Comparative Effectiveness of Biofeedback, Sacral Nerve Stimulation, and Injectable Bulking Agents for Treatment of Fecal Incontinence: The Fecal Incontinence Treatment (FIT) Study

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Comparative Effectiveness of Biofeedback and Injectable Bulking Agents for Treatment of Fecal Incontinence: The Fecal Incontinence Treatment (FIT) Study

Protocol Version 10.0

Approved: 06/11/2022

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Please read and acknowledge your approval of the Version 9.0 of the Comparative Effectiveness of Biofeedback and Injectable Bulking Agents for Treatment of Fecal Incontinence: The Fecal Incontinence Treatment (FIT) Study protocol. If you agree with the protocol in this version, as it is stated below, please sign and date this face page and return this face page to William Whitehead or Sundass Khan. This can be faxed to [redacted] or sent via email to [redacted]

Investigator Signature: _____ **Date:** _____

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List of Abbreviations	
ABL	Accidental Bowel Leakage
AE	Adverse Event
ANOVA	Analysis of Variance
BM	Bowel Movement
BSFS	Bristol Stool Form Scale
CAT	Computer Adaptive Testing
CES-D	Center for Epidemiological Studies Depression scale
CEQ	Credibility/Expectancy Questionnaire
DCC	Data Coordinating Center
DSMB	Data and Safety Monitoring Board
EAS	External Anal Sphincter
EDC	Electronic Data Capture
EQ-5D	EuroQol 5 item health utilities questionnaire
EMG	Electromyographic
FDA	Food and Drug Administration
FI	Fecal Incontinence
FIQOL	Fecal Incontinence Quality of Life questionnaire
FISS	Fecal incontinence Severity Scale
FIT	Fecal Incontinence Treatment study
FU	Follow-Up
GI	Gastrointestinal
HUI-3	Health Utilities Index Mark 3
IAS	Internal Anal Sphincter
IBS	Irritable Bowel Syndrome
ICD-10	International Classification of Diseases, version 10
ITT	Intention-to-Treat analysis
IRB	Institutional Review Board for protection of subjects in research
MCID	Minimum Clinically Important Difference
MEP	Motor Evoked Potential
MRI	Magnetic Resonance Imaging
NIDDK	National Institute of Diabetes and Digestion and Kidney Diseases
PFDN	Pelvic Floor Disorders Network
PFE	Pelvic Floor Exercises
PHQ-15	Patient Health Questionnaire (checklist of 15 most common symptoms seen in primary care visits; treated as a measure of somatization)
PROMIS	Patient Reported Outcomes Measurement Information System
PTNS	Posterior Tibial Nerve Stimulation
QOL	Quality of Life
RCT	Randomized Controlled Trial

SAE	**Serious Adverse Event**
SNS	**Sacral Nerve Electrical Stimulation**
TLMS	**Trans Rectal Magnetic Stimulation**
TSMS	**Trans Sacral Magnetic Stimulation**
UI	**Urinary incontinence**
WPAI	**Work Productivity and Activity Index**

Summary of Changes from Previous Versions:

Version	Affected Section(s)	Summary of Revisions Made	Rationale
2.0 (December 10, 2018)	Throughout protocol	All wording regarding the frequency of FI required for inclusion in the trial was updated to include staining in addition to solid and liquid episodes.	Staining episodes are a relevant part of FI.
	Throughout protocol	Clarifications and corrections of inconsistencies and typos.	Changes were made to ensure that the protocol is expressed as clearly as possible.
3.0 (May 2, 2019)	Throughout protocol, where appropriate	Wording was updated to include an optional 6th Biofeedback training session	In instances where the participant needs additional training to fully benefit from the Biofeedback training, a 6th optional training session may be provided at the discretion of the provider.
	Throughout protocol, where appropriate	Wording detailing the event windows was added to the protocol.	This was added to the protocol to provide clear guidance to site teams to ensure that the protocol is implemented consistently.
	Section 5.1	Wording for two exclusion criteria was updated and a third exclusion criterion was deleted. These criteria now read as follows: • History of previous anorectal surgery, such as stapled transanal rectal resection (STARR). Stapled hemorrhoidectomy is not an exclusion if performed more than 12 months previously. The FENIX procedure, artificial anal sphincter or transposed gracilis; surgical hemorrhoidectomy (other than stapled), and sphincteroplasty are permitted if performed more than 6 months previously and the patient meets inclusion criteria. • Patients who have 4 or more days with 4 or more bowel movements classed as a 6 or 7 on the Bristol Stool Scale per day in either (any) week during the Baseline will be excluded. The following criterion was deleted: • If the participant feels urgency to have a bowel movement but is able to reach a toilet in time without leaking stool/feces.	These changes were considered necessary by the investigators for the appropriate selection of participants.
	Throughout protocol but specifically in	Wording editing to clarify time period for which adverse events will be documented.	Adverse event data will be collected from the time that

