SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Implantable Electrical Stimulator for Incontinence

Device Trade Name: Medtronic® InterStim® Therapy System

Applicant's Name and Address: Medtronic Inc.
710 Medtronic Parkway NE
Minneapolis MN 55432-5604

Date(s) of Panel Recommendation: none

Premarket Approval Application (PMA) Number: P080025

Date of FDA Notice of Approval: March 14, 2011

Expedited: not applicable

II. INDICATIONS FOR USE

InterStim Therapy System is indicated for the treatment of chronic fecal incontinence in patients who have failed or are not candidates for more conservative treatments.

III. CONTRAINDICATIONS

Implantation of an InterStim neurostimulation system is contraindicated for the following patients:

- Patients who have not demonstrated an appropriate response to test stimulation; or
- Patients who are unable to operate the neurostimulator.

After implantation of any system component, the following contradiction applies:

Diathermy – Do not use shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy (all now referred to as diathermy) on any patients implanted with a neurostimulation system. Energy from diathermy can be transferred through the implanted system and can cause tissue damage at the location of the implanted electrodes, resulting in severe injury or death.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the InterStim Therapy System labeling.

V. DEVICE DESCRIPTION

The Medtronic® InterStim® Therapy System works by applying electrical stimulation to the sacral nerves (S2, S3 or S4). Electrical stimulation of the sacral nerve allows for activation or inhibition of effector organs that the sacral nerves innervate (bladder, urinary and anal sphincters, pelvic floor, and recto-sigmoid colon).

Patients undergo a test stimulation to temporarily experience the effects of the therapy on their symptoms. Test stimulation can be performed either with a temporary lead, that is removed following test stimulation, or with a permanent lead that remains implanted and is connected to the neurostimulator in a "staged implant." Patients with a successful test stimulation result may proceed with surgical implantation of the neurostimulation system for long-term therapy.

Test stimulation involves the use of an external test stimulator, lead, and accessories. The neurostimulation system involves the use of a neurostimulator, lead, lead extension and external patient and physician programmers. The InterStim Therapy System is implanted in a "two-phase" fashion: test stimulation to evaluate whether the patient will respond to the therapy and if the patient exhibits at least a fifty percent decrease in the number of incontinent episodes in a week, permanent implantation of the InterStim Therapy System.

Test stimulation phase: This phase is accomplished in two parts. The first part ("acute test stimulation phase") involves locating the appropriate sacral nerve (S2-S4) using a foramen needle (advanced under fluoroscopic guidance) connected to the test stimulator. Accurate placement of the needle tip is verified by observation of the appropriate motor responses and patient sensory responses; such as contraction of the levator ani muscles (bellows-like contraction), flexion of the greater toe, pulling in the rectum, leg/hip rotation, and plantar flexion of the entire foot. Once the optimum sacral nerve stimulation site has been located, the lead is percutaneously placed at the sacral nerve site using a lead introducer, and the percutaneous lead extension and test stimulator are connected. Appropriate lead placement is again verified by observing the appropriate motor responses. Once electrode placement is confirmed, the patient is sent home to complete the second part of the test stimulation – the sub-chronic test stimulation period (conducted for up to 14 days).

Change in bowel function is evaluated using the Medtronic bowel diary. If the bowel diary demonstrates at least a 50% reduction in the number of incontinent episodes, and/or incontinent days compared to baseline over the 14 day period, then the patient is eligible for the chronic implant phase. If, however, the patient does not have at least a 50% reduction in incontinent episodes, the lead and percutaneous extension are removed, and the patient will not have the device implanted.

Chronic implant phase: During the chronic implant phase the percutaneous extension and test stimulator are removed and replaced with the implanted lead extension and implanted neurostimulator. After connecting the lead extension to the lead, the extension is

tunneled to the upper buttock (or abdomen) where it is connected to the neurostimulator. The neurostimulator is implanted subcutaneously in the upper buttock (or abdomen). After recovering from surgery, the neurostimulator is programmed by the physician using the physician programmer (loaded with the InterStim application software). Based on patient feedback, programming adjustments can be made by the physician. Additionally, the physician can allow the patient to make certain adjustments in pulse amplitude using the patient programmer. At any time, the patient can turn the stimulator ON or OFF using either the patient programmer or the control magnet.

The components of the InterStim Therapy System are identical to those used for the urinary control indication (P970004 and subsequent supplements). No hardware or software changes were made, or were required, to use the InterStim Therapy System for the bowel control (fecal incontinence) indication. Both the urinary control and fecal incontinence indications use the same stimulation parameters and software algorithm.

Device Components:

- Implanted neurostimulator (Model 3023 InterStim or Model 3058 InterStim II) – electrical power sources.

- External test stimulator (Model 3625) – a hand held device used to provide electrical output similar to a neurostimulator; used for intraoperative acute testing and for test stimulation.

- Implanted lead (Models 3093/3889) – a tined lead implanted percutaneously, and tunneled, for positioning near the sacral nerve.

- Implanted lead extension (Model 3095) – provides additional length and an electrical bridge between a tined lead and the neurostimulator.

- N'Vision Clinician Programmer (Model 8840) – a non-sterile, hand held, portable device with a single programming platform. The device is battery powered and used by the clinician to interrogate and program neurostimulator parameters using radiofrequency (RF) telemetry.

- Patient programmer (Model 3031A Patient Programmer or Model 3037 iCon Patient Programmer) – hand-held, battery operated programmer used by the patient to control and monitor the neurostimulator.

- Application-specific software (InterStim Therapy Application Software, loaded on a Model 8870 N'Vision Software Application Card) – provides the user interface for the clinician to view system data and to customize the therapy for each individual patient.

- Test stimulation kit (Model 3065U) – contains a percutaneous nerve evaluation (PNE) lead and accessories for prepping the patient, performing acute sacral nerve

stimulation with foramen needles, and securing the lead to the patient. The components of the kit include:

- Model 3057 test stimulation lead – implanted percutaneously, through a foramen needle and then connected to a short test stimulation cable.
- Model 041826 ground pad – provides the positive electrode when connected to the external test stimulator for acute testing and test stimulation.
- Model 041827 long and short test stimulation cables – long cable connects to the patient cable for acute testing, and the short cable connects to the PNE lead for sub-chronic test stimulation.
- Model 041828 9.0 cm (3.5 in) foramen needle – sterile, stainless steel needle used for acute testing and placement of the PNE Lead.
- Model 041829 12.5 cm (5.0 in) foramen needle – sterile, stainless steel needle used for acute testing and placement of the PNE Lead.
- Model 041831 patient cable – connects the foramen needle (or PNE lead) to the external stimulator.

