A PHASE II Study of Sacral Nerve Stimulation for Low Anterior Resection Syndrome or Fecal Incontinence in Patients Following a Low Anterior Resection or Proctectomy with Coloanal Anastomosis or in Patients after Pelvic Chemoradiation (RESTORE)

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Principal Investigator:
Craig A. Messick, MD

Collaborators:
Department of Surgical Oncology:
George Chang, MD, MS
John Skibber, MD
Miguel Rodriquez-Bigas, MD
Nancy You, MD
Barry Feig, MD
Brian Bednarski, MD

Department of Radiation Oncology:
Prajnan Das, MD

Department of Medical Oncology:
Van Karlyle Morris, MD

Department of Gynecologic Oncology:
Nicole Fleming, MD
Kathleen Schmeler, MD

Department of Urology:
Ouida L. Westney, MD

Department of Biostatistics:
Rebecca S. Slack

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1. OBJECTIVES

Primary Objectives

1. To investigate the efficacy of sacral nerve stimulator placement in patients with fecal incontinence (FI) or low anterior resection syndrome (LARS) who have previously undergone chemoradiation treatment (XRT) and/or a restorative partial or complete proctectomy with colorectal or coloanal anastomosis for cancer treatment as per standard of care (restorative surgery cohort).

2. To evaluate the feasibility of sacral nerve stimulator placement in patients with fecal incontinence (FI) or other defecatory dysfunction who have received pelvic radiation treatment without undergoing rectal or other pelvic surgery as per standard of cancer care (radiation only cohort).

Secondary Objectives

1. To evaluate the effectiveness of sacral nerve stimulation (SNS) as measured by validated questionnaires in patients with FI or LARS within both patient cohorts.
2. To evaluate pelvic floor and sphincter physiology using anorectal manometry (ARM) before and after SNS in patients with FI or LARS within both patient cohorts.
3. To assess potential impact of SNS on urinary incontinence measuring a post-void urinary bladder residual and validated urinary symptom questionnaires in both patient cohorts.
4. To assess efficacy of SNS on long-term bowel dysfunction at 1 and 3 years post battery implantation as measured by validated questionnaires for both patient cohorts.

2. BACKGROUND AND RATIONALE

Development of FI and LARS after Surgery

Post-operative bowel dysfunction, specifically fecal incontinence (FI) and the low anterior resection syndrome (LARS), characterized by a change in bowel habits including urgency, alternating diarrhea and constipation, fragmentation, obstructive defecation and stacking, affects up to a reported 90% of patients following rectal surgery and is debilitating.[1, 2] The development of FI and LARS is likely complex and proposed mechanisms include internal anal sphincter dysfunction through injury or transection of sympathetic and parasympathetic pelvic nerves,[3-5] decreased anal canal sensation leading to loss of discrimination of feces from flatus,[6, 7] post-surgical loss of the rectal-anal inhibitory reflex (RAIR) due to disruption in nitric oxide signaling pathways from pelvic nerve injury,[8, 9] and loss of both compliance and reservoir capacity of the neorectum.[10, 11] Although historical primary treatment typically consists of fiber and dietary adjustments, alternate treatment options including pelvic floor physical therapy (biofeedback/pelvic floor rehab), anal sphincter repair, and frequent colonic irrigation, outcomes remain variable and are not readily available for all patients. An alternative treatment for FI, sacral nerve stimulation (SNS), was first reported in 1995.[12] Originally FDA

approved for voiding dysfunction (urinary frequency, urgency, urge incontinence and non-obstructive urinary retention), it has since been approved for use in patients with FI and now accepted as a promising alternative compared to previous strategies including an end colostomy for patients with benign disease causes for FI and LARS. For FI and LARS, SNS works through somatic afferent fibers enhancing anal sensation [13], which alters rectal and anal smooth muscle activity and facilitates external sphincter contraction [14] resulting in increased resting pressure and voluntary contraction of the rectum, reduction in the initial pressure for first sensation and urge to defecate, and a reduction in the rectal volume for urge sensation [15].

Current Methods of Symptoms Control

Historical management of FI has been ingestion of bulk-forming dietary foods including oatmeal, bananas, cheeses, and peanut butter. Additional therapy for LARS included additional Metamucil, a supplemental fiber taken as a slurry or as a dry wafer and used to absorb additional water essentially bulking the stool. For persistent uncontrolled bowel habits, the additions of Imodium or Lomotil have been included as primary medical options. Despite these treatments, patients may experience uncontrolled bowels and are unable to leave the house due to erratic and unpredictable bowel patterns. Physical therapy for the pelvic floor, or biofeedback, has been reportedly successful in improving bowel dysfunction in patients with FI, but compliance is low.[1] Best results are reported when patients complete six therapy sessions with a reported 10x greater odds ratio of success compared to those who fail to complete therapy.[16] While the majority of patients are women with prior vaginal deliveries, vaginal tears, or pelvic floor surgery including hysterectomy, very few studies report efficacy of biofeedback following rectal surgery. In the few publications, which are largely small studies, improvement in anal sphincter tone measured by anorectal manometry, episodes of FI, and frequency of bowel movements were all reported.[17-19] For FI due to sphincter defects from prior trauma, episiotomies or tears during labor, surgical repair by an overlapping sphincteroplasty is difficult to master and lacks sustainable long-term results. As a last resort, surgical removal of the anal canal may be considered and patients live with an end colostomy.