	Sections 4.1.2 and 9.2		the participant is consented through the 24-month follow-up visit.
	Throughout protocol but specifically in Section 4.3.2	Wording edited/added to clarify the time-points at which the CEQ will be completed by the participant.	The CEQ should be completed each time a study treatment is started, once the treatment has been initiated.
	Section 4.3.8 and throughout the protocol, as necessary	It was specified that the anal ultrasound/MRI imaging studies need not be repeated at Baseline if the participant had an imaging study within the previous 12 months to assess the sphincters as long as the sphincters appeared normal and there has been no history of anorectal trauma, surgical procedures, or vaginal deliveries in the intervening period between the imaging exam and study participation.	It was felt that it is unnecessary medically/scientifically to subject the participant to additional imaging as long as there is good data to indicate that the sphincters are normal.
	Throughout protocol, where appropriate	Wording added to clarify the time-points at which the BET, ARM and MEP are performed.	Participants who initially respond to EMM but are then randomized after they are identified as non-responders at the 3-month follow-up visit will not have the BET, ARM and MEP repeated at their second 3-month follow-up visit, that is, at the follow-up visit 3 months after they initiated the randomized treatment.
	Appendices B - H	Removed from protocol	These appendices are separate Standard Operating Procedures (SOP) and questionnaires which are submitted to the IRB as separate documents, as appropriate.
4.0	Synopsis; Section 2 (SCHEMA) – *Item 1*	Added to protocol: For patients who have a variable pattern of FI and the investigator believes that the initial two-week diary data collection did not adequately capture the extent of the FI, then the baseline bowel diary may be kept by the patient for an additional two weeks.	Some patients have a variable pattern of FI and, consequently, the initial two-week diary may not reflect the extent of the FI they experience. Keeping the diary for an additional two weeks allows the opportunity for the team to better assess the extent of FI. If a second two-week data collection occurs, then only

			the data from the last two weeks (second diary completed) will be reported in the study's EDC.
	Section 5.1 (Inclusion/Exclusion Criteria)	Wording for one inclusion and four exclusion criteria was updated. The fourth exclusion criteria changed mirrors the inclusion criterion related to the degree of internal anal sphincter defect that is acceptable. These criteria now read as follows: • **Inclusion criterion:** ○ Meets criteria for SNS and dextranomer treatment except an internal anal sphincter defect of 180 degrees or less is acceptable. • **Exclusion criteria:** ○ Internal anal sphincter separation >180 degrees on ultrasound or magnetic resonance imaging. ○ History of pelvic radiation within previous 12 months or presence of active radiation proctitis. ○ Patients who have overflow diarrhea with rectal impaction with stool or an abnormal balloon expulsion test plus predominant symptoms of constipation. ○ Previously failed an adequate (1-2 weeks) trial of SNS.	The investigators believe that certain eligibility criteria may be unnecessarily limiting enrollment. The DSMB agrees that these changes will not affect the scientific integrity of the protocol.
	Synopsis; Section 2 (SCHEMA) – *Item 2;* Section 3 (Study Design) – Item 8	Protocol updated to indicate that whether or not participants are EMM responders or not, data regarding ongoing adherence to the EMM prescriptions will be collected from participants at the end of the one month EMM period and then also at the 3-; 6-; 12-; and 24-month follow-up visits.	This was requested by the DSMB.
5.0	Throughout protocol, as necessary	Two additional FIT Study sites, The University of Alabama at Birmingham, and University of Michigan, have been added to the study protocol.	In view of the current rate of enrollment, the Steering Committee has decided to implement the contingency plan for low enrollment (outlined in Section 5.6 of the protocol). The plan allows for additional sites to participate in the study if approved by the NIDDK program staff.

	Section 4.3.7	Specified that the two additional sites, The University of Alabama at Birmingham and the University of Michigan, will not perform the translumbosacral magnetic evoked potential test.	The equipment for the translumbosacral magnetic evoked potential test is costly and since it is not a core study procedure.
	Section 4.3.8	Specified that The University of Alabama at Birmingham will perform the anorectal ultrasound using a 2-dimensional BK probes rather than the 3-dimensional BK probe noted in the protocol.	The University of Alabama at Birmingham routinely uses 2 dimensional BK probes when performing anorectal ultrasound and will thus not use a 3-dimensional BK probe.
	Appendix A	Deleted Appendix A (UNC consent form)	Although the consent forms are all developed from a template study consent and are very similar, each of the six sites has a site-specific consent form; thus, it is more appropriate to have the consent forms all submitted to the IRB as separate documents.
6.0	Section 3; 6.2; and 6.4	Wording updated to be consistent with the practice of using prophylactic antibiotics for 2 days starting on the day of the injection (per the injection procedure SOP).	Previously it was indicated in the injection procedure SOP that the first dose of the prophylactic antibiotic will be administered 4 hours prior to the procedure; however, the SOP has been updated to indicate that the first dose may be administered 4 hours before or immediately after the procedure. This is consistent with clinical practice.
	Section 5.1 (Inclusion/Exclusion Criteria)	Wording for one exclusion criteria was updated. <u>Previous wording</u>: o Patients who have overflow diarrhea with rectal impaction with stool or an abnormal	The wording was updated for clarification.

		balloon expulsion test plus predominant symptoms of constipation. <u>Updated wording</u>: o Patients who cannot expel the rectal balloon during the balloon expulsion test and who have constipation most of the time.	
	Section 5.1 (Inclusion/Exclusion Criteria)	The following exclusion criterion was deleted: Presence or history of any medical disorder likely to require follow-up with MRI of the body (not head or neck), diathermy, microwave, or RF energy therapy.	The SNS leads previously used were MRI-incompatible; however, the new design leads are not.
	Section 6.3 (Sacral nerve stimulation)	Removal of the specific model number of the lead used for SNS	This model of the lead will no longer be supported by the manufacturer and will thus no longer be used for this study treatment.
	Throughout protocol	Wording updated so that 6-, 12-, and 24-month follow-up events are now referred to as "assessments" instead of "visits". The 18-month telephonic follow-up also now referred to as an "assessment" so that terminology is consistent.	6-, 12-, and 24-month follow-up assessments (previously visits) which do not require in-person procedures may now be conducted remotely.
7.0	Throughout protocol	Updated number of study sites to five.	CRSA will no longer be an enrolling site.
	Throughout protocol	Wording updated throughout protocol to remove SNS as a randomized treatment but to be retained as an optional treatment.	SNS has been removed as a randomized treatment as some patients are concerned about being randomized to an invasive treatment before trying more conservative options.
	Section 5.1 (Inclusion/Exclusion Criteria)	Wording for an inclusion criterion was updated. <u>Previous wording</u>: Meets criteria for SNS and dextranomer treatment except an internal anal sphincter defect of 180 degrees or less is acceptable. <u>Updated wording</u>: Meets criteria for dextranomer treatment except an internal	Updates made to these three criteria were made as SNS is no longer a randomized study treatment.