- Model 3550-05 percutaneous lead extension – the lead extension provides an electrical bridge between a tined lead and an external stimulator for test stimulation.
- Model 3550-03 twist-lock screening cable – connects a percutaneous lead extension to an external test stimulator.
- Model 3550-80 torque wrench and boot kit – accessory kit contains a sterile torque wrench and a boot used to connect the lead to the stimulator and the lead to the lead extension.
- Model 3550-18/042294 lead introducer kit – accessory used to facilitate a minimally invasive lead implant.
- Models 7440/37092 external antennae – may take the place of the antenna built into the patient programmer to allow communication between the programmer and the neurostimulator.
- Model 7452 control magnet – a hand-held, optional component used by the patient to turn the neurostimulator ON or OFF

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Fecal incontinence, the involuntary loss of flatus, liquid or solid stool, is a condition that can have distressing effects on the working life, social life and well being for people

affected by the condition. Individuals who suffer from the condition often alter their lifestyle to minimize the likelihood of bowel accidents. Fecal incontinence may result from a variety of disease processes including injury to the anal sphincter from obstetrical or surgical procedures, trauma, rectal prolapse, neurological diseases or impairments, intestinal infection, fecal impaction, and collagen vascular diseases.

There are several other alternatives for the management of fecal incontinence. In some patients, fecal incontinence can be managed with dietary modifications, pharmacological therapy, and/or biofeedback. Surgical intervention is available to patients with chronic fecal incontinence who are not successfully managed by more conservative treatment. Surgical interventions include sphincter repair or implantation of an artificial bowel sphincter. Some patients are faced with the choice of a permanent ostomy when other medical therapies have failed or are not appropriate. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyles.

VII. MARKETING HISTORY

Medtronic received CE Mark for InterStim Therapy in 1994 in the European Community for the management of chronic intractable (functional) disorders of the pelvis and lower urinary or intestinal tract. InterStim therapy is also approved for the same indication in Australia and Canada.

In 1997, InterStim Therapy was approved for the treatment of urinary urge incontinence in the United States (P970004). In 1999, the indication was expanded to include urinary urgency-frequency, and urinary retention.

InterStim therapy has not been withdrawn from the market in any country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

- Adverse change in voiding function (bowel and/or bladder) including diarrhea, constipation, urinary retention, defecation urgency, micturition urgency, incontinence, and frequent bowel movements.

- Changes in sensation of stimulation which has been described as uncomfortable (jolting or shocking) by some patients including muscle spasms, vaginal pain, vulvovaginal discomfort, scrotal pain, paralysis, and paraesthesia. There is also the potential for nerve injury.

- Allergic or immune system response to the implanted materials that could result in device rejections.

- Pain at neurostimulator and/or lead site including skin irritation, skin ulcer, infection, wound dehiscence, erythema, erosion of the neurostimulator, seroma, hemorrhage, and hematoma.

- Malfunction of the components of the InterStim Therapy System including neurostimulator programming error, lead migration/dislodgement, lead fracture, erosion of the lead into the colon with perforation, neurostimulator battery depletion, extension fracture, neurostimulator migration.

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

The components of the InterStim Therapy System for bowel control are identical to those that are approved under P970004 for urinary control and its supplements. The method of placement, the placement location, and the stimulation parameters are identical to the urinary control indication. Therefore, no additional laboratory or bench testing was needed for this PMA.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study under G010206 to establish a reasonable assurance of safety and effectiveness of the InterStim Therapy System for the treatment of chronic fecal incontinence in patients who have failed or are not candidates for more conservative treatments. The study was conducted at 14 sites in the US, one site in Australia, and one site in Canada for a total of 16 sites. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were implanted with the InterStim Therapy System between May 3, 2002 and August 4, 2006. The database for this PMA reflected data collected through November 10, 2008, and included 285 patients.

The pivotal study was a prospective, multi-center, single-arm, un-blinded, non-randomized clinical trial in which each patient served as his or her own control. Patients who had motor and/or sensory response to an acute needle test (e.g., pulling sensation in the rectum extending forward to the scrotum or labia, bellows response, clamp of anal sphincter, leg/hip rotation, plantar flexion of the entire foot) and who had a successful test stimulation (at-home evaluation during which only symptom responses were recorded) were eligible for permanent implant of InterStim system in the pivotal study. The primary outcome of the pivotal study was fecal incontinence episodes per week as measured by patient bowel diary. Patients who showed at least a 50% reduction in the number of fecal incontinence episodes per week at 12 months

relative to the baseline value were considered therapeutic successes; the primary effectiveness endpoint was the proportion of therapeutic successes. Secondary endpoints included: the proportion of patients with at least a 50% reduction in fecal incontinence days per week, improvement in each of the four subscales of the fecal incontinence quality of life (FIQOL) instrument, and the proportion of patients with at least a 50% reduction in urgent episodes of fecal incontinence.

The primary analysis was a two-sided exact binomial test of the proportion of therapeutic successes in the trial. The sample size of the trial (120 patients with an implanted device) was selected to ensure sufficient power to test the hypothesis that the success proportion was significantly greater than 50%. Missing data was imputed using a modified worst case method, where missing observations of the 12 month outcome were imputed as a failure unless there was a measurement after 12 months; if so, the later observation was used for the missing 12 month outcome.

Several analyses were performed to examine the consistency of the therapeutic effect. Logistic regression was used to assess whether any baseline covariates were significantly associated with the primary endpoint; a chi-square test for homogeneity was used to assess whether the effect of the device was significantly different at different clinical centers; and a sensitivity analysis was performed using different methods of imputing missing observations.

Primary Data imputation Method for Missing Data
A "modified worst case method" was used as the primary data imputation method for missing 12 month diaries or FIQOL scores.

In the case of missing 12 month diaries, the modification to the worst-case method was that patients missing 12 months diary data were treated as therapeutic failures (baseline carried forward) unless there was a subsequent diary available (i.e., collected after the 12 month visit), in which case the subsequent diary was substituted for the missing 12 month diary.

1. **Clinical Inclusion and Exclusion Criteria**
   Enrollment in the InterStim Sacral Nerve Stimulation Therapy for Bowel Control: Fecal Incontinence study was limited to patients who met the following inclusion criteria.