Use of a Sacral Nerve Stimulator in Patients with FI, LARS, and Urinary Incontinence

Early studies specifically excluded patients with rectal cancer and those with chemoradiation therapy, and though they reflected a very small group of patients with FI, outcomes were favorable decreasing median incontinence episodes per week from 7.5 to 0.67 and median incontinence days from 4 per week to 0.5 with sustained long-term results[1, 16-20] Although urinary symptoms were present in 40% of this patient population, the pre-SNS symptoms and responses have not been objectively quantified with a validated urinary-specific questionnaire. The largest study assessing SNS for FI was by Wexner *et al*, which included 14 US institutions and two international sites (Canada and Australia). They reported on 120 patients with a median follow-up of 28 months (range 2.2-69.5) with patients completing bowel diaries and FI questionnaires in 94% and 96%, respectively.[21] The authors defined success as ≥50% improvement from baseline FI questionnaires and stool diaries, and has been accepted as the

marker for success with SNS. They reported an 83% success rate at 12 months, 85% at 2 years, and 87% at 3 years, $p<0.0001$.[21] Similar quality of life improvements were also reported. The results were significant and since its publication, the SNS procedure has become the favored surgical technique for FI in patients without prior pelvic radiation or rectal cancer.

Despite the paucity of literature, reports of FI have certainly been reported following radiation alone and include radiation for cancers of the prostate, anal canal, and gynecologic organs (uterus, cervix, vagina, and vulva). In 2012, Barraclough *et al* reported fecal urgency and FI at 3 years post radiation treatment in 69% (40% daily) and 18%, respectively.[22] Additionally, a systematic review of FI in radiation-treated prostate cancer in 2011 reported soiling and FI occurred in 58% and 57%, respectively.[23] With regard to anal cancers (mostly squamous cell carcinoma), symptoms reported after completion of chemoradiation included fecal leakage (22%), difficulty controlling flatus (50%), daily use of a pad for accidents (39%), dietary adjustment to assist with control of bowels (35%), and significant daily lifestyle impairment (29%).[24] Unfortunately, there are no published data of the use of SNS for FI or other defecatory dysfunction following radiation treatment without surgery.

Rationale: FI and LARS are often debilitating and recalcitrant to current medical therapies including medicinal and biofeedback. A recent systematic review of the literature for patients with FI or LARS and who underwent SNS placement following chemoradiation and surgery for rectal cancer reported data on 42 patients from 7 articles with promising results. Ramage *et al* reported an overall permanent implantation rate of 79.1% with the lowest reported at 47%.[25] The efficacy of SNS in these few patients revealed significant decrease in nocturnal defecation from 3 (pre-SNS) to 0.5 (post-SNS) episodes/night, decrease in incontinence from 7 (pre-SNS) to 0.2 (post-SNS) episodes/day episodes, and 67% of patients reported complete resolution of LARS (fragmented defecation, urgency, or soiling).[25] The majority of literature specifically excluded patients with cancer and although reported in 42 patients following rectal cancer treatment (chemoradiation and surgery), this study aims to prospectively evaluate the efficacy of SNS placement in cancer patients who have undergone pelvic combined chemoradiation therapy for their rectal cancer treatment followed by a restorative proctectomy with either a low colorectal or coloanal anastomosis who exhibit subsequent significant, debilitating FI or LARS with or without urinary symptomatology. Additionally, we aim to assess the feasibility of SNS placement in patients who have developed FI or defecatory dysfunction (including urgency and leakage) following radiation treatment without surgery for cancers including anus, prostate, uterus, cervix, vagina, and vulva as this has not been reported.

The results of this study will be useful in the management of patients with bowel dysfunction either from FI or LARS following restorative rectal cancer surgery expanding available treatment alternatives including SNS. Future directions from this study include expansion of the patient population for a phase 2 trial and include an efficacy arm for patients treated with pelvic radiation without surgery including anal, gynecologic and urological malignancies.