		anal sphincter defect of 180 degrees or less is acceptable. Wording for one exclusion criterion was updated. Previous wording: Anatomic limitations to placement of SNS or dextranomer injections. Updated wording: Anatomic limitations to placement of dextranomer injections. The following exclusion criterion was deleted: Previously failed an adequate (1-2 weeks) trial of SNS.	
	Throughout protocol	Wording updated to indicate that the following procedures may be optional at the 3-month assessment: • ARM • MEP • Endoanal ultrasound (INJ participants only)	
	Throughout protocol	Wording updated to indicate that the 3-month follow-up assessment may be completed in-person or remotely.	
8.0	Section 5.1 (Inclusion/Exclusion Criteria)	Language below the table of inclusion/exclusion criteria was updated as follows: Patients with ~~clinically evident diabetic neuropathy, Parkinson's disease, multiple sclerosis, other neurological disorders, and~~ obstetric injuries with or without previous sphincter repair who have less than 1/3 external anal sphincter (EAS) separation, and patients with rectal reconstructions or ileoanal pouches, will be permitted. Medical history will be documented to test for predictors of response.	The deleted text conflicted with wording in an exclusion criterion.
9.0	Section 3.1 Event Windows	The following event window for initiation of the optional treatment was added: Optional additional treatment initiation should occur within 0 days to 4 weeks after the 3-month visit post randomization.	The same window used for initiation of the randomized treatment has been applied to the initiation of the optional treatment. 0 days is the 3-month visit at which it is determined that the participant has not responded to the randomized treatment.

	Section 5.1 (Inclusion/Exclusion Criteria)	Added an inclusion criterion regarding age as follows: Age >=18 years Wording for two exclusion criteria was updated. • *First criterion change is as follows:* *<u>Previous wording</u>*: History of previous anorectal surgery, such as stapled transanal rectal resection (STARR). Stapled hemorrhoidectomy is not an exclusion if performed more than 12 months previously. The FENIX procedure, artificial anal sphincter or transposed gracilis; surgical hemorrhoidectomy (other than stapled), and sphincteroplasty are permitted if performed more than 6 months previously and the patient meets inclusion criteria. *<u>Updated wording</u>*: History of previous anorectal surgery, such as stapled transanal rectal resection (STARR). Stapled hemorrhoidectomy is not an exclusion if performed more than 12 months previously. The FENIX procedure, artificial anal sphincter or transposed gracilis; surgical hemorrhoidectomy (other than stapled), sphincteroplasty, rectal reconstructions and ileoanal pouches are permitted if performed more than 6 months previously and the patient meets inclusion criteria. • *Second criterion change is as follows:* *<u>Previous wording</u>*: Immunotherapy or chemotherapy in the last 12 months. *<u>Updated wording</u>*: Patients currently receiving immunotherapy or chemotherapy.	The protocol specifies that study participants will be "adults" and the eligibility CRF specifies 18 years or older, but this criterion has been specifically added to the inclusion/ exclusion criteria table for completeness. *First criterion change:* Wording from the paragraph below the inclusion/ exclusion table was added to an existing criterion to make its intent as an exclusion clearer. *Second criterion change:* The wording has been updated to specifically exclude patients who are currently receiving immunotherapy or chemotherapy and not those who previously received these therapies since only current therapy is specifically noted as a contra-indication in the Solesta package insert.

	Section 5.1 (Inclusion/Exclusion Criteria)	Language below the table of inclusion/exclusion criteria was updated as follows: ~~Patients with obstetric injuries with or without previous sphincter repair who have less than 1/3 external anal sphincter (EAS) separation, and patients with rectal reconstructions or ileoanal pouches, will be permitted.~~ Medical history will be documented to test for predictors of response.	The wording regarding obstetric injuries was deleted as it not required/correct in this instance. The wording regarding rectal reconstructions or ileoanal pouches was deleted as it was specifically incorporated into an exclusion criterion (*see above*).
	Section 5.6 (Contingency Plan)	Section deleted.	Two additional sites have already been added to the study protocol and no additional sites will still be added.
	Section 6.2 (BIO training) – last paragraph on page 32	Language referring to audiotaping the Biofeedback sessions as part of the training program was removed.	Therapists and investigators were not comfortable about recording the Biofeedback sessions and it was decided previously that sessions will not be recorded. The consent forms were updated as part of Protocol Modification 7.0 (approved 4/23/2021) but this part of a sentence regarding various aspects of the training program was missed at that time.
10.0	Synopsis protocol summary (Section 3) and in Table 2 in main body of protocol	Wording added to clarify that the endoanal ultrasound may be performed as an optional procedure for participants who elect to receive INJ as an optional treatment. If performed this would be done at their follow-up visit following completion of that treatment (likely their 6-month follow-up visit).	This procedure is performed specifically when Solesta is administered as it is used to monitor migration of the bulking agent.
	Section 4.3.7 (*Motor evoked potentials)*	Wording was updated to indicate that MEP data will not be collected at the University of North Carolina at Chapel Hill.	The MEP data are collected at some but not all of the study sites. Previously data were to be collected at UNC, but this is no longer planned.