   - 18 years of age or older.
   - Diagnosed with chronic fecal incontinence of a duration greater than 6 months (>12 months post-vaginal childbirth) and defined as > 2 incontinent episodes on average per week of more than staining recorded during the baseline diary period.
   - Failed or are not candidates for more conservative treatments (such as diet modification, medical management, or biofeedback therapy).

Patients were not permitted to enroll in the InterStim Therapy study if they met any of the following exclusion criteria:

- Congenital anorectal malformations
- Present rectal prolapse
- Previous rectal surgery (such as rectopexy or resection) or sphinteroplasty done less than 12 months prior to study enrollment (24 months for cancer)
- Neurological diseases such as clinically significant peripheral neuropathy or complete spinal cord injury (i.e., paraplegia)
- Grade III hemorrhoids
- Known or suspected organic disorders of the bowel (i.e., inflammatory bowel disease such as Crohn's or Ulcerative Colitis)
- Chronic watery diarrhea, unmanageable by drugs or diet, as primary cause of fecal incontinence. (Incontinent episodes with a Bristol stool consistency of ≥ 6 for ≥ 4 days during the baseline diary period will be exclusionary, unless the investigator determined that the diary was not indicative of chronic watery diarrhea
- Pregnant or planned pregnancy
- History of pelvic irradiation who presented with visible or functional effects of irradiation
- Active anal abscesses or fistulas
- Anatomical limitations that would have prevented the successful placement of an electrode
- Knowledge of planned magnetic resonance imaging (MRI), diathermy, microwave, or radiofrequency (RF) energy
- Defect of external anal sphincter of > 60 degrees or amenable to surgical repair

Treatments Administered

The patient was eligible to undergo test stimulation if all of the following criteria were met:

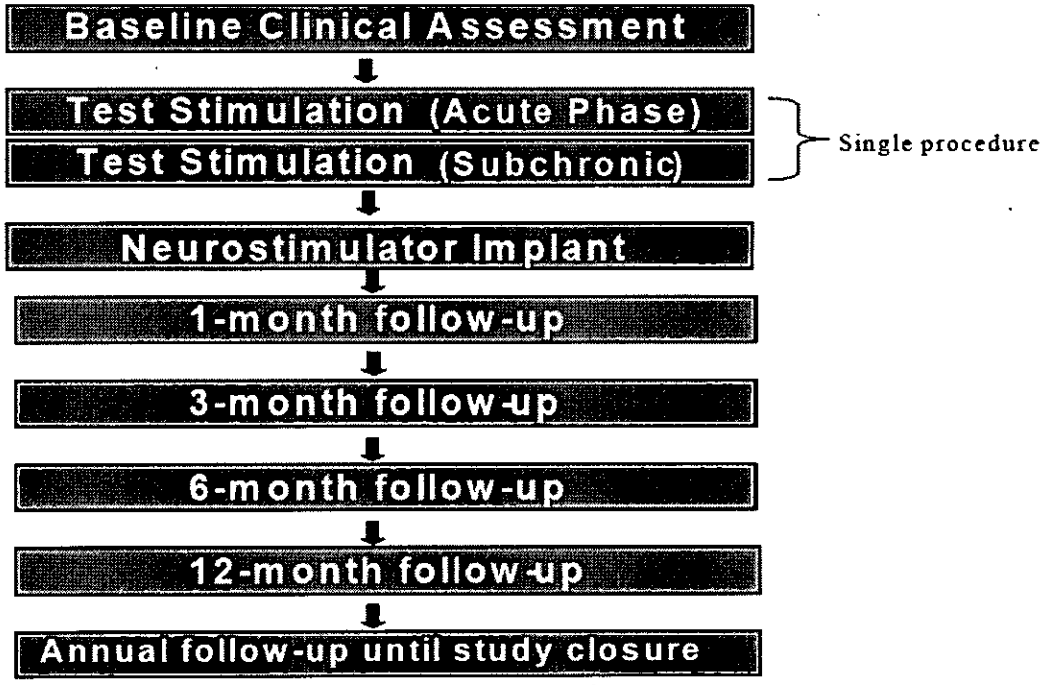
The patient had:

- Signed informed consent,
- Met all of the inclusion criteria and none of the exclusion criteria,
- Completed the history and physical exam,
- Completed a baseline bowel diary,
- Completed the baseline Fecal Incontinence Quality of Life (FIQOL) questionnaire, and
- Completed a baseline Fecal Incontinence Severity Index (FISI).

The description of the test stimulation phase (acute and sub-chronic) and the chronic stimulation phase are in the Section V "Device Description" of this Summary.

2. **Follow-up Schedule**
All patients were scheduled to return for follow-up examinations post-implantation at 3 months, 6 months, and 12 months and then annually (Figure 1).

Figure 1: Follow-up Schedule



Preoperatively, the Medtronic bowel diary (including a question regarding pad use), was completed two weeks prior to the scheduled pre-operative visit. Fecal Incontinence Quality of Life (FIQOL) [1], and Fecal Incontinence Severity Index (FISI)[2], self rated bowel health questions (overall perception of bowel health), and anal manometry (maximal mean incremental squeeze pressure, and maximal mean resting pressure) were also completed. Postoperatively, the same tests completed at baseline (pre-operative) were conducted at each follow-up visit (see Table 1). Adverse events and complications were recorded at all visits.

Table 1: Schedule of Evaluation Conducted Pre-and Post-Implantation.

		BASELINE	FOLLOW UP			
			3 mo	6 mo	12 mo	Annual
Procedures	Bowel Diary (14 day)	X	X	X	X	X
	FIQOL/ FISI*	X	X	X	X	X
	Anal Manometry	X	X	X	X	Optional
	Endoanal Ultrasound or Magnetic Resonance Imaging (MRI)	X				
	Electromyography (EMG) or Pudendal Nerve Terminal Motor Latency (PNTML)	X				
	Physical Exam	X				
	Pregnancy Test	if applicable				

*Fecal Incontinence Qualify of life (FIQOL)/Fecal Incontinence Severity Index (FISI)

3. Clinical Endpoints

Primary Endpoints included:

Safety – characterization of adverse events experienced with use of the InterStim Therapy System in patients with fecal incontinence during both the test stimulation and permanent implantation.

