medical Follow-Up Form	Difference in rate between the PTNS and Sham Groups
Cost of PTNS Maintenance Schedules	Treatment Form	Mean # of PTNS treatments/year in Part II Mean Treatment interval for those receiving PTNS in Part II

The Rockwood FIQL has been selected as the principal condition QOL outcome measure in this study because it is most frequently reported in the literature on neuromodulation for FI. It was graded "B" (Recommended) by the International Consultation on Incontinence (ICI) in their assessment of QOL measures for anal incontinence (59). A Minimally Important Difference (MID) for the FIQL has been published by Bols as 1.1-1.2 using two anchor-based methods (60). The MID was calculated on a population that was similar to NOTABLe, adults with refractory FI for > 6 months, reporting a baseline St. Mark's score of > 12. We will also administer the Modified Manchester/FSFI at baseline (Visit 2), and at Visits 11 and 15 in Part I; and then at Visit 19 (6 months) and Visit 26 (12 months) from the first treatment. Change from baseline in this measure will be compared to data from the FIQL and the PFDN-developed ABLE measure. The Modified Manchester/FSFI data will also be used in the PFDN ABLE validation study which is being conducted using data from CAPABLe.

Bowel Diary: The bowel diary data will be entered on a phone app during Weeks 1 and 4 of the Run-In Phase (for participants who own smartphones), during the 2 weeks between the baseline visit and randomization, for two weeks starting at the time of the 6^{th} and 12^{th} stimulation sessions in Part I, at 6 and 9 months after starting treatment for participants in Part II, and at the end of Part II. The phone app will optimize the veracity and completeness of the diary data through a date and time stamp, as well as notifications that will be sent to the phone twice each day reminding participants to record the bowel events of the day. The data elements collected by the PFDN Phone App Bowel Diary will focus on one of three experiences:

- Bowel movement (BM) event
- Leakage event distinct from a BM
- Bowel movement and Leak

This study will use the International Continence Society (ICS) definition of fecal urgency: sudden, compelling desire to defecate that is difficult to defer. Each "event" will be qualified by the presence of urgency.

A BM event may be associated with:

a. Fecal urgency but no stool leakage (fecal urgency);
b. Urgency and stool leakage (fecal urgency incontinence (FUI)); or
c. Discovery of stool leakage without warning or urgency (passive leakage).

In the PFDN phone app bowel diary, BMs with and without leak will be collected separately.

A bowel leakage event may be recorded in the absence of urgency (passive leakage), or associated with urgency (FUI). Events that are qualified by urgency (leakage and BM) are reflective of the ability to delay defecation and/or the availability of an accessible toilet.

	No Urgency, No Leak		Urgency, No Leak	
BM	BM		Fecal Urgency	
		No Urgency, Leak		Urgency, Leak
BM with LEAK		Passive Incontinence		FUI
	No Urgency		Urgency	
LEAK	Passive Incontinence		FUI	

The protocol committee elected not to include daily recording of pad use and constipating medications on the phone app bowel diary to simplify event recording. Information about medication and pad use will be ascertained in our primary outcome, the St. Mark's questionnaire.

Push Notification: A "push notification" will be sent to participants at prespecified times. Notifications will ask participants to confirm the data they have reported for the preceding interval (since last push notification). They can edit or "add" additional events using the standard icons.

Participants will be instructed to "record as you go" throughout the day. Each data entry will be date/time stamped enabling investigators to identify events that are "recorded live" vs. data recorded in response to receiving the push notification reminder. To limit recall bias, participants will be instructed only to enter data retrospectively since the last push notification (approximately 12 hours).

Schedule of Measures:

In general, most QOL measures will be administered at baseline, Visit 11, and Visit 15 in Part I and then Visit 19 and Visit 26 in Part II. With the addition of the 6-month extended follow-up, a limited set of QOL measures (PGSC, St. Mark's Score, PGI-I, FIQL, and Adaptation Index) will be administered between the last Part II PTNS treatment session and 26 weeks post the last PTNS treatment session. An email with a secure link to the questionnaires will be sent to participants in the PRN group who do not schedule treatments at those time points of Part II described above. If a participant is unable to attend a study visit during those time points in Parts I and II, an email with a secure link to the questionnaires can be given to the participant so that the participant can complete the questionnaires within the study visit window or as close to the window as possible.

The Patient Global Symptom Control (PGSC) Rating (modified for ABL) is a single question and will be administered at each visit beginning with Visit 2 (end of "Run-In Phase") and continuing through Part II. It will be administered between visits by phone in Part II to the PRN group. The frequency of this minimal burden question serves two purposes: to capture a change in symptoms that may be subjectively appreciated between administrations of the monthly (Part I) and every 3 months (Part II) panel of QOL measures and to identify when subjects in the PRN group of Part II should be offered an appointment for treatment. With the addition of the 6-month extended follow-up, the PGSC will be administered by phone at 6, 10, 14, 18, 22, and 26 weeks after the last Part II PTNS treatment session.

Estimated Time to Complete Questionnaires: The estimated time for participants to complete the PGSC at every visit in Part I and every visit or scheduled phone encounter for the PRN group in Part II is <5 minutes. The estimated time to complete the full panel of QOL measures in Part I (at baseline and Visit 15) and in Part II (at 12 months from first stimulation session) is 45 minutes. The estimated time to complete the small panel of QOL measures in Part I (at Visit 7 and Visit 11) and in Part II (at 6 months and 9 months) is between 5 and 30 minutes. Participants who exit Part I or Part II prematurely (withdraw or are withdrawn) will be administered the full panel of questionnaires (i.e., same battery as Visit 15 or Visit 26 at the time they exit the study. The estimated time to complete the limited ePRO panel during the 6-month extended follow-up is 15 minutes (reduced from 45 minutes).