3. PATIENT ELIGIBILITY

Cohort 1: Restorative surgery cohort

Inclusion Criteria:

1. Patients with pathologically proven diagnosis of primary rectal cancer
2. Patients who have previously undergone surgical resection and anastomosis (restorative) with curative intent treatment with or without chemoradiation
3. Patients treated with restorative surgical resection without radiation
4. Patients with any T-stage or N-stage rectal cancer that underwent treatment with radiation and restorative surgery
5. Patients with self-reported FI or LARS
6. Patients must be at least 18 years old and be able to speak and understand English
7. Patients must be willing to and able to sign an approved informed consent document
8. Patients must be ≥ 24 months post-resection of rectal cancer
9. Patients must have failed prior conservative measures such as Metamucil and motility medications and already been assessed and treated in a pelvic floor rehabilitation program (biofeedback) designed to treat FI and LARS, and continue to experience significant defecatory dysfunction, allowable per PI discretion.
10. Patients must be willing and able to complete Patient Reported Outcomes Questionnaires for before device placement, during the testing phase following lead placement, and after implantation of the battery
11. Patients must be willing and able to undergo elective ARM testing to measure pelvic floor function
12. Patients who have an average resting tone <40mmHg (normal >40mmHg) and maximal tolerance <200 milliliters (normal 200-300 milliliters) as measured by ARM

Exclusion Criteria:

1. Patients with co-morbid illnesses or concurrent disease, which in the judgment of the clinician obtaining informed consent, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens
2. Any diverting bowel ostomy at the time of consent to this study
3. Patients with an ANC <1.7, INR >1.3, platelet count <50K within 30 days of consent
4. Patients currently being treated with chemotherapy or within preceding 30 days at the time of consent
5. Patients previously treated with a SNS for urinary or FI
6. Patients who were documented to have an anastomotic leak following their restorative surgical resection
7. Patients with an ECOG performance status >2 at the time of consent
8. Patients with an active infection requiring systemic therapy at the time of consent

9. Patients with a significant history of uncontrolled cardiac disease including, but not limited to hypertension, unstable angina, myocardial infarction within the last 4 months, and uncontrolled congestive heart failure

Cohort 2: Radiation only cohort

Inclusion Criteria

1. Patients with pathologically proven malignancy of the pelvis, other than rectal cancer (e.g. prostate, bladder, anus, vagina, vulva, cervix, uterus, or ovary)
2. Patients treated with standard of care radiation therapies without surgical resection
3. Patients with self-reported FI or other defecatory dysfunction
4. Patients must be at least 18 years old and be able to speak and understand English
5. Patients must be willing to and able to sign an approved informed consent document
6. Patients must be ≥ 18 months post-pelvic chemoradiation
7. Patients must have already been assessed and treated in a pelvic floor rehabilitation program design to treat FI or other defecatory dysfunction and continue to experience significant defecatory dysfunction
8. Patients must be willing and able to complete Patient Reported Outcomes (PROs) and bowel and bladder diaries (Medtronic) at multiple times during the study
9. Patients must be willing and able to undergo elective ARM testing to measure pelvic floor function
10. Patients who have an average resting tone <40mmHg (normal >40mmHg) and maximal tolerance <200 milliliters (normal 200-300 milliliters) as measured by ARM

Exclusion Criteria

1. Co-morbid illnesses or other concurrent disease, which in the judgment of the clinician obtaining informed consent, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens
2. Patients with an ANC <1.7, INR >1.3, platelet count <50K, within 30 days of consent
3. Patients currently being treated with chemotherapy or within the preceding 30 days at the time of consent
4. Patients previously treated with a sacral nerve stimulator for urinary or fecal incontinence
5. Patients with an ECOG performance status >2 at the time of consent
6. Patients with an active infection requiring systemic therapy at the time of consent
7. Patients with a significant history of uncontrolled cardiac disease including, but not limited to hypertension, unstable angina, myocardial infarction within the last 4 months, and uncontrolled congestive heart failure
8. Patients with an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or

resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study

4. STUDY DESIGN

This study has two cohorts: 1) a restorative surgery cohort evaluating the efficacy of SNS for FI or LARS in patients who have previously undergone restorative partial or total proctectomy for treatment of rectal cancer with or without radiation as per standard of cancer care and 2) a radiation only cohort assessing the feasibility of SNS in patients treated with radiation without surgical intervention for treatment of a pelvic cancer, other than rectal cancer, as per standard of care, that developed FI or other defecatory dysfunction.

5. STUDY METHODS

Patient Selection

Both study cohorts will be evaluated and managed at the same. Total accrual to this study is 66 patients for enrollment of 60 evaluable patients to the study, 30 patients into each cohort, at the UT MD Anderson Cancer Center (UTMDACC) in Sugar Land, Texas. Patients meeting study eligibility will be screened prospectively in relevant UTMDACC clinics, which are a likely source of patients to be identified for screening, or through physician referral to the study.

Study Enrollment

All patients will undergo a complete history and physical, per routine standard of care. Patients disclosing FI or LARS will sign consent and be pre-registered on the study in CORe for screening and will complete questionnaires (on paper, over the phone/teleconference system, or electronically through REDCap) related to general quality of life, FI severity, and LARS. Patients may access the questionnaires electronically in the REDCap system via a link sent to them by email or MyChart (Appendix K). Patients will then undergo an anorectal manometry for pelvic pressure readings per standard of care. Then, patients who disclose appropriate bowel dysfunction (urgency, alternating diarrhea and constipation, fragmentation, obstructive defecation, and stacking) and with abnormal anorectal manometry readings and questionnaire responses indicating study eligibility, will proceed with enrollment in the study. Patients who are found not to meet eligibility based on bowel dysfunction reporting, questionnaire responses and anorectal manometry results will be removed from the study. Patients meeting all eligibility criteria with insurance pre-authorization for all procedures will be enrolled on the study.