	Section 5.1 (Inclusion/Exclusion Criteria)	Wording for this exclusion criterion was updated as follows: *Previous wording*: History of previous anorectal surgery, such as stapled transanal rectal resection (STARR). Stapled hemorrhoidectomy is not an exclusion if performed more than 12 months previously. The FENIX procedure, artificial anal sphincter or transposed gracilis; surgical hemorrhoidectomy (other than stapled), sphincteroplasty, rectal reconstructions and ileoanal pouches are permitted if performed more than 6 months previously and the patient meets inclusion criteria. *Updated wording*: History of ileoanal pouch; history of anal sphincteroplasty, rectopexy, or rectocele repair within the past 6 months; or history of pelvic surgery with synthetic graft and suspected graft erosion into the anus, rectum, or skin or if the graft ends less than approximately 1" above the upper limit of the anal canal.	Wording was updated to more clearly define which surgical procedures should be permitted/excluded.
	Section 9.2 (*Reporting of Adverse Events*)	The language bolded below was added to the text: "All adverse events that occur from the time that the participant is consented through the 3-month follow up visit will be recorded on designated CRFs. Following the 3-month follow up assessment and through the 24-month follow-up assessment, the research coordinators will record only AEs of grade II or higher; **however, any AE, regardless of severity/grade, should be reported through the 24-month follow-up visit if it is possibly related to the randomized or optional study treatments.** Failure of the study interventions to adequately control fecal incontinence symptoms (failure of efficacy) will be captured by the study endpoints and will not be recorded as an adverse event."	This change was made to ensure compliance with safety reporting.

Synopsis

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the NIDDK Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

PROTOCOL SUMMARY

1. SYNOPSIS

Title: Comparative Effectiveness of Biofeedback and Injectable Bulking Agents for Treatment of Fecal Incontinence: The Fecal Incontinence Treatment (FIT) Study

Study Description: Patients with severe fecal incontinence (2 or more episodes of staining, solid, or liquid FI per week) who meet inclusion criteria for Injection of Solesta (INJ; an inert bulking agent), or Biofeedback (BIO) will be enrolled. The baseline rate of FI will be assessed using a two-week daily stool diary. For patients who have a variable pattern of FI and the investigator believes that the initial two-week diary data collection did not adequately capture the extent of the FI, then the baseline bowel diary may be kept by the patient for an additional two weeks. All participants will be enrolled into a 4-week trial of Enhanced Medical Management (EMM; education, pelvic floor exercises, and use of non-prescription drugs to normalize stool consistency). Those who improve by at least 75% reduction in FI frequency will not be randomized to another treatment but will be followed for two years. Those not improving by 75% reduction in FI frequency will be randomized to BIO (5 required weekly sessions with an optional 6th session if needed) or INJ and they will be evaluated 3 months later. If they show a 75% decrease in FI at 3 months compared to baseline, they will be followed for two years. To assess the long-term response to treatments, those who improve less than 75% in FI episodes will be offered an additional treatment, either the randomized treatment to which they were not originally randomized or sacral nerve stimulation (SNS) and will also be followed for two years from the start of their randomized treatment. Note that participants who previously (prior to their participation in the study) were treated unsuccessfully with SNS will not be offered SNS as an optional treatment. Anorectal manometry and Magnetic Evoked Potentials will be used to subtype the

physiological basis for FI. Quality of life and psychological factors will be used to assess outcomes.

Outcomes:

Primary Outcomes: To show that, by 3-month follow-up, the two treatments, biofeedback and dextranomer injection, will have different effects on (a) reduction in the frequency of FI compared to baseline, (b) number of people with abdominal events, and (c) the cost of delivering the treatment.
Secondary Outcomes: To show that by 3 months follow-up, those two treatments will have different effects on the severity of fecal incontinence (measured with the Fecal Incontinence Severity Scale), the impact of FI on quality of life (measured with the Fecal Incontinence Quality of Life Scale), and psychological symptoms (measured with the PROMIS scales for Anxiety, Depression, and Self-Efficacy Symptom Management).

Endpoints:

Primary Endpoint:

1. The frequency of FI will be measured with a validated symptom diary. The definition of a responder is a reduction of 75% or greater in the frequency of FI from baseline, measured with the Fecal Incontinence Bowel Diary.
2. The primary measure of safety is the proportion of participants with specified AE's reported during treatment rated on the Common Terminology Criteria for Adverse Events.
3. Costs will be measured from three sources: (a) Number of treatment visits multiplied by the Medicare reimbursement rates. (b) An Out-of-Pocket Treatment Cost Questionnaire. (c) A Work Productivity and Impairment Questionnaire for direct and indirect costs. These costs will be combined to establish costs.

Secondary Endpoints:

1. Fecal Incontinence Severity Scale.
2. Fecal Incontinence Quality of Life Scale.
3. Measures of psychological distress are the PROMIS Anxiety Scale, the PROMIS Depression Scale, and the PROMIS Self-Efficacy Symptom Management Scale.