3.4 Timeline of Visits/Calls and Schedule of Measures for Run-In and Part I. (PTNS vs. Sham)

Study Visit Number	**Visit 1**		**Phone Call**		**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14**	**Visit 15**
Study Visit Title	Start of Run-In Phase (4 weeks total)	Run-In Diary Week 1	Phone Call Week 3	Run-In Diary Week 4	Baseline	TX 1 (2 weeks after baseline)	TX 2	TX 3	TX 4	TX 5	TX 6	TX 7	TX 8	TX 9	TX 10	TX 11	TX 12	Closure≠
Time in relation to **start of treatment**	-6 weeks	-6 weeks	-4 weeks	-3 weeks	-2 weeks	0	7d	14d	21d	28d	35d	42d	49d	56d	63d	70d	77d	91d
Window	None	None	None	None	2 weeks	1 week	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d
Consent	**X**																	
Assess Eligibility	**X**																	
Pelvic/Rectal Exam	**X**																	
NIDDK Pamphlet	**X**																	
Bowel Diary Instruction	**X**				**X***													
"Run-In" Bowel Diary Recording Begins		**X**		**X**														
Reminder Phone Call to Start Paper Bowel Diary			**X**															
Push Notification to Start Phone Bowel Diary			**X**															
Paper Bowel Diary Collection, Review for Validity & Payment					**X**													
Assess Eligibility to Begin Part I					**X****													
Pregnancy Test					**X*****													
Part I Randomization						**X**												
Blood Specimen Collection						**X******												
Part I Bowel Diary Begins					**X**						**X**						**X**	
Review Phone Diary Data for Validity & Participant Payment					**X**	**X**							**X**					**X**
PTNS v. Sham Session						**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Safety Stimulation Checklist						**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
AE/SAE						**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

Study Visit Number	**Visit 1**		**Phone Call**		**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11**	**Visit 12**	**Visit 13**	**Visit 14**	**Visit 15**
Study Visit Title	Start of Run-In Phase (4 weeks total)	Run-In Diary Week 1	Phone Call Week 3	Run-In Diary Week 4	Baseline	TX 1 (2 weeks after baseline)	TX 2	TX 3	TX 4	TX 5	TX 6	TX 7	TX 8	TX 9	TX 10	TX 11	TX 12	Closure≠
Time in relation to **start of treatment**	-6 weeks	-6 weeks	-4 weeks	-3 weeks	-2 weeks	0	7d	14d	21d	28d	35d	42d	49d	56d	63d	70d	77d	91d
Window	None	None	None	None	2 weeks	1 week	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d
Unmasking (Deviation Recorded)						**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Query of Treatment Assignment																		**X**
CRFs/Questionnaires																		
Demographics	**X**																	
Dietary Screener	**X**																	
Physical Exam	**X**																	
PMHx (Update)	**X**				**X**					**X**				**X**				**X**
St. Mark's Score	**X**				**X**					**X**				**X**				**X**
PAC-SYM					**X**													**X**
PISQ-IR					**X**													**X**
Adaptation Index					**X**													**X**
SF-12					**X**													**X**
FIQL					**X**									**X**				**X**
ABLE					**X**									**X**				**X**
PFDI-20					**X**									**X**				**X**
PFIQ-7					**X**									**X**				**X**
Modified Manchester/FSFI					**X**									**X**				**X**
PGSC					**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
PGI-I (FI)										**X**				**X**				**X**

≠Participants who exit Part I prematurely will be administered the same panel of questionnaires completed at Visit 15 at the time they exit the study.

*Subjects who did not use the phone app diary in the Run-In phase, will be provided a smartphone and instructed on the Bowel Diary phone app.

** In Part I, a valid diary is defined as 3 consecutive days completed and 10/14 days completed in the 14-day diary.

***As applicable

****Blood collection will be done at Visit 3 for participants who have not been randomized. Blood collection will be done at a time convenient for participants who have already been randomized.

3.5 Timeline of Visits/Calls and Schedule of Measures for Part II. (Fixed vs. Flexible PTNS sessions)

Study Visit Number	**Visit 15**	**Visit 16**	**Visit 17**	**Visit 18**	**Visit 19**	**Visit 20**	**Visit 21**	**Visit 22**	**Visit 23**	**Visit 24**	**Visit 25**	**Visit 26**
Study Visit Title	Part II Randomization Fixed TX 13	Fixed TX 14	Fixed TX 15	Fixed TX 16	Fixed TX 17	Fixed TX 18	Fixed TX 19	Fixed TX 20	Fixed TX 21	Fixed TX 22	Fixed TX 23	Part II Closure*
Time in relation to **first treatment in Part II**	Part II Start Time 0	+2 weeks	+5 weeks	+8 weeks	+12 weeks (6 mo)	+16 weeks	20 weeks	24 weeks (9 mo)	28 weeks	32 weeks	36 weeks	38 weeks (12 mo)
Window	±3d	±3d	±3d	±3d	±7d	±7d	±7d	±7d	±7d	±7d	±7d	±7d
Assess Eligibility for Part II ≠	**X**											
Part II Randomization ≠	**X**											
Bowel Diary Recording Begins					**X**			**X**			**X**	
Review Diary Data for Validity						**X**			**X**			**X**
FIXED Schedule GROUP												
PTNS Treatment	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Safety Stimulation Checklist	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
AE/SAE	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Unmasking (Deviation Recorded)	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
CRFs/Questionnaires												
PAC-SYM	**X**											**X**
PISQ-IR	**X**											**X**
Adaptation Index	**X**											**X**
SF-12	**X**											**X**
FIQL	**X**				**X**							**X**
ABLE	**X**				**X**							**X**
PFDI-20	**X**				**X**							**X**
PFIQ-7	**X**				**X**							**X**
Modified Manchester/FSFI	**X**				**X**							**X**
PMHx (Update)	**X**				**X**			**X**				**X**