Patients on-study with lab results described below before SNS placement will be given 30 days to improve and will be re-evaluated. Patients will have these tests ordered for routine standard of care based on the determination of the physician. If no improvement at 30 days, patients will be taken off study, data collected up to this point may be used in study reporting.

- ANC <1.7, INR >1.3, platelet count <50K

On-study patients requiring systemic therapy for an infection before SNS placement will be given 30 days to improve and will be re-evaluated. If no improvement at 30 days, patients will be taken off study, data collected up to this point may be used in study reporting.

Procedure to Obtain Informed Consent

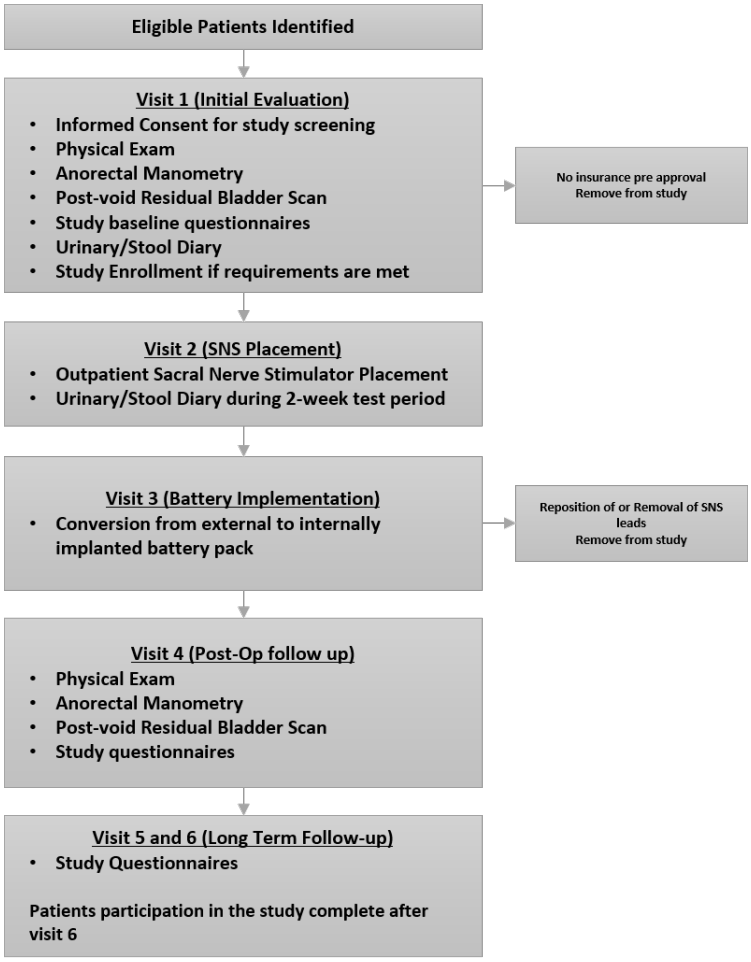
The investigator must obtain documentation of consent from each potential subject prior to participating in a clinical trial.

The protocol and informed consent documentation for this study must conform to institutional regulations and local and national laws and regulations. As soon as a potential subject is considered for this study and prior to any other study procedures, each prospective subject will be given a full explanation of the purpose of the study, the procedures to be carried out and the potential hazards. Once this essential information is provided to the subject and once the Investigator believes that the subject understands the implications of participating in the study, the subjects will be asked to provide written informed consent and authorization to access medical records needed for study documentation. Subjects will be required to read, sign, and date a properly executed written Informed Consent Form prior to enrollment and will be assured that they may withdraw from the study at any time without jeopardizing their medical care. They will be given a copy of their Informed Consent Form.

Patients will either be consented in person, or contacted via phone, or through an Institutionally-approved teleconferencing system (i.e., Zoom) and will complete the consent process through Institutionally-approved remote-consenting procedures.

Study Procedures

After study enrollment, patients will undergo scheduled, elective surgery for placement of the sacral nerve stimulator. The initial surgical placement is performed using fluoroscopy-guidance to place a single electrode through the sacral foramen of nerve root 3 via passage through a needle. The SNS device is self-anchoring and device migration is extremely rare; however, this can be surgically corrected. Stimulator migration rarely affects the device function although it impairs patient quality of life.[26] This technique has been previously described.[10] The electrode is then tunneled under the skin in the soft tissue of the buttocks and out the skin toward the hip where it is then connected to an external battery pack and covered, maintained in a sterile dressing and adjusted over the next 2 weeks by the patient. A bowel and bladder habit diary is maintained by the patients for the interval 2 week period.