Predictions of Treatment Response:

1. Demographic variables: sex, age, race, ethnicity, and education.
2. Clinical history variables: FI frequency, volume, duration, association with urgency and loose / watery stools and hard / lumpy stools.
3. Pelvic floor physiology: Anal rectal pressures, squeeze pressures, squeeze duration, sensory threshold, structural integrity of sphincter, innervation of the rectum.

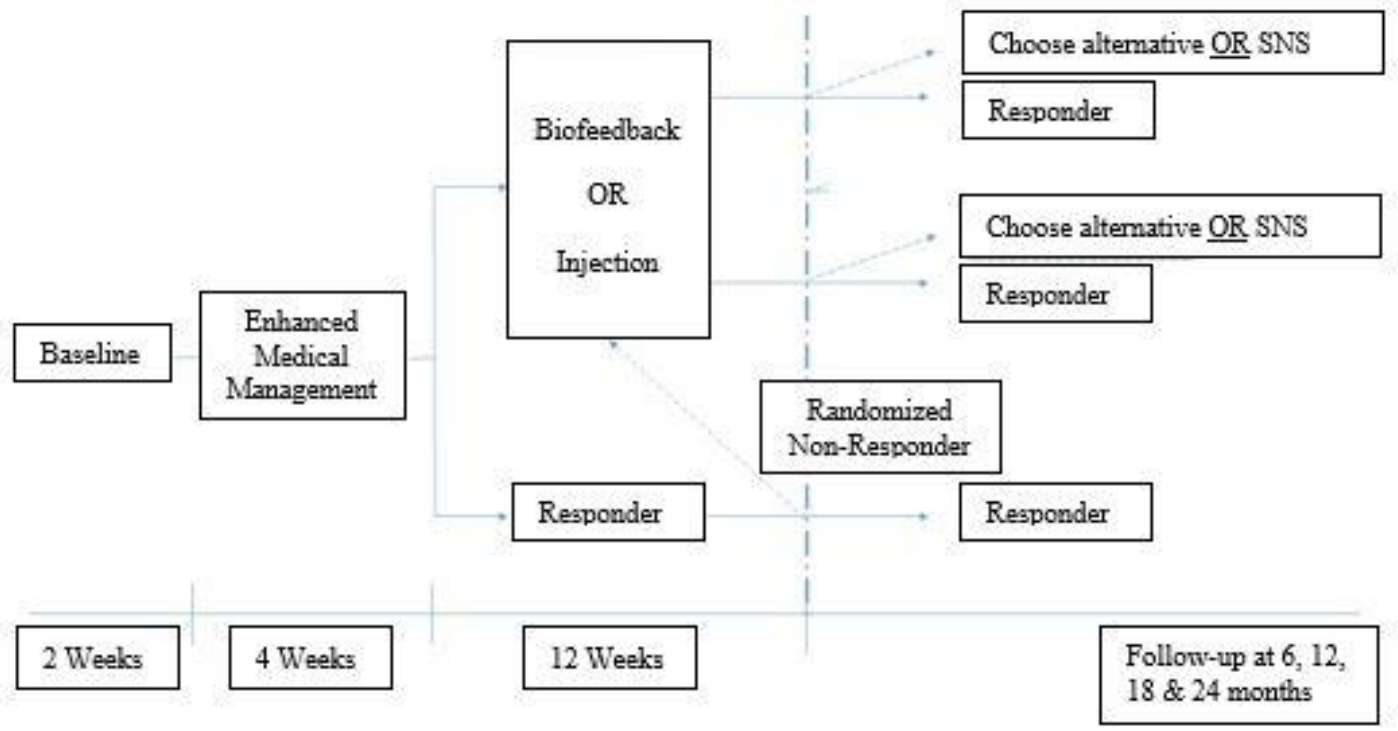
Moderators of outcome:

1. Patient's expectation of benefit from the treatment they are randomized to.
2. Somatization score on the Physical Healthy Questionnaire 12.

Study Population:	97 adult people with FI who did not benefit from EMM will be recruited into each of two treatment arms. Patients will be recruited into the EMM group until there are 97 randomized to each treatment arm. We anticipate recruiting approximately 285 into the EMM condition, but this will be adjusted if necessary. The subjects may be referred from clinicians or may respond to posted advertisements about the study. The study is open to male and female patients. An effort will be made to recruit African American and Hispanic subjects.
Phase:	Compare BIO and INJ for the treatment of moderate or severe fecal incontinence, with respect to efficacy for reducing the frequency of fecal incontinence, safety of the interventions, and cost of providing care.
Description of Sites/Facilities Enrolling Participants:	Five clinical sites are enrolling patients: (1) Mayo Clinic in Rochester, Minnesota, headed by Adil Bharucha. (2) Augusta University in Augusta, Georgia, headed by Satish Rao. (3) University of North Carolina at Chapel Hill headed by William Whitehead. (4) The University of Alabama at Birmingham, headed by Isuzu Meyer. (5) University of Michigan, headed by William Chey. Each of these facilities is a major referral center for the treatment of fecal incontinence.
Description of Study Intervention:	Each treatment protocol will be based on previously described treatment algorithms. The EMM protocol will follow a protocol developed by the University of North Carolina group, which is similar to protocols used at the Mayo Clinic and Augusta University. The BIO treatment will follow the biofeedback program developed for the Pelvic Floor Disorders Network by Whitehead and colleagues. The INJ treatment will follow the Graf study.
Study Duration:	The duration of the study will be approximately 6 years from first enrollment to completion of the last subject.
Participant Duration:	Each participant will be studied for 24-27 months, following the completion of the month of EMM.