Study Visit Number	**Visit 15**	**Visit 16**	**Visit 17**	**Visit 18**	**Visit 19**	**Visit 20**	**Visit 21**	**Visit 22**	**Visit 23**	**Visit 24**	**Visit 25**	**Visit 26**
Study Visit Title	Part II Randomization Fixed TX 13	Fixed TX 14	Fixed TX 15	Fixed TX 16	Fixed TX 17	Fixed TX 18	Fixed TX 19	Fixed TX 20	Fixed TX 21	Fixed TX 22	Fixed TX 23	Part II Closure*
Time in relation to **first treatment in Part II**	Part II Start Time 0	+2 weeks	+5 weeks	+8 weeks	+12 weeks (6 mo)	+16 weeks	20 weeks	24 weeks (9 mo)	28 weeks	32 weeks	36 weeks	38 weeks (12 mo)
Window	±3d	±3d	±3d	±3d	±7d	±7d	±7d	±7d	±7d	±7d	±7d	±7d
St. Mark's Score	**X**				**X**			**X**				**X**
PGI-I (FI)	**X**				**X**			**X**				**X**
PGSC	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
PRN Schedule GROUP (Visits 15 and 26 must be in-person)												
PTNS Treatment (Projected)	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Safety Stimulation Checklist	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
AE/SAE (at treatment visits or by phone)	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Unmasking (Deviation Recorded)	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
CRFs/Questionnaires**												
PAC-SYM	**X**											**X**
PISQ-IR	**X**											**X**
Adaptation Index	**X**											**X**
SF-12	**X**											**X**
FIQL	**X**				**X**							**X**
ABLE	**X**				**X**							**X**
PFDI-20	**X**				**X**							**X**
PFIQ-7	**X**				**X**							**X**
Modified Manchester/FSFI	**X**				**X**							**X**
PMHx update (visit or by phone)	**X**				**X**			**X**				**X**
St. Mark's Score	**X**				**X**			**X**				**X**
PGI-I (FI)	**X**				**X**			**X**				**X**
PGSC*** (at visits or by phone)	**In-person***	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**In-person***

≠An improvement in St. Mark's $\geq$ 4 from the participant's baseline

*All participants will attend Visit 26. Those who exit Part II prematurely will be administered the Visit 26 panel of questionnaires at the time they exit the study.

**The PRN group will complete the questionnaires electronically via an email link at the 6 and 9 month time point if they do not have a treatment visit at 6 months and/or 9 months. They will attend Visit 26 in-person and will complete the questionnaires in-person. Mailing or administering paper questionnaires should be used only as a back-up. Other planned assessments (e.g., AE collection and medical history update) will be done by phone if the participant does not attend a treatment visit in-person.

***The PGSC will be administered to participants in the PRN group in-person at Visits 15 and 26. At all other timepoints, the coordinator will administer the PGSC by phone if the participant does not schedule an in-person treatment.

3.6 Timeline of Calls and Schedule of Measures for Part III: 6-Month Extended Follow-Up

The instruments that would inform on the above aims include:

Schedule of measure to be completed online through secure email link						
Weeks after last PTNS treatment	6 weeks	10 weeks	14 weeks	18 weeks	22 weeks	26 weeks Part III EXIT
PGSC by phone	**X**	**X**	**X**	**X**	**X**	**X**
ePRO						
St. Mark's Score	**X**	**X**	**X**	**X**	**X**	**X**
PGI-I (FI)	**X**	**X**	**X**	**X**	**X**	**X**
FIQL	**X**	**X**	**X**	**X**	**X**	**X**
Adaptation Index	**Only if PGSC ≤2**					**X**

The estimated time to complete the limited ePRO panel is 15 minutes (reduced from 45 minutes).

4 Selection of Participants

Written informed consent will be obtained prior to the subject participating in the Run-In Phase, providing baseline information, or undergoing any study-related procedures.

4.1 Study Population

Subjects will be women ≥ 18 years, with ≥ 3 months of refractory symptoms of ABL. In this study, subjects will have failed to achieve satisfactory symptom control from two first-line treatments for ABL: supervised pelvic muscle training (PMT) and constipating medications. The PMT must have been conducted by a health provider experienced with treating ABL (minimum 2 treatment sessions). The lack of response to constipating agents may be due to ineffectiveness, intolerance, unwillingness, or contraindication. Supplementary fiber bulking will not be considered a treatment for ABL due to lack of data supporting its effectiveness for ABL.

4.2 Study Eligibility

To be enrolled into NOTABLe, participants will report a minimum score of 12 on the St. Mark's Questionnaire. This eligibility threshold will provide a study population with severity of symptoms that have the potential to achieve a response within our stated effect size of 4.0.

Subjects must have a current negative colon cancer screening based on the 2016 US Preventative Services Task Force (USPSTF) recommendation for colorectal cancer screening (67). For subjects ages 50-75 years old, the USPSTF recommends either: an annual screening

with high-sensitivity fecal occult blood testing or sigmoidoscopy within 5 years done along with high-sensitivity fecal occult blood testing at least every 3 years; OR a screening colonoscopy every 10 years. Routine colon cancer screening is not required for those who are ≥ 76 years old as the benefit of early detection and intervention declines after age 75.

4.3 Inclusion/Exclusion Criteria

4.3.1 Inclusion Criteria:

Participants must meet all the listed inclusion criteria by patient self-report.

- Women ≥ 18 years of age
- FI symptoms ≥ 3 months
- Baseline St. Mark's score of ≥ 12
- Attended ≥ 2 supervised PMT for ABL
- Intolerance, unwillingness, or inadequate response to constipating medications (i.e., Imodium, Lomotil, cholestyramine, and bentyl)
- Current negative colon cancer screening based on the USPSTF's recommendation for colorectal cancer screening (2016)

4.3.2 Exclusion Criteria:

Subjects who meet any of the following criteria by patient self-report (or pregnancy test) are ineligible for enrollment in the study. Criteria pertaining to the site of the PTNS or sham needles or surface electrodes only exclude a participant from the study if she does not have an unaffected leg to which PTNS or sham can be applied).