After 2 weeks, the patients return to the OR for either removal of the leads if the stimulator did not work, or implantation of a subcutaneous titanium battery with internalization of the electrode as per standard of care. Prior to lead extraction in patients who do not meet criteria for battery implantation, lead position will be re-investigated for appropriate positioning, and if incorrectly positioned due to migration, lead repositioning will be performed and the two week trial period restarted. The patients are discharged home from this outpatient surgery and will complete the bowel and bladder habit diaries. The patients will be required to return to the office at 1 month following their surgery to perform a wound check, symptom evaluation, and again complete study questionnaires (on paper, over the phone/teleconference system, or electronically through REDCap) for comparison, and undergo repeat anorectal manometry and a post-void residual bladder scan.

Validated Questionnaires/Instruments:

1. Fecal Incontinence Quality of Life (FIQoL): this is a quality of life instrument validated for patients with fecal incontinence. This will be provided to all patients.
2. Fecal Incontinence Severity Index (FISI): this is a scoring system validated to objectively quantify fecal incontinence severity. This will be provided to all patients.

3. EQ-5D-5L: This is a general quality of life instrument that is currently used in the GI surgery clinics as part of the prospective rectal cancer study that collects longitudinal quality of life and function outcomes. This will be provided to all patients.
4. Memorial Sloan Kettering Cancer Center Bowel Function Instrument (MSKCC BFI): This is a validated instrument for resected rectal cancer patients designed to assess bowel dysfunction including LARS. This will be provided to patients in the restorative surgery cohort only.
5. Cleveland Clinic Incontinence Score (CCIS): This is a validated instrument for FI specifically in patients whose rectums have not been surgically removed. This will be provided to the radiation only cohort patients.
6. Bowel Diary: Validated bowel diary provided by the device company used to collect daily bowel function.
7. Bladder Diary: Validated urinary diary provided by the device company used to collect daily urinary function.
8. International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms (ICIS-FLUTS) if female and International Continence Society Male Short Form (ICSmaleSF) if male: Validated instruments to measure urinary dysfunction.
9. Low Anterior Resection Syndrome (LARS) Bowel Function Questionnaire: This is a validated instrument, to be provided only to the restorative surgery cohort, designed to assess clinical severity of symptoms of LARS outside of just FI and will be a significant tool to address extending criteria for SNS use outside of FI.
10. EORTC QLQ-CR29: this is a quality of life instrument validated for patients with colorectal cancer. This will be provided to all patients.

Study Visits

Initial Evaluation/Visit 1: Patients are referred to the clinic for reported refractory FI or LARS. Upon arrival to their initial clinic visit, the patients will complete the validated questionnaires and instruments (on paper, over the phone/teleconference system, or electronically through REDCap), as well as an ARM. A minimum score from the FISI will not be required as this was not required for the initial studies in the benign disease patients, though it is anticipated that their scores will be around a score of 30, a number defined as what is typical for patients who have a significant quality of life impairment due to their reported fecal incontinence. The results will then be reviewed for appropriateness to be considered eligible for the study. Patients will sign consent and then be enrolled after appropriate evaluation by the clinical and research teams and all inclusion and exclusion criteria are met. The remaining questionnaires will be completed and a complete review of symptoms and physical exam will be performed per standard of care. A post-void residual bladder scan will be performed at this visit after enrollment as well. After all objective data are collected, each patient will be scheduled for surgery for placement of a sacral nerve stimulator under general anesthesia in the operating room as per standard of care. All patients are asked to begin recording all daily bowel and bladder habits in the bowel and bladder

trackers to serve as their baseline function. Necessary preoperative testing will be ordered and completed at UTMDACC including appropriate consultant visits as per standard of care for any operation.

Visit 2 (Sacral Nerve Stimulator Lead Placement): Surgery for stage 1 sacral nerve stimulator placement will occur within 30 days after enrollment in the study. The patient will arrive at the pre-operative holding areas at UTMDACC's main campus for their outpatient surgery. The representative for the implantable SNS company (Medtronic) will be present at the operation for assistance with placement of the leads per standard of care and for assistance with patient education following lead placement. The patients are sent home with a diary to record daily bowel and bladder habits during the interval period.

Visit 3 (Assessment of Symptoms and Battery Implantation or Lead Removal): Surgery for stage 2 sacral nerve stimulator battery implantation or lead removal will occur around 2 weeks (+7 days) after SNS placement. The patient will arrive to the holding area with their post-implantation bowel and bladder habit diary from visit 2. Review of the bowel diary information and a review of symptoms from visit 1 and visit 2 with the patient will be completed and then a decision made to either implant the battery or remove the stimulator leads as per standard of care. If the bowel diary reveals ≥50% decrease in FI or LARS symptoms between visit 1 and visit 2, the external temporary battery will be replaced with an implantable battery. If the bowel diary reveals <50% decrease in FI or LARS symptoms, the previously placed leads and external battery will be evaluated for proper positioning and functioning in the OR and removed if they remain properly positioned. Following the procedure, the patient is discharged home. If the device is removed, their participation in the study is complete, but data collected to this point will still be used in study analysis and reporting.