2. SCHEMA

Study Design



Study sequence is shown above for all steps following informed consent in Visit 1.

1. Subjects who meet the inclusion criteria are first asked to keep a symptom diary for two weeks to determine whether they have an adequate amount of staining, solid or liquid fecal incontinence to be enrolled. The number of FI episodes during baseline will become the reference for judging whether they demonstrate a 75% reduction in the frequency of FI. For patients who have a variable pattern of FI and the investigator believes that the initial two-week diary data collection did not adequately capture the extent of the FI, then the baseline bowel diary may be kept by the patient for an additional two weeks.

2. Subjects who have an adequate amount of FI during baseline and who fulfill other inclusion criteria are enrolled in a 4-week EMM protocol to determine whether this will reduce their FI episodes by 75% or more. If it does, they are not included in the randomized trial but are scheduled to return at 3 months for a follow-up assessment. If the subject does not achieve at least a 75% reduction in FI, they are randomized to one of two therapies: BIO or INJ. Whether or not participants are EMM responders, data regarding ongoing adherence to the EMM prescriptions will be collected from participants at the end of the 1-month EMM period and then also at the 3-; 6-; 12-; and 24-month follow-up assessments.

3. Each treatment intervention follows a printed protocol document. The number of treatment visits varies somewhat, from 2-3 visits for INJ, and 5-6 visits for BIO.

At 3 months, all subjects who received a randomized therapy are assessed to determine whether they meet the criteria for treatment success. If they fail to demonstrate a 75% decrease in FI compared to baseline, they are labelled as treatment failures and are offered the opportunity to try the other randomization treatment or SNS. Those subjects who were initial responders to EMM but who are determined at 3 months follow-up to no longer be responding to EMM will be eligible to be randomized to one of the two treatment therapies (BIO or INJ). For all participants, follow-up assessments occur at 6, 12, 18 and 24 months. The 3-, 6-, 12 and 24-month follow-up assessments may be completed in-person or remotely. The more limited follow-up data collection at 18-month should always be collected during a telephone call.

4. Anorectal manometry and magnetic evoked potential tests are performed at baseline and may be performed at the 3-month follow-up assessment. Questionnaires to assess FI severity, FIQOL, and psychological tests are given at the same intervals.

3. SCHEDULE OF ACTIVITIES (SOA)

The Table of Measures shows the assessment measures in column 1 and the part of the study during which these measures are made in the remaining columns. Additionally, participants will complete the Credibility/ Expectancy Questionnaire (CEQ) each time that they start one of the study interventions. All study participants will complete the CEQ when they start EMM, all randomized participants will complete the CEQ when they start BIO or INJ as a randomized treatment, and participants will complete the CEQ if they select BIO, INJ or SNS when they are identified as non-responders to the randomized treatment at the 3-month follow-up assessment.

Table of Measures for all participants

Schedule of assessments*	Screening	Baseline	Randomize	3 mo	6 mo	12 mo	18 mo	24 mo
Socio-demographics and examination	X							
Bowel diary, including BSFS		X	X	X	X	X		X
Endoanal ultrasound		X**		X*** (INJ arm only)				
Balloon Evacuation Test (BET)		X**						
Anorectal manometry (ARM)		X**		X***				
Magnetic Evoked Potential (MEP)		X**		X***				
Fecal Incontinence Severity Scale (FISS)		X	X	X	X	X		X
Fecal Incontinence Quality of Life (FIQOL)		X	X	X	X	X		X
PHQ-12 Somatization scale			X	X	X	X		X
PROMIS Anxiety-7			X	X	X	X		X
PROMIS Depression-8			X	X	X	X		X
PROMIS Self-Efficacy Symptom Management			X	X	X	X		X
Assessment of AEs, SAEs		X	X	X	X	X	X	X
Cost (treatments, # of visits, out of pocket)		X	X	X	X	X	X	X
Work Productivity and Impairment (WPAI)		X	X	X	X	X	X	X
EuroQol 5D (EQ-5D)		X	X	X	X	X	X	X
Burden of Treatment Questionnaire		X	X	X	X	X	X	X
GI Symptom Questionnaire		X						
ABLe			X	X	X	X		X
Continence Rating			X	X	X	X		X

* Additionally, participants will complete the Credibility/ Expectancy Questionnaire (CEQ) each time that they start one of the study interventions. So, all study participants will complete the CEQ when they start EMM all randomized participants will complete the CEQ when they start BIO or INJ as a randomized treatment, and participants will complete the CEQ if they select BIO, INJ or SNS when they are identified as non-responders to the randomized treatment at the 3-month follow-up assessments.

** The endoanal ultrasound, BET, ARM and MEP may be conducted at the randomization visit, if not done at Baseline but must be conducted prior to randomization. If an imaging study (US or MRI) was performed in the previous 12 months to assess the sphincters, then this need not be repeated at Baseline if the sphincters appeared normal and there has been no history of anorectal trauma, surgical procedures, or vaginal deliveries in the intervening period between the imaging exam and study participation.

*** The endoanal ultrasound (INJ only), the ARM (all participants) and the MEP (all participants) may be performed at the 3-month follow-up assessment. Participants who complete **two** 3-month follow-up visits should only have the ARM and MEP performed at the first 3-month follow-up visit. This will only apply to participants who initially respond to EMM but are later identified as non-responders at the 3-month follow-up visit and are then randomized to BIO or INJ. They will complete another 3-month follow-up visit, this time three months after they have initiated one of the randomized treatments. NOTE: Participants who elect to receive INJ as an optional treatment may have an endoanal ultrasound at their follow-up visit following completion of that treatment (likely their 6-month follow-up visit).