Effectiveness – demonstrate that at least 50% of patients will achieve at least a 50% reduction in the number of incontinent episodes per week at 12 months post implantation compared to baseline.

Secondary endpoints included:

- Demonstrate that at least 50% of patients will achieve at least 50% reduction in the number of incontinent days per week at 12 months post implant compared to baseline.

- Demonstrate improvement in Fecal Incontinence Quality of Life (FIQOL) scores at 12 months post-implant compared to baseline. The four component scales of the FIQOL instrument will be analyzed separately.

    - Scale 1 – Lifestyle
    - Scale 2 – Coping/Behavior
    - Scale 3 – Depression/Self-Perception
    - Scale 4 – Embarrassment

- Demonstrate that at least 50% of patients will achieve at least 50% reduction to the number of urgent incontinent episodes per week at 12 months compared to baseline.

Additional Evaluation

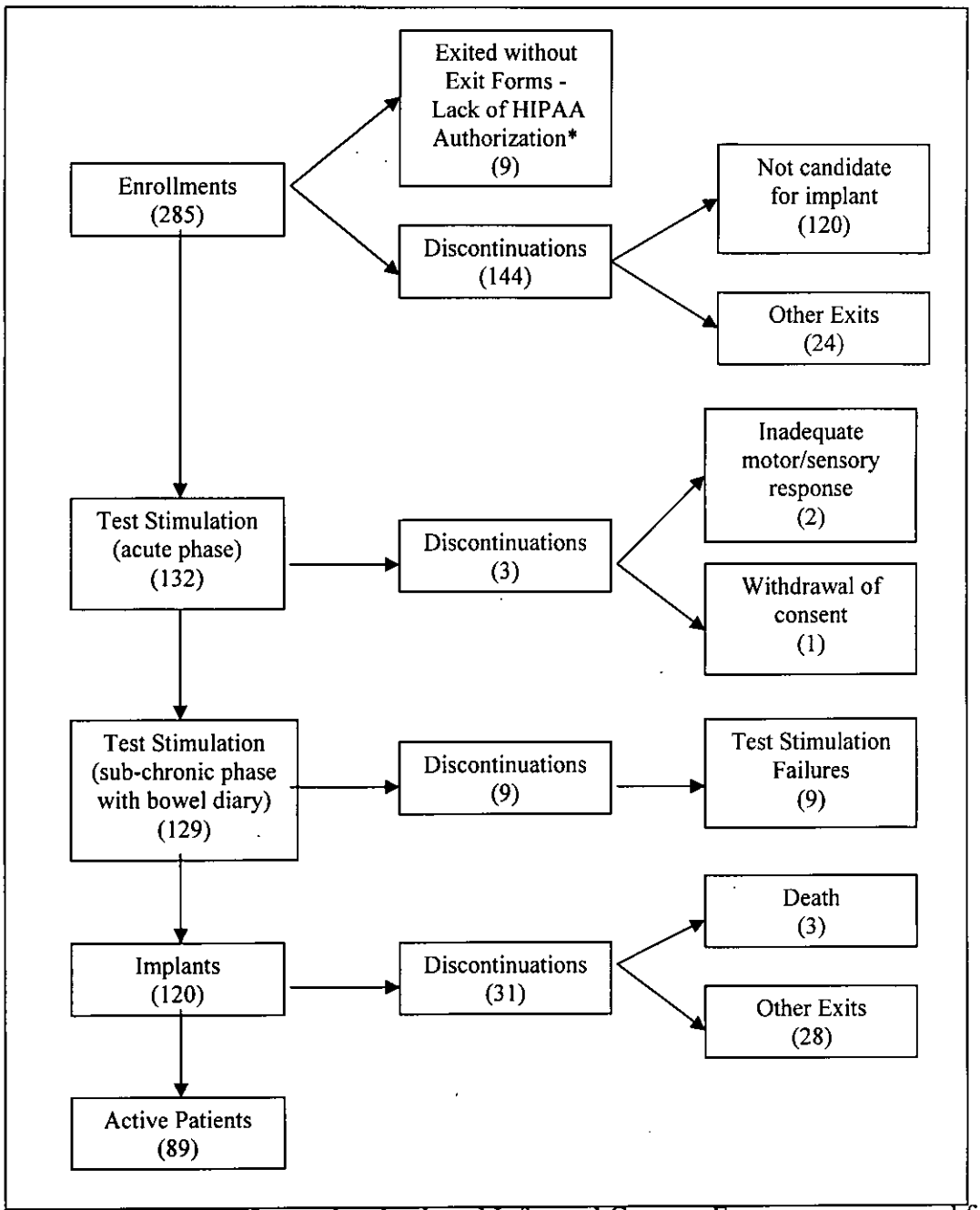
Although not evaluated as a secondary endpoint, anorectal manometry was conducted at baseline, 3 months, 6 months, and 12 months. Manometry was performed to assess maximal mean resting pressure and maximal mean incremental squeeze pressure.

B. Accountability of PMA Cohort

At the time of database lock, 285 patients had been enrolled in the clinical study; patients are considered enrolled after signing the informed consent. One hundred and fifty three (153) patients were not eligible to undergo test stimulation; nine (9) did not complete the Health Insurance Portability and Accountability Act (HIPAA) authorization, 24 exited the study prior to completing the baseline evaluations, and 120 patients were found to be not eligible for test stimulation after undergoing the baseline evaluations. The remaining 132 patients underwent acute and sub-chronic test stimulation procedures and 120 patients qualified for permanent implantation of the InterStim Therapy System. As of November 10, 2008, 89 patients (74.2%) patients are still active in the study; all patients have more than 12 months of follow-up. The study is ongoing until completion of the post approval study.

Patient study status is explained in Figure 2.

Figure 2: Study Patient Status



* Nine (9) patients who previously signed Informed Consent Forms were removed from the clinical database per the request of the reviewing IRB due to lack of HIPAA authorization. All nine (9) were exited prior to test stimulation and the data for these patients do not appear in this report.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a study evaluating fecal incontinence treatments performed in the US.

- The mean age of the 120 implanted patients was 60.5 years (range 30.4 to 88 years).
- There were 10 males (8%) and 110 females (92%) implanted with the InterStim Therapy System.
- The mean duration of fecal incontinence was reported to be 6.8±8.8 years (range 1-44 years).
- The most frequent etiology for fecal incontinence was obstetric trauma occurring in 55 (46%) of patients.
- Passive incontinence (no awareness of stool loss) occurred in 54 patients (45%), urge incontinence (inability to defer defecation) in 49 patients (41%), and both urge and passive in 17 (14%).