Visit 4 (Post-operative Assessment): Post-operative evaluation. The patients return to clinic at 1 month (+/- 2 weeks) after completion of visit 3 for a wound evaluation, device check, and symptom review. At this point, the patients will complete study questionnaires (on paper, over the phone/teleconference system, or electronically through REDCap) and undergo a repeat ARM.

Visits 5 (1-Year Follow Up) and 6 (3-Year Follow Up): Patients will return to clinic at 1 and 3 years (+/- 3 months) for evaluation, per routine standard of care, from their SNS battery for evaluation. Patients will again complete validated questionnaires (on paper, over the phone/teleconference system, or electronically through REDCap) at this visit. After collection of this data, their participation in this study is complete. If for any reason patients are not able to return to the clinic at these time points, study questionnaires may be filled out via mail or over the phone/teleconference system, or electronically through REDCap.

Table 1. Study Assessment Calendar

	Initial Evaluation/ Visit 1	**Visit 2 (+ 4 weeks)**	**Visit 3 (+ 7 days)**	**Visit 4 (+/- 2 weeks)**	**Assessment at 1 and 3 years***

Physical exam + anorectal manometry + Post-void residual Bladder scan	X			X	
SNS Lead Placement		X			
Battery Implantation or Lead Removal			X		
FIQoL and FISI Instrument	X			X	X
MSKCC Bowel Function Instrument	X			X	X
LARS Score Questionnaire	X			X	X
EORTC QLQ-CR29	X			X	X
Cleveland Clinic Incontinence Score Instrument	X			X	X
EQ-5D-5L Instrument	X			X	X
ICSmaleSF or ICIS-FLUTS (as appropriate) Instrument	X			X	X
Bowel/Bladder Diary	X	X			
Adverse Events**			X		

* +/- 3 months

** See Section 7. Risk Management

Clinical Data Collection

Data regarding patients, tumors, treatments, and disease/vital status will be obtained from existing medical records. Patient data collected will include, but is not limited to: demographic information, lab values, comorbidities and medical history, medications, test results (i.e., EKG). Tumor data collected will include, but is not limited to: site, stage, histology, distance from anal verge, histologic grade, clinical TNM stage, method of clinical stage, tumor size, biomarker status (e.g., microsatellite status, KRAS, BRAF mutation status, etc.) as available. Treatment data for the primary cancer diagnosis will be collected including chemotherapy and radiation regimens as well as surgical procedures, complications and outcomes. Clinical data will be collected until the patient is taken off study.

6. STATISTICAL CONSIDERATIONS

6.1. Summary Statement

Patients will be in one of 2 cohorts, those receiving 1) curative intent surgical resection of primary rectal cancer or 2) radiation therapy without surgical resection for treatment of

pelvic cancer, other than of the rectum. For the patients who have had surgical resection, preliminary safety and efficacy data exist so this will be an efficacy trial confirming the preliminary data. For patients who were treated with XRT only, this is a preliminary trial to establish safety and provide a first estimate of efficacy. In this initial study, stratification based on type of radiation, method and/or dose will only be conducted in a hypothesis generating manner to explore future trial options if battery implantation rates are extremely low in cohort 2. While the methods will be carried out the same, the level of evidence for conclusions at the end of the trial will be different for each.

6.2. Analysis Subgroups

All patients who sign consent and take the visit 1 questionnaires, and do not have insurance denial as the reason for no SNS placement, will be considered evaluable for this study. Patients who return for their SNS placement appointment will be included in analyses of the endpoints.

6.3. Endpoints

Primary Endpoints

The primary endpoint is SNS Success. *SNS Success* will be measured as a patient having the battery implanted at visit 3 which can only happen if they've achieved improvement in fecal incontinence at visit 3. Patients who do not have the SNS placed, for any reason other than insurance coverage issues, will count as not having a success.

Fecal incontinence will be measured by the physician as the total number of gas, mucus, liquid stool, and solid stool accidental leakage events reported in the bowel diaries. *Improvement* will be determined *by the physician based on* bowel diary comparisons recorded before SNS lead placement at visit 1 to after lead placement at visit 2. This is done at visit 3 when the patient presents for consideration of placement of the implantable battery. Any patient who comes in for SNS placement but the SNS cannot be successfully placed for any reason other than insurance reasons will count as not having improvement. Patients meeting this improvement will have their *battery implanted.* Patients will be counted as having their battery implanted if it is implanted at Visit 3 if they had the SNS placed at Visit 2.