- Previous PTNS treatment
- History of uncontrolled diarrhea defined as Bristol Stool Form 7 (watery, no solid pieces) as the usual or most common stool type over the preceding 3 months
- History of severe constipation defined as Bristol Stool Form 1 (separate hard lumps, like nuts) as the usual or most common stool type over the preceding 3 months
- History of inflammatory bowel disease (includes Crohn's disease and ulcerative colitis, but does not include irritable bowel disease)
- Unrepaired rectovaginal fistula/chronic 4th degree laceration
- Full thickness rectal prolapse
- History of congenital anorectal malformation
- History of bowel resection surgery for any indication
- Minor anal procedures within 6 months for treatment of ABL (injection of bulking agent or radiofrequency energy) or ligation of hemorrhoids
- Prior pelvic or abdominal radiation

- Diagnosis of cancer of the descending colon or anus
- Diagnosis of cancer in the region where the PTNS or sham needles or surface electrodes would be placed
- Pacemaker, implantable defibrillator
- Current use of Interstim sacral nerve stimulator or TENS in the pelvic region, back, or legs
- Clinically significant neurological disorders known to affect anal continence
- Coagulopathy
- Severe peripheral edema preventing accurate placement of PTNS needles
- Chronic swollen, infected, inflamed skin or skin eruptions (e.g., phlebitis, thrombophlebitis, varicose veins) in the region where the PTNS or sham needles or surface electrodes would be placed
- Metal implant in foot/toes near TENS electrode location
- Marked sensory deficit (numbness) of feet or ankles in the region where the PTNS or sham needles or surface electrodes would be placed
- Childbirth within the last 3 months
- Pregnant or planning to become pregnant during the study duration 1 year; a urine pregnancy test will be performed and must be negative by the first intervention visit if the participant is of childbearing potential
- Unwilling to use acceptable form of contraceptive if the participant is of childbearing potential
- Participation in another intervention trial impacting bowel function
- Inability to provide informed consent, complete questionnaires independently, or to attend intervention sessions
- Unable or unwilling to complete the bowel diary in Run-In Phase (valid diary defined as data from ≥ 10 of 14 days with minimum of 3 consecutive days per week)
- Unwilling to download bowel diary app onto smartphone if the participant owns a smartphone
- Visual impairment prohibiting reading the paper diary, the smart phone screen
- Unable to speak, read, or write in English or Spanish at a basic level

To be eligible for randomization into Part I: Enrolled subjects will have completed the 4-week Run-In Phase which includes receiving standardized verbal and written education on FI as delineated in the NIDDK brochure and have demonstrated their ability to complete a bowel diary (providing ≥ 10 of 14 days of diary data with minimum of 3 consecutive days per week). All subjects randomized in Part I will have a St. Mark's score of ≥ 12 points.

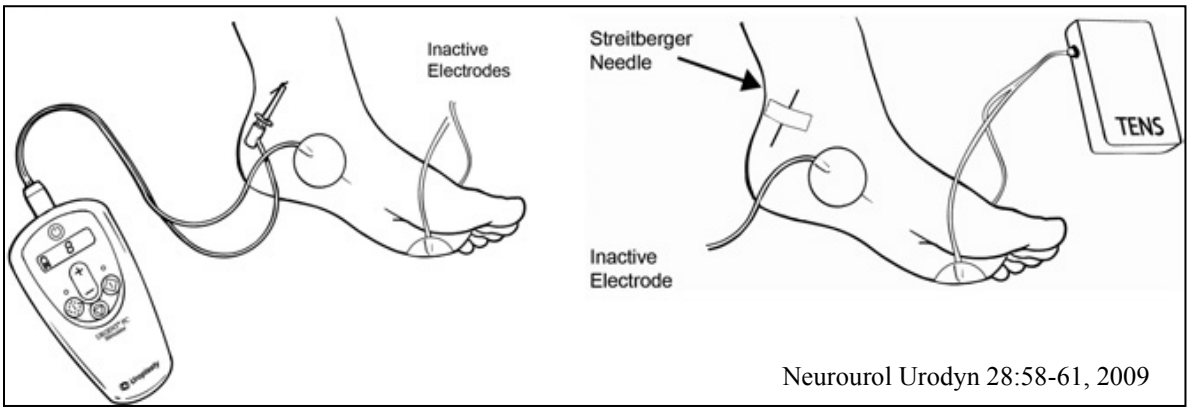
To be eligible for the 6-month extended follow-up after the final PTNS session: NOTABLe subjects will have been randomized to Part II and have completed a total of ≥6 months of PTNS treatment (≥6 months from randomization into Part I). NOTABLe subjects with <6 months of PTNS sessions (i.e., those who exited Part II) will not be enrolled in the 6-month extended follow-up. Those who initiate new FI treatment during Part II are ineligible to enter Part III.

5 Description of Study Interventions

5.1 Masking

Participants will remain masked to treatment assignment throughout the trial. To maintain masking of participants, the duration of treatment sessions for both the PTNS and sham groups will be 30 minutes and will be conducted with subjects in a supine position with the knees comfortably abducted and flexed. The leg and foot involved in treatment will be obscured from the subject's view with a portable anesthesia drape frame to which an exam sheet will be secured. Additionally, each patient will have 3 surface electrodes positioned on their foot: the ground for PTNS and two TENS adhesive surface electrodes for the active sham as detailed by Peters (52). The TENS adhesive electrode pad will be positioned on the bottom and top of the foot near the fifth (smallest) toe. The PTNS grounding electrode will be placed near the calcaneus. During PTNS treatments, the PTNS ground electrode will be connected to the pulse generator while the two TENS electrodes will not be connected to an energy source. During the sham stimulation, the two TENS electrodes will be connected to a TENS unit and the PTNS ground pad will not be connected to an energy source. Additionally, each subject will have a "needle" positioned 5 cm above the medial malleolus and posterior to the tibia (Figure a). The interventionists will remain with the subject throughout the treatment session.

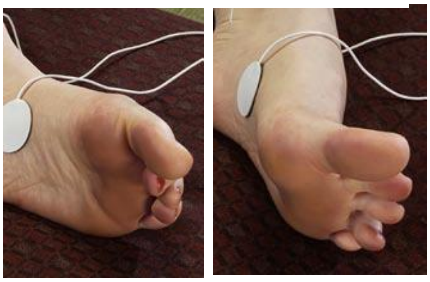
Figure a. Needle and adhesive electrode location for PTNS and Sham set-up