Table 2 shows the mean number of fecal incontinent episodes per week (9.4 ± 7.3) at baseline. More than 50% of patients reported over 6 fecal incontinence episodes per week.

Table 2: Baseline Fecal Incontinence Symptoms

Symptom	N	Mean	Standard Deviation	Minimum	Median	Max
Weekly incontinent episodes	120	9.4	7.3	2.3	6.98	42.00
Weekly incontinent days	120	4.5	1.6	1.0	4.4	7.0
Weekly urgent incontinent episodes	120	4.9	4.9	0.00	3.3	26.7

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on both the patients undergoing test stimulation and permanent implantation of the InterStim Therapy System. Adverse effects are reported in Tables 3 to 6.

Adverse effects that occurred in the PMA clinical study:

Staged implant test stimulation

A total of 142 test stimulation procedures were conducted on 132 patients. As shown in Table 3, there were 35 adverse events related to the device or use of the therapy reported in 23 patients (17.4%) during the test stimulation phase.

Table 3: Device or Therapy Related Adverse Events During Test Stimulation

Adverse event	Number of Events	Number (%) of patient (n=132)
Implant site pain	5	5 (3.8%)
Lead fracture	3	2 (1.5%)
Hematoma	2	2 (1.5%)
Lead migration/dislodgement	2	2 (1.5%)
Pain in extremity	2	2 (1.5%)
Skin irritation	2	2 (1.5%)
Buttock pain	1	1 (0.8%)
Chest pain	1	1 (0.8%)
Constipation	1	1 (0.8%)
Device malfunction	1	1 (0.8%)
Diarrhea	1	1 (0.8%)
Discomfort	1	1 (0.8%)
Ecchymosis (bruising)	1	1 (0.8%)
Extension fracture	1	1 (0.8%)
Hemorrhage	1	1 (0.8%)
Implant site effusion	1	1 (0.8%)
Implant site infection	1	1 (0.8%)
Incision drainage	1	1 (0.8%)
Nausea	1	1 (0.8%)
Pain	1	1 (0.8%)
Paraesthesia	1	1 (0.8%)
Urinary incontinence	1	1 (0.8%)
Urinary retention	1	1 (0.8%)
Urinary tract infection	1	1 (0.8%)
Vaginal pain	1	1 (0.8%)
Total	35	23 (17.4 %)

Note: The total number of patients may not add down columns, as the same patient may have experienced more than one type of event.

Post-neurostimulator implant

A total of 120 patients had the neurostimulator implanted following success staged implant test stimulation. As shown in Table 4, there were 237 adverse events related to the device or use of the therapy reported in 88 patients (73.3%) during the implant phase. The reported adverse event rate is cumulative through the duration of the study (average post-implant follow-up was 28 months). The majority of these adverse events resolved spontaneously, with re-programming, or with medications.

For the total device- or therapy- related adverse events, 78 patients experienced 182 adverse events (76.8%) which occurred in the first year; 26 patients experienced 33 adverse events (13.9%) between one and two years post implantation; and 22 patients experienced 17 adverse events (79.3%) after the second year post implantation. Information on when the adverse events occurred, post implantation,

is also provided in Table 4. Adverse events which occurred in at least 5% of the patients include:

Implant site pain
Thirty seven (37) adverse events were reported in 31 patients (25.8%). Treatment included no intervention, medication, or device reprogramming for the majority of events (28 patients, 90%). In the other cases, patients underwent a surgical intervention such as a device revision (3), replacement (2), or explant (3).

Paraesthesia
Nineteen (19) reports of paraesthesia or the sensation of tingling, pricking or numbness of a person's skin with no apparent long term effects in 15 patients (12.5%). Thirteen (13) of the events were managed with device reprogramming and three (3) with no intervention. None of the events were serious.

Implant site infection
Fourteen (14) events of implant site infection occurred in 13 patients (10.8%). Five (5) resolved with medication and the devices remained implanted. One (1) of these events was serious and required hospitalization. One (1) infection resolved spontaneously. Seven (7) patients required surgical intervention; one (1) device was explanted and then reimplanted with a new device. Two (2) patients had the device explanted and then reimplanted at a later time. One (1) patient had the lead explanted only and the device remained implanted. Two (2) patients had the device explanted and not reimplanted.

Change in sensation of stimulation
Ten (10) patients (8.3%) reported 12 adverse events of change in sensation of stimulation. Nine (9) events were managed with reprogramming.

Urinary incontinence
Eight (8) patients (6.7%) reported urinary incontinence. Five (5) events resolved with no intervention; two (2) required reprogramming; one (1) event was the result of lead fracture and required a lead revision.

Diarrhea
Six (6) patients (5.0%) reported diarrhea. The majority of these events were treated with medication.

Table 4: Device or Therapy Related Adverse Events Post Implant

Adverse Events Preferred Term	Number of Events (Cumulative)	Number (%) of Patients (Cumulative) (n=120)	Number of Events (Number of Patients) (≤ 1 year)	Number of Events (Number of Patients) (1 - 2 years)	Number of Events (Number of Patients) (> 2 years)
Implant site pain	37	31(25.8%)	29(25)	7(7)	1(1)
Paraesthesia	19	15(12.5%)	12(11)	5(5)	2(2)
Implant site infection	14	13(10.8%)	10(9)	3(3)	1(1)
Change in sensation of stimulation	12	10(8.3%)	8(6)	0(0)	4(4)
Urinary incontinence	8	8(6.7%)	7(7)	0(0)	1(1)
Diarrhea	6	6(5.0%)	5(5)	1(1)	0(0)
Constipation	5	5(4.2%)	5(5)	0(0)	0(0)
Neurostimulator programming error	5	5(4.2%)	5(5)	0(0)	0(0)
Pain	5	5(4.2%)	3(3)	0(0)	2(2)
Pain in extremity	5	5(4.2%)	5(5)	0(0)	0(0)
Urinary tract infection	5	5(4.2%)	3(3)	2(2)	0(0)
Back pain	4	4(3.3%)	4(4)	0(0)	0(0)
Buttock pain	4	4(3.3%)	4(4)	0(0)	0(0)
Proctalgia	4	4(3.3%)	3(3)	1(1)	0(0)
Seroma	4	4(3.3%)	4(4)	0(0)	0(0)
Urinary retention	4	4(3.3%)	3(3)	0(0)	1(1)
Lead migration/dislodgment	5	3(2.5%)	2(1)	1(1)	2(2)
Coccydynia	3	3(2.5%)	1(1)	1(1)	1(1)
Defecation urgency	3	3(2.5%)	2(2)	0(0)	1(1)
Implant site erosion	3	3(2.5%)	3(3)	0(0)	0(0)
Incontinence	3	3(2.5%)	3(3)	0(0)	0(0)
Neurostimulator battery depletion	3	3(2.5%)	0(0)	2(2)	1(1)
Skin irritation	3	3(2.5%)	3(3)	0(0)	0(0)
Therapeutic product ineffective	3	3(2.5%)	3(3)	0(0)	0(0)
Urinary tract disorder	3	3(2.5%)	3(3)	0(0)	0(0)
Unclassified (pain/tingling, pain)	2	2(1.7%)	0(0)	0(0)	2(2)
Cystitis	2	2(1.7%)	1(1)	1(1)	0(0)
Erythema	2	2(1.7%)	1(1)	0(0)	1(1)
Lead fracture	2	2(1.7%)	2(2)	0(0)	0(0)