Secondary Endpoints

- **FISI** overall questionnaire summary
- **FIQOL** overall questionnaire summary
- **ARM** score
- **EQ-5D-5L**
- **ICSmaleSF** or **ICIS-FLUTS** (females)
- **MSKCC BFQ (for restorative surgery cohort)**
- **LARS Score Bowel Function Questionnaire (for restorative surgery cohort)**

- **CCIS (for radiation only cohort)**
- **Bowel Diaries**
- **Bladder Diaries**
- **EORTC QLQ-CR29**
- **FISI, FIQOL, EQ-5D-5L, ICSmaleSF or ICIS-FLUTS, MSKCC, EORTC QLQ-CR29 and CCIS will also be collected at 1 and 3 years for long-term evaluation.**

6.4. Sample Size

Up to 30 patients will be entered in each cohort, monitored after every 6 patients according to the interim analyses plans below. The selection of 30 patients per cohort combines feasibility of accrual and operating characteristics of the decision rules. If a cohort accrues to full size and has a 50% SNS success rate (15/30) then the 90% credible interval using a prior of beta(1,1) would be (35.7%, 64.3%). Patients who complete baseline measures and sign consent but who are not able to undergo SNS implant for insurance issues will not be evaluable for this study. Accrual numbers have been inflated by 10% to allow for unevaluable patients taken off study for a total study enrollment of up to 66 patients to have an evaluable 60 patients.

6.5. Interim Analyses

A Bayesian sequential monitoring design (Thall et al. 1995 and 1998)[27, 28] will be used to monitor the trial for response and adverse events. Interim assessments will be performed in groups of 6 patients, with accrual held for evaluation for each cohort until enough information is available to determine the outcome. Each patient cohort will be evaluated separately and will continue if patients are exhibiting reasonable adverse event rates and SNS response rates. If one cohort stops, the other cohort will continue according to the monitoring rules. Calculations were performed in MultcLean Desktop version 2.1.0.

Interim Analyses for Futility

A patient will be considered to have SNS success as defined above. The patient cohort will be stopped early if $Pr[\theta_S < 0.50 \mid data] > 0.95$, where θ_S denotes the SNS success rate. That is, given the outcomes from the patients who have already been evaluated, if it is determined that there is a more than 95% chance that the response rate is less than 50% (constant), the arm will be stopped for futility. Assuming a prior distribution of θ_S for each experimental treatment of ~beta(1,1), pre-defined stopping boundaries corresponding to this probability criterion are provided in the following table.

If there are this many patients evaluable for SNS success	6	12	18	24	30*
Stop the cohort if there are this many or fewer SNS successes	0	3	5	7	10

* The cohort will stop at 30 regardless of the number of SNS successes, but if there are 10 or fewer, then the implant is not promising enough for future trials in this patient cohort.

Assuming the cohort does not stop for adverse events first, 6 patients will be accrued. If none of the 6 patients have SNS success, stop the cohort and the implant will be declared as ineffective for this population. Patients will continue to be enrolled on the other cohort as long as it is open. If there is at least 1 success, the next 6 patients will be entered in the cohort, unless they need to stop according to the adverse event boundaries below. Continue checking after every 6 patients for sufficient SNS success assuming the trial does not stop for adverse events first. The operating characteristics for efficacy and adverse events are summarized after the adverse event rules below.

Interim Analyses for Safety

Under the same model described for SNS success, adverse events will be monitored assuming an *a priori* probability of limiting adverse events following Beta(0.6, 1.4) in the current patient cohort. Cohort limiting events (CLE) are defined as perioperative cardiovascular events, readmission if it is related to the SNS procedure, SNS lead removal due to any reason other than failure, or perioperative death due to surgery or complications. The patient cohort will be terminated if Prob(CLE> 0.30 | data) > 0.95. The specific rules for stopping after each cohort are included in the table here.

If there are this many patients (or more) with CLE	5	7	9	12	14
Stop the patient cohort if there are this many (or fewer) patients who are evaluable (have CLE, had battery implant without CLE, or had leads removed for failure without CLE.	6	12	18	24	30*

* The cohort will stop at 30 patients, but if 14 or more patients have CLE, then the implant is too dangerous for this cohort.

Six patients will be accrued before the first analysis. If 5 or more of the 6 patients have CLE, stop the cohort and the implant will be declared as too dangerous for this population. If there are 4 or fewer CLEs, enroll the next 6 patients assuming the cohort didn't stop for futility. The operating characteristics are summarized in the following table:

The operating characteristics for each patient cohort are shown in the following table.