5.2 PTNS Treatment

PTNS treatment entails insertion of a 36-gauge needle electrode at a 60 degree angle 3-4 cm deep towards the tibial nerve, approximately 5 cm or 3 finger breadths cephalad to the medial malleolus and posterior to the tibia. As noted above, the 3 adhesive grounding pads are positioned on one foot. The PTNS grounding electrode, placed near the calcaneus and the needle electrode will be connected to the pulse generator and the stimulation settings are increased from a current level of 0 to 9 mA at 20 Hz until the patient reports a sensation of tingling in the bottom of the foot. Flexion of the greater toe (Figure b) and/or sensory stimulation confirmed proper needle placement. Interventionists will be instructed to elicit one of the two responses prior to commencing the treatment session. If a sensory or motor response is not reported by the participant or the participant reports a burning sensation at the needle insertion site, the interventionist will employ trouble shooting strategies including advancing, repositioning or replacing the needle on the same or contralateral leg. The stimulation session will be delivered at the maximum comfortably tolerated intensity. If a participant does not report a sensory or motor stimulation response during a treatment session, the interventionist should continue and complete the 30 minute treatment session. Furthermore, if a participant does not report a sensory or motor stimulation response during multiple treatment sessions, the interventionist should continue and complete all treatment sessions as described in this protocol (i.e., weekly treatments during Part I and monthly treatments during Part II). The participant will not be withdrawn from the study if she reports no sensation at one or multiple treatment sessions. The type of stimulation (sensory and/or motor) or lack of stimulation reported by the participant as well as the pulse generator setting will be recorded on the case report form. At the end of the procedure, the needle and grounding pads are removed and discarded. The leg stimulated may be alternated at each visit and recorded on the appropriate case report form (CRF).

Figure b.



5.2.1 Pulse Generators for PTNS

There are numerous pulse generators commercially available for nerve and muscle stimulation. Effective stimulation parameters are highly variable between subjects. Stimulation variations in pulse width, voltage/current, biphasic/uniphasic pattern are not known to be therapeutically relevant in facilitating effective peripheral neuromodulation as long as a sensory/motor threshold is reached with the combination of stimulus parameters. Most of the FI literature on PTNS has used a version of the Stoller Afferent Nerve Stimulator (SANS) (UroSurge, Coralville, Iowa, USA) including Urgent(R) PC (Cystomedix, Andover, MN) the Urgent PC (Uroplasty Inc. Minnetonka, MN). The original SANS unit generated a pulse width of 100-300 micro sec, a pulse intensity of 1-10 mA, a pulse cycle time of 20-80 msec with different waveforms “to achieve the desired therapeutic result” (US Patent No.: US 6,493,588). Subsequent modifications to the pulse generator locked down stimulation parameters and developed integrated lead electrodes designed to self-destruct to assure

single use. The revised SANS device is currently sold under the name Urgent PC (Cogentix). In 2013 the Nuro Neuromodulation System received Food and Drug Administration (FDA) approval for PTNS under section 510(k) as substantially equivalent to Urgent PC. It is currently sold by Medtronic (Dublin 2, Ireland). The stimulator distinguishes itself from Urgent PC by being programmable with respect to purchased treatment session credits.

As there is no FDA-approved device to administer PTNS for the treatment of FI, the NOTABLe protocol committee considered available generators FDA-approved for human use in consultation with University of Pittsburgh faculty experienced in peripheral neuromodulation (Drs. William C Degroat and Changfeng Tai). Additionally, we considered the clinical experience of a PFDN clinical site (Kaiser Permanente of Southern California) which has been using the ES-130 (ITO, Tokyo, Japan) pulse generator in their PTNS treatment sessions for UUI. The ES-130 (ITO, Tokyo, Japan) is a portable 9V battery powered pulse generator approved by the FDA under a 510(k) application for electro-acupuncture. It generates electrical stimulation to a needle electrode and can be programed with settings similar to the original Stoller Afferent Nerve Stimulation unit. Specifically, it is capable of delivering a threshold voltage/current to induce toe twitch/sensation. Additionally, its three channels provide the option of delivering bilateral tibial nerve stimulation should that be a future research interest. The advantages of using the ITO ES-130 “generic” pulse generator in the NOTABLe trial include:

a. Generalizability of study findings to various pulse generators on the market globally.

b. Intellectual freedom from Cogentix and Medtronic, current manufacturers of a pulse generator with FDA approval for treatment of UUI.

c. Cost savings for the NOTABLe trial and also for the *ReFINE* comparative effectiveness trial of PTNS and SNS.

The device will be used for the indication of “Posterior Tibial Nerve Stimulation for the treatment of fecal incontinence” using the FDA-approved protocol for treatment of UUI in the PFDN NOTABLe study. There is no PTNS device cleared by the FDA for the indication of FI treatment; therefore, this is considered an investigational device.

To reduce the risk of administering stimulation at non-protocol settings, research staff will use a Stimulation Safety Checklist which will require them to confirm that the pulse generator is programmed per protocol.

5.3 Sham Treatment

Sham treatment will use the Streitberger acupuncture placebo needle in the same location as the needle electrode for PTNS (5 cm cephalad to the medial malleolus and posterior to the tibia).

The Streitberger needle is a two-piece needle comprised of a needle handle and blunt-tip retractable shaft. It causes the sensation of a slight prick when touched to the skin; however, the shaft retracts as it touches the skin which results in no skin puncture (Figure c). The Streitberger needle is taped in position. The sham uses an active gel surface electrode pad placed on the bottom of the foot just below the fifth (smallest) toe. This location is not part of the acupuncture nerve pathway connected to the bladder, pelvis or any major organs (52). Electrical current is delivered to this pad via a TENS unit resulting in sensory stimulation. Another gel electrode is placed on the top of the foot just above the small toe for conduction. The surface electrodes are connected by lead wires to the TENS unit set for continuous stimulation at 20 Hz (as in PTNS). The current generated by the TENS unit will be slowly increased until the subject reports stimulation in the bottom of the foot or toe. The TENS unit will remain on for 30 minutes. At the end of the test session, the surface electrodes and the Streitberger needle will be removed. The leg stimulated may be alternated at each visit and will be recorded on the appropriate CRF.