1.0 Study Overview

Fecal incontinence (FI) is very common: 3% of US adults report that it occurs at least weekly[1]. It often has a devastating impact on quality of life and may lead to premature admission to a nursing home[2]. In August 2013, the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) invited leaders in the field to a workshop to develop a clinical research agenda for FI. Overwhelmingly, participants identified biofeedback, sacral nerve electrical stimulation, and perianal injection of an inert bulking agent as potentially useful treatments[3] but felt that a critical barrier to progress is the lack of consistent evidence from well-designed, randomized controlled trials (RCTs) regarding their efficacy. The workshop identified trials comparing the effectiveness, safety, and costs of these treatments as the highest priority for research funding. Our goal is to address this significant gap in knowledge by conducting a multisite study comparing the effectiveness, safety, and costs of two treatments. In our proposed Fecal Incontinence Treatment (FIT) study, approximately 285 people with moderate to severe FI will be enrolled in this multi-site study. All participants will first be treated with 4 weeks of Enhanced Medical Management (EMM), and 194 who do not respond to EMM will be randomized to the two interventions, Biofeedback (BIO) or injections of Dextranomer bulking agent (INJ). Three months thereafter, non-responders (less than a 75% reduction in FI episodes) may choose to undergo a different (i.e., a second) intervention from the 3 options of BIO, INJ, or Sacral Nerve Stimulation (SNS).

Our specific aims are as follows:

1.1 Specific Aims

A. Compare the effectiveness, safety, and cost of two treatments for moderate to severe FI in 194 male and female patients in a multi-center RCT; the interventions are biofeedback therapy (5 required weekly sessions with the option of an additional 6th visit, as needed) and perianal injection of the inert bulking agent dextranomer (INJ; Solesta). A $\geq$75% reduction in average weekly FI episodes compared to baseline will define a responder. The primary efficacy analysis will occur 3 months following the start of each treatment, with long-term follow-up through 2 years. Secondary outcomes will include a validated FI severity scale,[4, 5] a disease-specific quality of life[6] scale, and measures of psychological distress[7].

- Research objective 1 (primary). For the primary test of efficacy, the null hypothesis is that the proportion of responders in the two treatment groups will not be different. Secondary analyses will test for equivalence at other time points (e.g., 6, 12 and 24 months follow up) and will compare treatment groups on other secondary outcome measures.
- Research objective 2 (primary). For the primary test of safety, the null hypothesis is that at 3 months follow up, the proportion of patients with adverse events (AEs) of pelvic pain of grade II or higher based on Common Terminology Criteria for AE (CTCAE) criteria, treatment site infection, or SAEs requiring hospitalization will not be different in the BIO or INJ groups. Secondary analyses will evaluate this outcome at 6, 12, 18, and 24 months follow up.
- Research objective 3 (primary). At 3 months follow up, the estimated average cost for enhanced medical management non-responders will not be different for the two treatments. Secondary analyses will evaluate this outcome at 6, 12, 18, and 24 months.

B. Compare efficacy in patients who complete all assigned treatment visits. Efficacy may be influenced by the number of BIO treatment sessions and the requirements to learn and practice new skills. Thus, in a secondary analysis, the primary efficacy outcome will be compared between treatment groups in the subset of participants who completed the treatment to which they were randomized.

C. Identify baseline predictors of responsiveness to each intervention and the mechanistic basis for each treatment. Candidate predictors are (a) demographic variables (e.g., sex, age, race, ethnicity, education); (b) clinical history variables (e.g., FI frequency, volume, duration, and association with urgency and diarrhea); and (c) baseline pelvic floor physiology (e.g., anal canal resting pressure, squeeze pressure, duration of squeeze, rectal sensory threshold for first sensation and urgency, maximum tolerable volume, structural integrity of anal sphincters assessed by ultrasound, and integrity of the pelvic floor innervation by trans-sacral and trans-lumbar magnetic evoked potentials).

D. Evaluate treatment combinations. Patients who do not meet the responder criterion by 3 months follow up will be offered the option of choosing additional therapy. This constitutes a pragmatic clinical trial which mimics clinical practice and will provide preliminary data for a future study. A second reason for allowing patients to add an additional preferred treatment if they do not show at least a 75% improvement is to facilitate recruitment; in our feasibility survey, subjects told us that the opportunity to try another treatment if the first failed would increase their willingness to be randomized. Data analysis will estimate 95% confidence intervals for the percent of responders to each treatment combination and to each monotherapy, and differences in responder rates between groups will be assessed.
   - Research objective 4. To compare the improvement in FI after combination treatment versus monotherapy and compare improvement among various treatment combinations, up to 24 months after administration of each treatment combination, compared to monotherapy.
   - Research objective 5. To estimate differences in the magnitude of improvement in FI from baseline to end of treatment between the treatment combinations.

E. Assess the efficacy and durability of enhanced medical treatment and identify patient characteristics that predict treatment response.
   - Research objective 6. To estimate the responder rate during the last two weeks of enhanced medical treatment and also during follow up at 3, 6, 12, and 24 months.
   - Research objective 7. To assess the proportion of patients reporting AEs of pelvic pain of grade II or higher, or SAEs requiring hospitalization, during all weeks of medical treatment.
   - Research objective 8. To estimate the cost of delivering medical treatment and compare to the cost of delivering any of the other two treatments.