Adverse Events Preferred Term	Number of Events (Cumulative)	Number (%) of Patients (Cumulative) (n=120)	Number of Events (Number of Patients) (≤ 1 year)	Number of Events (Number of Patients) (1 - 2 years)	Number of Events (Number of Patients) (> 2 years)
Micturition urgency	2	2(1.7%)	2(2)	0(0)	0(0)
Muscle spasms	2	2(1.7%)	2(2)	0(0)	0(0)
Neurostimulator migration	2	2(1.7%)	1(1)	1(1)	0(0)
Pelvic pain	2	2(1.7%)	1(1)	1(1)	0(0)
Pollakiuria	2	2(1.7%)	1(1)	1(1)	0(0)
Wound dehiscence	2	2(1.7%)	2(2)	0(0)	0(0)
High impedance	2	1(0.8%)	1(1)	0(0)	1(1)
Scrotal pain	2	1(0.8%)	2(1)	0(0)	0(0)
Abdominal pain	1	1(0.8%)	1(1)	0(0)	0(0)
Abnormal feces	1	1(0.8%)	0(0)	1(1)	0(0)
Anal discomfort	1	1(0.8%)	1(1)	0(0)	0(0)
Anorectal disorder	1	1(0.8%)	1(1)	0(0)	0(0)
Arthralgia	1	1(0.8%)	1(1)	0(0)	0(0)
Bursitis	1	1(0.8%)	1(1)	0(0)	0(0)
Chest pain	1	1(0.8%)	1(1)	0(0)	0(0)
Depression	1	1(0.8%)	1(1)	0(0)	0(0)
Dermatitis	1	1(0.8%)	1(1)	0(0)	0(0)
Device malfunction	1	1(0.8%)	1(1)	0(0)	0(0)
Ecchymosis	1	1(0.8%)	1(1)	0(0)	0(0)
Extension fracture	1	1(0.8%)	1(1)	0(0)	0(0)
Faecaloma	1	1(0.8%)	1(1)	0(0)	0(0)
Flatulence	1	1(0.8%)	1(1)	0(0)	0(0)
Frequent bowel movements	1	1(0.8%)	1(1)	0(0)	0(0)
Gastrointestinal disorder	1	1(0.8%)	0(0)	1(1)	0(0)
Gastrointestinal motility disorder	1	1(0.8%)	0(0)	1(1)	0(0)
Genital pruritus female	1	1(0.8%)	1(1)	0(0)	0(0)
Hematoma	1	1(0.8%)	1(1)	0(0)	0(0)
Headache	1	1(0.8%)	0(0)	1(1)	0(0)
Hypoesthesia	1	1(0.8%)	0(0)	1(1)	0(0)
Implant site discharge	1	1(0.8%)	1(1)	0(0)	0(0)
Implant site effusion	1	1(0.8%)	1(1)	0(0)	0(0)
Implant site erythema	1	1(0.8%)	1(1)	0(0)	0(0)

Adverse Events Preferred Term	Number of Events (Cumulative)	Number (%) of Patients (Cumulative) (n=120)	Number of Events (Number of Patients) (≤ 1 year)	Number of Events (Number of Patients) (1 - 2 years)	Number of Events (Number of Patients) (> 2 years)
Implant site irritation	1	1(0.8%)	0(0)	1(1)	0(0)
Implant site swelling	1	1(0.8%)	1(1)	0(0)	0(0)
Incision site complication	1	1(0.8%)	1(1)	0(0)	0(0)
Insomnia	1	1(0.8%)	1(1)	0(0)	0(0)
Nausea	1	1(0.8%)	1(1)	0(0)	0(0)
Pyrexia	1	1(0.8%)	1(1)	0(0)	0(0)
Rash	1	1(0.8%)	1(1)	0(0)	0(0)
Rectal discharge	1	1(0.8%)	1(1)	0(0)	0(0)
Sacral pain	1	1(0.8%)	1(1)	0(0)	0(0)
Sciatica	1	1(0.8%)	1(1)	0(0)	0(0)
Sensation of heaviness	1	1(0.8%)	1(1)	0(0)	0(0)
Sensory disturbance	1	1(0.8%)	0(0)	0(0)	1(1)
Tenderness	1	1(0.8%)	1(1)	0(0)	0(0)
Toe deformity	1	1(0.8%)	1(1)	0(0)	0(0)
Vaginal pain	1	1(0.8%)	1(1)	0(0)	0(0)
Vomiting	1	1(0.8%)	1(1)	0(0)	0(0)
Vulvovaginal discomfort	1	1(0.8%)	1(1)	0(0)	0(0)
Wound	1	1(0.8%)	1(1)	0(0)	0(0)
Wound complication	1	1(0.8%)	1(1)	0(0)	0(0)
Total	237	88(73.3%)	182(78)	33(26)	22(17)

Note: The total number of patients may not add across rows, as the same patient may have experienced the same type of event more than once; similarly the total number of patients may not add down columns, as the same patient may have experienced more than one type of event.

Serious Adverse Events

Device or therapy related serious adverse events that occurred post implant are provided in Table 5.