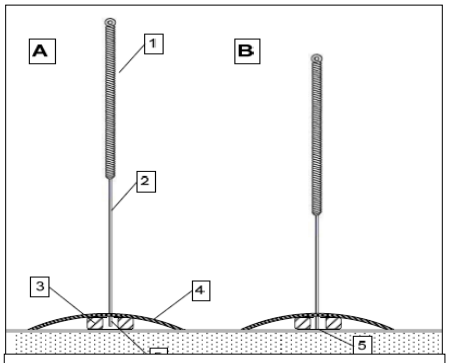


Figure c. Streitberger Needle extended and retracted into handle

5.4 Treatment Regimen

Part I. (RCT PTNS vs. Sham)

The randomization assignment of PTNS to sham participants will be 2:1. Treatment sessions will be delivered weekly (±3day window) for a total of 12 sessions. Adherence to the study regimen will be defined as completing 10 of the 12 stimulation sessions within a 14-week window.

Part II. (RCT Fixed vs. Flexible treatment schedule)

At the conclusion of Part I (two weeks after the 12th stimulation session), those determined to be "responders" in both the PTNS and sham groups will be offered continuation of their assigned treatments in a randomized study of two maintenance strategies: fixed intervals vs. a patient symptom driven (PRN) schedule. The randomization assignment will be 1:1. The total study duration is 52 weeks from the subject's first treatment in Part I. Monthly treatment windows will be extended to ±7 days. Masking of participants will be maintained.

The fixed schedule will include 11 treatment sessions of increasing intervals as follows:

Q 14 days x 2 sessions, Q 21 days x 2 sessions, Q 28 days x 7 sessions

Adherence to the Part II schedule will be defined as attendance at 9 of 11 sessions for those assigned to the fixed schedule. The patient symptom driven schedule is projected to average 11 sessions, 1.1-1.3 sessions per month based upon OAB studies.

Criteria for Scheduling PRN Treatments

Research staff will administer the PGSC to subjects assigned to the PRN treatment schedule by phone at the same intervals as the fixed schedule treatment visits or sooner if the subject calls reporting symptom worsening or requesting a treatment. A PRN treatment will be scheduled within 3 working days for subjects who report a PGSC score of 1 or 2. Subjects who report a PGSC score of 3, 4, or 5 will not be offered a treatment. If a participant reports a score of 3 and specifically requests a treatment, she may receive a treatment, but a protocol deviation will be documented.

The Patient Global Symptom Control (PGSC) Rating (modified for ABL)

My current treatment is giving me adequate control of my Accidental Bowel Leakage.

Disagree Strongly	1	2	3	4	5	Agree Strongly

6 Statistical Considerations and Analytical Plan

6.1 Sample Size/Power Calculation

This randomized, single-masked controlled trial is designed to evaluate the effect of PTNS for FI by comparing the effectiveness of PTNS to a validated sham in women with FI. The St. Mark's (Vaizey) score has been selected as the primary outcome measure. This decision was based upon the information collected as a part of the CAPABLe study design activity. This sample size estimate has taken into consideration the background literature on properties of the Vaizey scale as utilized in the CAPABLe design and the published literature on use of PTNS for FI. Key information that is relevant to the NOTABLe study design is summarized in bullet form below:

- While several small studies on PTNS have been conducted, the measure most frequently used for those studies was the Wexner score rather than the St. Mark's (Vaizey) score.
- The MID for the St. Mark's (Vaizey) scale for FI selected for the CAPABLe study was a difference between arms of 5 units, based on Bols (58). While the information on the effect of PTNS based on the Vaizey scale is limited, the effect sizes found to date are smaller than this difference. Given the limited data available, estimates were developed that would allow us to detect effect sizes ranging from half of the MID to the MID.

- While very limited information is available, the work done by Vaizey during the original development of the scale indicates that the underlying variability of the Wexner scale is comparable to the variability of the St. Mark's (Vaizey) scale (standard deviation of 5.9 versus a standard deviation of 6). Consequently, while we can't use information on the Wexner directly for this study, the information presented in Table 1 that shows the relative consistency of variability before and after treatment with the Wexner and the consistency of the variability of the Wexner and the Vaizey scores provides some indication that the preliminary estimates of variability should be relatively robust.
- Three manuscripts (Bols, 2010, de la Portilla, 2009, and Queralto, 2006) provide sufficient information to estimate the correlation of measures before and after treatment, although the treatment for the Queralto study is transcutaneous PTNS. Preliminary calculations indicate that the correlation can be estimated conservatively to be about 0.35.
- Although the original Vaizey manuscript indicated that the standard deviation of the outcome measure is around 6, the other studies available suggest that that standard deviation is at the high end of the range. Unpublished data from CAPABLe indicate that the standard deviation for the change from baseline in St. Mark's score at 12 weeks among women assigned to education and placebo drug was close to 7. Based on the range of available data, we have elected to conservatively design the trial for a standard deviation of 7.

Based on the results outlined above, preliminary sample size estimates were generated under the assumption that the effect size of interest (difference in the change from baseline in Vaizey score at the end of the treatment period between the PTNS arm and the sham arm) was in the range of 2.5 to 5, and that the standard deviation was 4.5, 5, 6, or 7. The calculations assumed that we wanted the study to achieve a power of 90% and the outcome measure of interest is the change from baseline in Vaizey score at the end of the treatment period. The results of the preliminary calculations are shown in Table 2.

Because one interest of the study is to evaluate alternative maintenance strategies for the PTNS treatment, calculations were generated under the assumption that the ratio of randomization of PTNS to sham participants was 2:1. The sample sizes in the table represent the total sample size for both the treatment and sham arms.

The protocol committee elected a mid-range effect size of 4.0 accepting that it was less than the MID of 5.0. Based on these assumptions, a minimum of 147 women (98 randomized to PTNS and 49 to sham) would need to have outcomes assessed after 12 weeks of stimulation to have 90% power to detect a significant difference between groups in change from baseline in St. Mark's (Vaizey) score using a two-sided test with an alpha

level of 0.05. To account for a potential 10% drop out rate during Part I, the sample size has been inflated to 165 (110 assigned to PTNS and 55 to sham).

Table 2.