		Stop if Prob{ $\theta_S < 0.50$ |data} > 0.95 or Stop if Prob{CLE> 0.30 | data} > 0.95		
True	True	Pr(stop early)	Mean Number of	Median

Adverse Event Rate	Response Rate		Patients	(25th %ile, 75th %ile)
0.1	0.30	0.68	18.5	12 (12, 30)
0.2	0.30	0.68	18.5	12 (12, 30)
0.3	0.30	0.71	18.0	12 (12, 30)
0.4	0.30	0.79	16.5	12 (12, 24)
0.5	0.30	0.90	14.0	12 (12, 18)
0.1	0.40	0.33	24.6	30 (18, 30)
0.2	0.40	0.33	24.5	30 (18, 30)
0.3	0.40	0.38	23.7	30 (12, 30)
0.4	0.40	0.55	21.0	18 (12, 30)
0.5	0.40	0.79	16.8	12 (12, 24)
0.1	0.50	0.10	28.3	30 (30, 30)
0.2	0.50	0.11	28.1	30 (30, 30)
0.3	**0.50**	**0.18**	**27.1**	**30 (30, 30)**
0.4	0.50	0.40	23.7	30 (18, 30)
0.5	0.50	0.72	18.4	18 (12, 30)
0.1	0.60	0.02	29.6	30 (30, 30)
0.2	0.60	0.03	29.5	30 (30, 30)
0.3	0.60	0.10	28.4	30 (30, 30)
0.4	0.60	0.34	24.7	30 (18, 30)
0.5	0.60	0.69	19.0	18 (12, 30)
0.1	0.70	0.003	30.0	30 (30, 30)
0.2	0.70	0.01	29.8	30 (30, 30)
0.3	0.70	0.08	28.7	30 (30, 30)
0.4	0.70	0.33	25.0	30 (18, 30)
0.5	0.70	0.68	19.1	18 (12, 30)

6.6. Analysis Plan

The proportion of patients who experience SNS success will be reported with a 90% credible interval using a beta(1,1) prior for each cohort. For the patients in the reconstruction cohort, a success rate of 50% or better will establish confirmation of efficacy of SNS implant that would warrant offering SNS implant to alleviate bowel symptoms following anal reconstruction. In the chemoradiation therapy only cohort, a success rate of 50% or better would warrant studying SNS implant further in this patient population. The secondary measures will be reported descriptively with graphs or tabulations for categorical survey outcomes, CLEs, and anorectal manometry measures. Exploratory logistic regression models will be performed to identify patients who may be more likely to have SNS success using baseline measures and visit 2 bowel/bladder diaries. Analysis of SNS success, safety, and measures up through visit 4 measures will be completed and published once all patients are enrolled and complete the first 4 visits or are off study. Additional analyses will be completed and published after the long-term 1 and 3 year follow-up questionnaires are completed.

7. RISK MANAGEMENT

Restore is a low risk trial. Any of the risks encountered by the participant are those associated with surgery for the treatment of fecal incontinence or LARS. In the event that readmissions or SNS lead removals are high, the study will be terminated as described in the previous section. We feel that any risk associated with participation in *Restore* is minimal and will be offset by improved patient reported outcomes. The knowledge obtained by the study personnel regarding the feasibility of sacral nerve stimulation for the treatment of fecal incontinence and LARS in association with colorectal cancer will be used to assess the potential of expanded cohorts as previously described. Adverse events (AE), >/= grade 3, using CTCAE v. 4 and serious adverse events (SAE) related to the procedure that occur within 30 days after will be reported. Reportable AE and SAE would include, but are not limited to, lead migration, wound infection, pneumonia, intractable pain related to surgical complications such as wound infection, unplanned or unanticipated readmission within 30 days, stroke, myocardial infarction, perioperative cardiovascular events, readmission if it is related to the SNS procedure, SNS lead removal due to any reason other than failure, or perioperative death due to surgery or complications.

8. DATA MANAGEMENT

The study team is committed to protecting patient confidentiality at all times and in all circumstances. No patient identifying information will be used in the publication of findings and all information extracted from the medical record will be entered onto coded data sheets which will be maintained on databases stored in approved locations and only accessible by delegated UTMDACC employees. All printable hard copies of study documents such as bladder and bowel diaries or other study related instruments, will be stored in a secured location on the UTMDACC campus. If needed, hard copies of the coded study data may also be stored in a locked cabinet in

the principal investigator's office. All electronic data will be entered and stored in an institutionally approved database (e.g., REDCap) on a secured UTMDACC server.

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10. APPENDICES

A. Combined Fecal Incontience Quality of Life Questionnaire (FIQoL) and Fecal Incontinence Severity Index (FISI)

B. Memorial Sloan-Kettering Cancer Center (MSKCC) Bowel Function Instrument

C. Low Anterior Resection Syndrome (LARS) Score Bowel Function Questionnaire

D. EuroQol Group EQ-5D-5L™ (EQ-5D-5L)

E. Cleveland Clinic Incontinence Score (CCIS) Instrument

F. International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms (ICIQ-FLUTS)

G. International Continence Society Male Short Form (ICSmaleSF)

H. Bladder Symptom Tracker (Medtronic) as part of the urinary diary

I. Bowel Symptom Tracker (Medtronic) as part of the bowel diary

J. EORTC QLQ – CR29©

K. REDCap Survey Message and MyChart Survey Reminder