Table 5: Device or Therapy Related Serious Adverse Events Post Implant

Adverse Event Preferred Term	Number of Serious Events	Number (%) of Patients (n=120)
Implant site infection	6	5 (4.2%)
Implant site pain	4	3 (2.5%)
Seroma	3	3 (2.5%)
Implant site erosion	2	2 (1.7%)
Defecation urgency	1	1 (0.8%)
Lead migration/dislodgment	1	1 (0.8%)
Therapeutic product ineffective	1	1 (0.8%)
Urinary retention	1	1 (0.8%)
Urinary tract infection	1	1 (0.8%)
Total	20	13 (10.8%)

Note: The total number of patients may not add down columns, as the same patient may have experienced more than one type of event.

Surgical Injury

No surgical injuries were reported during the implant procedure or during any subsequent revisions, replacements, or explants.

Surgical Revisions

Out of 120 patients implanted with the InterStim system, 22 had at least one revision or replacement. In addition, 14 patients (11.7%) had their InterStim Systems explanted. Six (6) were explanted due to lack of effectiveness, two (2) for skin erosion, two (2) for implant site infection, one (1) for recurrent seroma, one (1) for implant site pain, one (1) for untreatable diarrhea, and one (1) was explanted to undergo an MRI secondary to an adrenal mass. The probability of the patient needing surgical revision (including device replacement) was 10% at 12 months and 17% at 24 months.

2. Effectiveness Results

The effectiveness of the InterStim Therapy System on incontinence symptoms; number of incontinent episodes per week (primary), number of incontinent days per week (secondary), and urgent incontinent episodes per week (secondary) at 12 months post implant compared to baseline are presented in Table 6.

Using the conservative assumptions (no change from baseline) for patients lost to follow-up or with missing diary data at 12 months post implant (modified worst-case analysis), 73% of patients (88 out of 120) had achieved at least 50% reduction in incontinent episodes per week. With per-protocol analysis, where only patients with complete data at baseline and at 12-months were evaluated, 83% of patients (88 out of 106) had achieved at least 50% reduction in incontinent episodes per week.

Table 6: Success Rates at 12-Months Post Implant

Effectiveness Outcome	Intent-to-Treat (Modified Worst-Case) Analysis (95% confidence level) (n=120)	Per-Protocol (Completers) Analysis (95% confidence level) (n=106)
≥50% reduction in incontinent episodes per week from baseline	**73% (64%, 81%) (88/120)**	**83% (74%, 90%) (88/106)**
≥50% reduction in incontinent days per week from baseline	73% (64%, 81%) (88/120)	83% (74%, 90%) (88/106)
≥50% reduction in urgent incontinent episodes per week from baseline	71% (62%, 79%) (85/120)	80% (71%, 87%) (85/106)

Secondary endpoints of incontinent days per week and urgent incontinent episodes per week also show significant improvement in both Intent to Treat and Per-Protocol groups.

Table 7 shows the average number of incontinent episodes per week, the average incontinent days per week, and the average urgent incontinent episodes per week as reported by patients at baseline and at 12-months post implant.

Table 7: Fecal Incontinence Symptoms at Baseline and 12-Months Post Implant

	Intent-to-Treat (Modified Worst-Case) Analysis (n=120)		Per Protocol (Completers) Analysis (n=106)	
Fecal Incontinence Symptoms	Baseline	12-Months	Baseline	12-Months
Average incontinent episodes per week	9.4	3.1	9.2	1.9
Average incontinent days per week	4.5	1.5	4.5	1.1
Average urgent incontinent episodes per week	5.0	1.7	4.9	1.2

Table 8 shows categorized percent improvement in incontinent episodes per week from baseline to 12-months post implant. With the intent-to-treat (modified worst-case) analysis, 35.8% of patients achieved full continence of bowel movements, and with the per protocol (completers) analysis, 40.6% achieved full continence.

Table 8: Improvement Categories (Incontinent Episodes Per Week).

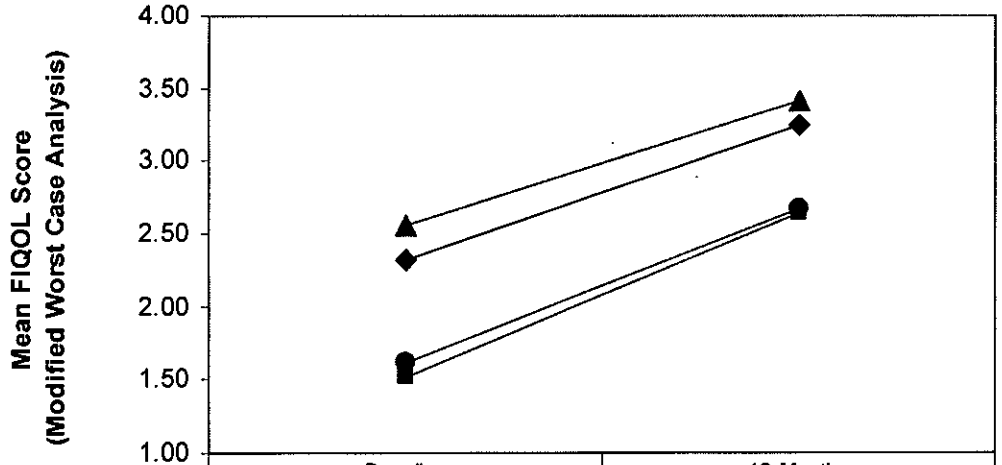
	Intent-to-Treat (Modified Worst-Case) Analysis (n=120)		Per Protocol (Completers) Analysis (n=106)	
Improvement Categories (Incontinent Episodes Per Week)	Number of Patients	Percent of Patients	Number of Patients	Percent of Patients
100%	43	35.8%	43	40.6%
75% - 99%	30	25.0%	30	28.3%
50% -74%	15	12.5%	15	14.2%
1% - 49%	10	8.3%	10	9.4%
≤ 0%*	22	18.3%	8	7.6%

* This includes 14 patients who did not complete the 12 month bowel diary; therefore, their baseline bowel diary was used as their 12 month bowel diary and thus did not show a decrease in bowel episodes per week.

Improvement in Quality of Life (Secondary Endpoint)

Patients implanted with the InterStim system reported improvements in various aspects of their quality of life. To evaluate these improvements, patients completed questionnaires that measured their quality of life, perception of bowel health, and severity of their fecal incontinence. As shown in Figure 3, patients reported significant improvement in their quality of life at 12 months. This included lifestyle, coping/behavior, depression/self-perception, and embarrassment. Patient perception of their bowel health, on average, doubled from baseline to a more favorable state at 12 months. Additionally, the leakage of gas, mucus, liquid and solid stool showed a significant decrease at 12 months. Use of minipads/panty liners and other forms of protective undergarment was significantly reduced during the follow-up period.