Effect Size (Difference in PTNS and Sham Score at Study End)	Total Sample Size Needed to Achieve 90% Power			
	SD=4.5	SD=5	SD=6	SD=7
2.5	156	192	276	372
3.0	111	135	192	261
3.5	81	99	141	192
4.0	63	78	111	147
4.5	51	63	87	117
5.0	42	51	72	96

In the Overactive Bladder Innovative Therapy (OrBIT) study of PTNS vs. Detrol for UI, 70% of participants randomized to PTNS were responders at 3 months. We conservatively assume that 60% of NOTABLe participants in the PTNS group will be classified as responders at the end of Part I and that the remaining 40% will be non-responders and/or will drop out of the study.

The goal of Part II is to estimate the percent of women assigned to each maintenance schedule who are still responders at one year from the start of PTNS treatment. In OrBIT, approximately 70% of participants who began Part II were responders at one year. Making a conservative assumption that the Part II responder rate in NOTABLe will be 50%, the table below shows the number of Part II participants needed in each maintenance group for the 95% confidence interval (CI) around a 50% responder rate in that group to have a half-width of 10% to 15%.

95% CI half-width	10%	11%	12%	13%	14%	15%
Part II participants	97	80	67	57	49	43

The protocol team decided that a 95% confidence interval half-width of 15% would provide adequate information about the PTNS maintenance strategies for planning a future study, thus requiring 86 PTNS responders to be enrolled in Part II (43 assigned to each maintenance strategy). To achieve that number under the previous assumption of a 60% responder rate after 12 weeks of stimulation, and assuming 90% of Part I responders enroll in Part II, an estimated 178 women need to begin PTNS treatment in order for 86 to be randomized to Part II.

In order to randomize 110 participants to PTNS and 55 to sham in Part I of the study, we anticipate needing to enroll 254 women in the Run-In Phase, assuming that 165 (65%) will be eligible to go on to Part I after the Run-In Phase. We expect that 53 women randomized

to PTNS in Part I will go on to Part II, assuming that 59/98 (60%) of those who complete Part I will respond to PTNS and 53 (90% of responders) will enter Part II. Thus, an additional 33 PTNS responders will need to be randomized to a maintenance strategy in order to meet the Part II randomization target of 86 participants. We expect that an additional 94 women will need to be enrolled in the Run-In Phase in order to complete Part II. This assumes that 68 (65%) will be eligible to begin PTNS after the Run-In Phase, 7 (10%) will be lost to follow up, 37 (60%) will be PTNS responders, and 33 (90% of responders) will be randomized to a maintenance strategy in Part II. Thus, a total of 359 participants will be enrolled in the Run-In Phase in order to complete both Part I and Part II.

All subjects (PTNS and sham) randomized to Part II (maintenance) and with ≥6 months total of assigned stimulation sessions will be asked to provide symptom updates through the extended 6-month follow-up of symptom control, improvement, and QOL after final PTNS treatment. Those who initiate new FI treatment during Part II are ineligible to enter Part III. Sham subjects will also be asked for symptom updates to maintain masking of all subjects. Subjects who completed Part II prior to approval of the protocol amendment for extended follow-up (Part III) will be contacted by study staff and invited to re-enter follow-up under an IRB approved consent amendment. A total of 86 subjects assigned to PTNS will be randomized to a Part II and based upon a 30% responder rate in the sham group up to 17 sham subjects will provide this extended post-stimulation follow-up data. Data will be analyzed from only those subjects who received PTNS.

6.2 Statistical Methods

The primary analysis for Part I will be conducted when all women randomized to PTNS or sham have completed the Part I outcome assessments. The analysis will use an intention to treat approach in which participants will be analyzed in the groups to which they were randomized. For the primary aim, the change from baseline in St. Mark's (Vaizey) score after 12 weeks of stimulation will be compared between the PTNS and sham groups using a longitudinal general linear model. The model will include changes from baseline at all Part I time points at which the St. Mark's (Vaizey) score was measured, a term for the interaction between treatment group and time, and a term for the stratification factor of site. The difference between the treatment groups after 12 weeks of stimulation will be estimated using the model and will be evaluated for statistical significance using a two-sided test with an alpha level of 0.05. A sensitivity analysis will be conducted in which additional terms will be included in the model for type of Run-In Phase diary (paper or phone app), and interactions between time, treatment group, and type of Run-In Phase diary. In addition, a per-protocol analysis will be conducted to compare PTNS and sham treatment among participants whose study intervention is implemented in a manner consistent with the protocol.

Changes from baseline in secondary outcomes after 12 weeks of stimulation will be compared between treatment groups using models similar to the primary outcome for continuous measures and analogous generalized linear models for categorical outcomes. Analyses of secondary outcomes will be considered exploratory, and confidence intervals and p values will be presented for descriptive purposes.

In Part II, the percent of responders and a 95% confidence interval will be estimated in each PTNS maintenance group at one year using Wilson score intervals. Participants who were not treated with PTNS will be excluded from Part II analyses. Participants who do not complete Part II will be considered non-responders for analysis purposes; however, sensitivity analyses will be conducted to assess the robustness of the Part II results to this assumption.

Models analogous to the ones described for Part I will be used to estimate changes from baseline in other functional outcomes at one year for each PTNS maintenance group. Time points through one year will be included in analysis, and models will include terms for maintenance group, time, and the interaction between maintenance group and time.

For the Run-In Phase, change in St. Mark's score and weekly FIEs from Week 1 to Week 4 will be estimated using general linear modeling. To assess differences between the modalities of the bowel diary (paper or phone app), type of diary will be included in the general linear models as an independent variable along with any characteristics that differ between the groups using the paper and phone app diaries.

Pearson correlation will be used to determine if the changes from baseline in FIEs recorded on the phone app diary correlate with changes from baseline in other measures of FI symptom severity.

For the 6-month extended follow-up after the final PTNS session, the associations between loss of symptom control and length of time since the last PTNS session will be evaluated using generalized linear mixed models. Models will include all time points assessed after the end of PTNS treatment, and they will account for correlations between repeated measures on the same participant by modeling the within-subject covariance structure. Continuous outcomes such as change in St. Mark's score will be modeled using analogous general linear mixed models.

6.3 Interim Analysis

The NICHD has established a Data Safety and Monitoring Board (DSMB) to oversee this study. Members of the DSMB are independent of the study investigators and include

representatives with urology, urogynecology, biostatistics expertise, and a lay member. The DSMB will have regularly scheduled meetings, either in person or by teleconference. There will be no formal interim analyses for efficacy. An approach for analyses of futility will be described in the statistical analysis plan (SAP). The DSMB will review futility data if the rate of enrollment falls below levels noted in the SAP.

7 Study Budget Estimates

Assumptions:

Run-In Phase

- 1 study visit
- 65% of consented subjects will remain eligible after the Run-In Phase.
- 359 women will need to be consented to provide the required sample size of 86 women into Part II.

Part I. RCT of PTNS vs. Sham

- Duration: 12 sessions in up to 14 weeks
- Sample size is 165 women, of whom 110 women will be assigned to PTNS and 55 women to Sham intervention. A 10% loss to follow up in Part I is assumed, so 147 women are expected to complete the Part I RCT (98 PTNS, 49 sham).
- The response rate for the PTNS group is conservatively estimated at 60%. Therefore, up to 59 women in the PTNS group (rounded up) will meet the eligibility criterion to enter Part II, the randomized comparison of a fixed vs. PRN treatment schedule.
- The response rate for the sham group will be a maximum of 30%. Therefore, up to 15 women from the sham group will advance to Part II.

Part II. RCT of Fixed vs. Patient Driven (PRN) Maintenance Treatment Schedule

- Up to 10% of eligible women will elect not to continue in Part II leaving 53 PTNS responders from Part I available for randomization to Part II.
- An additional 33 women will need to be randomized to a maintenance strategy to reach 86 participants with PTNS in Part II. Assuming 65% eligibility after the Run-In Phase, 10% loss to follow up, a 60% response rate, and 90% of responders agreeing to be randomized, we will need an additional 105 women to start the Run-In Phase for 68 to start PTNS, 61 to complete PTNS treatment, 37 to be responders, and 33 to be randomized to a maintenance strategy.
- Duration is 9 months or up to one year from the first treatment in Part I.
- Fixed maintenance schedule entails up to 11 treatment sessions.

- PRN maintenance schedule will average 1.1 sessions per month based upon the UUI literature. This equates to approximately 11 sessions. The outcome measures will be recorded and collected at study visits.
- Site research staff will contact participants in the PRN group by phone at the same intervals as the fixed treatment schedule to administer the PGSC, update their medical history, and record any AEs.
- Subject response of 1-2 on the PGSC will prompt scheduling of a treatment session within 3 working days of the call. If a participant reports a score of 3 and specifically requests a treatment, a treatment visit may be scheduled within 3 working days of the call. A protocol deviation will be documented in the latter case.
- The PRN group will also complete a packet of questionnaires electronically via an email link at the 6 and 9 month time points (paper questionnaires can be mailed only as a back-up plan). They will attend an in-person Part II study closure visit at 12 months where they will complete the questionnaires in-person.

6-Month Extended Follow-up After Last PTNS Session

For subjects who are eligible to participate in the 6-month extended follow-up after final PTNS session, we anticipate that most subjects will become symptomatic within 3 months of last stimulation session. A more realistic (whilst very conservative) estimate based upon the assumption that 50% of subjects exit follow-up by 3 months and the remainder exit follow-up at 6 months results in cost of $105,641.

- Coordinator time: [2 hours] x [$49/hour] x [6 study timepoints] x [103 subjects] = $60,5640
- Participant incentive: [$50 x6 time points x 103 participants] = $30,900
- **Total costs subject to indirects: [total = $91,464]**
- **Indirect costs: [total costs subject to indirects x 0.54] = $49,390**
- **Maximum total cost: $140,854** if every subject continues follow-up for 6 months

Participant Payments

Participant payments will reimburse subjects for their time and costs associated with traveling to and attending study visits and providing outcome data. The payments are graduated in Part I and reflect the importance of subject retention to the endpoint of Part I. We are cognizant that a third of participants with refractory ABL will be assigned to sham treatments. Their adherence to the 12 scheduled treatments until study closure will be critical to achieving our sample size for power. The total payment for subjects who complete all 15 visit requirements in the Run-In Phase and Part I is $925. If a subject completes Visit 1, but is found to be ineligible at Visit 2, she will receive $100 ($25 for each visit and $50 for completing the bowel diary).

The total payment for subjects who complete Part II is $350.

For subjects who are eligible to participate in the year-long study of Part I and Part II may be paid up to a total of $1275.

Visit	Study Assessment	Participant Payment
Visit 1	**Run-In**	$25
Visit 2	**Run-In:** $25 visit; $50 Run-In diary completion **Part I**: $25 questionnaires	$75 $25
Visit 3	**Part I**: $50 treatment visit; $50 baseline diary completion	$100
Visit 4	**Part I**: $50 treatment visit	$50
Visit 5	**Part I:** $50 treatment visit	$50
Visit 6	**Part I:** $50 treatment visit	$50
Visit 7	**Part I:** $50 treatment visit	$50
Visit 8	**Part I:** $50 treatment visit	$50
Visit 9	**Part I:** $50 treatment visit	$50
Visit 10	**Part I:** $50 treatment visit; $50 diary completion which starts after Visit 8	$100
Visit 11	**Part I:** $50 treatment visit	$50
Visit 12	**Part I:** $50 treatment visit	$50
Visit 13	**Part I:** $50 treatment visit	$50
Visit 14	**Part I:** $50 treatment visit	$50
Visit 15	**Part I:** $50 diary completion which starts after Visit 14; $50 for attending end of Part I Visit	$100
TOTAL RUN-IN + PART I		**$925**
Visit 19	**Part II:** $50 questionnaires	$50
Visit 20	$50 diary completion which starts after Visit 19	$50
Visit 22	**Part II:** $50 questionnaires	$50
Visit 23	$50 diary completion which starts after Visit 22	$50
Visit 26	**Part II:** $100 questionnaires; $50 diary completion which starts after Visit 25	$150
TOTAL PART II		**$350**
QOL Measures	**Part III (6-month extended follow-up after last PTNS session):** $50 x 6 time points for QOL measure completion	$300
TOTAL ENTIRE STUDY		**$1,575**

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9. Appendix: Supplementary Study of Acceptability, Performance and Reliability of PFDN Phone App Bowel Diary