Figure 3: Twelve Month Fecal Incontinence Quality of Life Results (n=120)



	Baseline	12-Months
Scale 1 - Lifestyle	2.32	3.24
Scale 2 - Coping/Behavior	1.52	2.64
Scale 3 - Depression/Self-Perception	2.55	3.41
Scale 4 - Embarrassment	1.62	2.67

Additional Evaluations

Anorectal manometry was performed at baseline and each post implant follow-up to assess maximal mean resting pressure and maximal mean incremental squeeze pressure. Significant improvement in fecal incontinence symptoms were observed without improvement in these specific anal manometry parameters.

3. Subgroup Analyses

As a supporting analysis, a logistic regression model was performed to examine the effect of baseline covariates: type, etiology and duration of fecal incontinence, and prior surgery related to bowel problems. Using a stepwise regression procedure, the final model adjusted for duration of fecal incontinence history, etiological cause of fecal incontinence (obstetric trauma vs. post-surgical), etiology (other vs. post-surgical), type of incontinence (other vs. urge and passive vs. urge), and presence of internal anal sphincter defect. Only internal anal sphincter (IAS) defect was significantly associated with outcome in this multiple regression model.

The presence of an IAS defect often implies that an obstetric tear has extended through the external anal sphincter (EAS) to involve the IAS. A disruption of the IAS may indicate a more severe injury. Based on a per-protocol (completers) analysis, the success rate among 20 patients with an IAS defect was 65%, compared to 87% among the 86 patients without an IAS defect. This suggests that the presence of an IAS defect may be associated with reduced success;

nonetheless, more than half of the patients (65%) with severe sphincter defect were still able to demonstrate effectiveness with the InterStim system.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Gastroenterology and Urology Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel (P970004).

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

There were 237 device- or procedure- related adverse events reported in 88 (73.3%) of the 120 implanted patients. The majority of the events resolved non-invasively either with reprogramming or with administration of medications. Twenty events in 13 patients were considered serious; defined by the sponsor as requiring hospitalization for over 24 hours.

Twenty two (22) patients (18.3%) underwent surgery to revise or replace the entire system or one of the components and 14 patients (11.7%) had the entire system explanted. Even though the probability of a patient needing a surgical revision (including device replacement) was 10% at 12 months and 17% at 24 months, the effectiveness of the InterStim System is substantial with 35.8% of patients (43 out of 120) gaining complete continence and 73% of patients (88 out of 120) h having at least a 50% reduction in incontinence episodes per week. There are really no other treatment options for the patient population that would be eligible for this therapy since patients can only undergo InterStim therapy if they have failed or are not candidates for more conservative treatments.

B. Effectiveness Conclusions

Of the 120 implanted patients, none experienced a surgical injury during implantation. The effectiveness of the device was demonstrated with over 73% of patients reducing the total number of incontinence episodes per week by at least 50%. At least 35.8% of patients reported being fully continent at 12 months.

C. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. There were no device- or procedure-related deaths or permanent injuries reported in this study. The adverse events seen in the study were consistent with the events seen in the clinical studies for the urinary incontinence indications. The primary effectiveness endpoint of at least a 50% reduction in incontinent episodes at 12 months post implant in at least 50% of the patients was met. Based on the risks and benefits observed in the clinical study, the

PMA for the Medtronic InterStim Therapy System for fecal incontinence should be approved.

D. CDRH DECISION

CDRH issued an approval order on March 14, 2011. The final conditions of approval cited in the approval order are described below.

The applicant agreed to continue follow-up of the patients enrolled in the premarket InterStim trial for five years. This post-approval study will continue to gather long-term performance data from the patients currently enrolled in the clinical trial (G010206). The post-approval study will be called the "InterStim Sacral Nerve Stimulation Therapy for Bowel Control: **F**ecal **I**ncontinence **P**ost **A**pproval **S**tudy (**FI-PAS**). The primary objective is to continue evaluation of incontinent episodes per week at yearly intervals through five years post-implant. Device and/or therapy related adverse events will be characterized through five years post implant. Secondary objectives to be evaluated include:

- Evaluation of the patient's quality of life at yearly intervals using the Fecal Incontinence Quality of Life (FIQOL) instrument through five years post implant;
- Evaluation of the number of incontinent days per week at yearly intervals through five years post implant;
- Evaluation of the number of urgent incontinent episodes per week at yearly intervals through five years post implant through five years post implant.
- Evaluation of the severity of the patient's fecal incontinence through completion of the Fecal Incontinence Severity Index (FISI) at yearly intervals through five years post implant;
- Evaluation of the patient's perception of their fecal incontinence through completion of the self-rated bowel health questionnaire at yearly intervals through five years post implant; and
- Evaluation of the severity of the patient's fecal incontinence through the documentation of pad use at yearly interval through five years post implant.

The applicant agreed to conduct two sets of analysis; the per-protocol (completers) analysis and the adjusted worst-case analysis. The per-protocol analysis will include only those patients who have bowel diaries at the follow-up visits in the analysis.

The adjusted worst case analysis is an intent-to-treat analysis which imputes missing data as follows:

- For patients who exit the study and/or have the device explanted due to a device or therapy related adverse event or due to lack of effectiveness or due to a death, their baseline diaries will be used as their follow-up data and therefore they will be considered failures.

- For patients who exit the study due to other reasons (i.e., site closure, patient-related adverse event, voluntary withdrawal from the study), and for patients who miss a study visit or fail to provide a bowel diary at the scheduled visit, the last-observation carried forward method will be used to impute the missing data.

The applicant's manufacturing facilities were inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

E. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

F. REFERENCES

1. Rockwood TH, Church JM, Fleshman JW, et al. Fecal Incontinence Quality of Life Scale: quality of life instrument for patients with fecal incontinence. Dis Colon Rectum. Jan 2000;43(1):9-16; discussion 116-17.

2. Rockwood TH, Church JM, Fleshman JW, et al. Patient and surgeon ranking of the severity of symptoms associated with fecal incontinence: the fecal incontinence severity index. Dis Colon Rectum. Dec 1999;42(12):1525-1532.