F. Compare the cost effectiveness of two treatments for moderate to severe FI.
   - Research objective 9: To estimate the average cost effectiveness (i.e., cost per quality adjusted life year gained excluding costs that are only for research purposes) among conservative medical management non-responders for the two treatments at 6, 12, 18 and 24 months.

This 4-site geographically dispersed study will identify the most optimal, durable, safe, and inexpensive treatment for moderate to severe FI patients. In addition, this project will demonstrate the efficacy of enhanced medical management of FI, explore the mechanisms of action for the study treatments, and identify the factors that predict the response to treatment. A successful outcome may result in changes to management strategies.

2.0 Background and Significance

2.0.1 Prevalence and epidemiology: Fecal incontinence (FI) is the involuntary passage of solid or liquid stool[8]. The age-adjusted prevalence of FI occurring in the past month in non-institutionalized U.S. adults is 9% in women and 8% in men, and this increases to 15% in men and women by age 70[1]. FI occurs at least weekly in 3% of non-institutionalized adults[1]. Up to one in five women in the community report one or more episodes of FI in the past year[9]. The prevalence of FI is higher in primary care clinics compared to the general population because poor health is a risk factor for FI; an estimated 37% of primary care patients self-report FI on questionnaires, although this is rarely reported to their physician or identified in their medical record[10].

2.0.2 Impact on quality of life and health care costs: FI has a major impact on quality of life[11, 12] being associated with symptoms of anxiety and depression and with avoidance of leaving home or inviting friends to visit[13]. FI increases the likelihood of admission to a nursing home[2], and the prevalence in nursing homes is 48%[14]. It is associated with high health care costs for the individual[13] and, partly through its impact on nursing home referral, also with high costs to society[2].

2.1 Rationale for conducting a comparative effectiveness trial

Evidence-based treatments available for FI: Several treatment approaches have been described for FI covering a spectrum from self-management with pads through biofeedback (BIO), drugs, injections with bulking agents (INJ), sacral nerve electrical stimulation (SNS), up to surgical reconstruction or implanting an artificial

anal sphincter[3]. At present, three treatments for FI are supported by randomized controlled clinical trials (RCTs) and are frequently employed; they are BIO[15], INJ of the bulking agent dextranomer[16], and SNS[17].

These three evidence-based treatments differ significantly in their proposed pathophysiological basis, mode of administration, acceptance by patients and providers, and availability. These treatments also differ in what is required from the participants. SNS and INJ are treatments provided by the physician and require no effort from the participant; however, BIO requires the participant to learn new skills and requires consistent practice over several weeks, resulting in a greater burden.

Discontinuation rates are greater for BIO than for SNS or INJ. These treatments also appear to differ in safety and cost (Table 1). However, comparisons between treatments are difficult because, with only one exception[18] (see Section 2.2.1), there are no head-to-head comparisons between these treatments. Inconsistencies between existing studies in design, inclusion criteria, and primary endpoints have hampered comparisons between treatment types and even between studies within the same treatment modality. Consequently, meta-analyses and systematic reviews for behavioral treatments, anti-diarrheal medications, BIO, mucosal electrical stimulation, SNS, and INJ have been inconclusive[3, 19-23].

Currently, SNS is often regarded as more effective than BIO, although it is associated with a greater risk of side-effects, and a widely accepted clinical algorithm requires patients with FI to have tried and failed conservative treatments before they can be considered candidates for SNS. BIO is usually categorized as one of the conservative treatments which should be tried first.

It could be argued that, even if BIO were to be equally effective as INJ of dextranomer, it would be logical to try BIO first because it is safer, and to only use INJ in those who fail BIO. In practice, however, there is no consistent standard for defining BIO or judging what "failing biofeedback" means. If the proposed comparative effectiveness study shows that BIO is equally effective or more effective than INJ, treatment algorithms and insurance reimbursement policies may need to be re-evaluated. An outcome such as this might also stimulate research into whether treatment combinations may be more consistently effective than trying these treatments one at a time.

An NIDDK Workshop hosted in 2014 addressed research priorities for FI and concluded that the highest priority for research should be "trials comparing the effectiveness, safety, and cost of current therapies"[3]. Such a comparative effectiveness study needs to be performed at multiple sites because (1) the number of patients currently referred for these treatments is relatively small at individual medical centers, (2) FI is a multi-faceted disorder and patient phenotypes may differ among centers, and (3) the success of BIO varies across clinical settings and is known to be influenced by the training and experience of the therapist.

Table 1: Summary of published studies testing the efficacy of BIO, INJ, and SNS

Outcome Domain	BIO	INJ	SNS
Efficacy (success rated by authors' definition)	55%[24] - 93%[15]	53%[16]	83%[25]
Efficacy (≥75% decrease in FI frequency)	78%[15]	32%[16]	56%[25]
Continence (%)	5%[24] - 44%[15]	5.9%[16]	25%[26] - 40%[25]
Adverse events (pain or infection)	0%[15, 24, 27]	10%[16]	6%[28] -11%[29]
Reimbursement (range in US $)	$1,235 – 2,300	$3,000 – 7,408	$29,000 – 69,000

2.2. Summary of Published Research

2.2.1. BIO treatment of FI: Eight randomized controlled trials of BIO for FI have been published[15, 18, 24, 27, 30-32], of which four showed BIO to be superior to the comparison group (i.e., diet and drug treatment for altered bowel habits plus pelvic floor exercises[15, 30], education and pelvic floor exercises[31], and electrical stimulation[32]). However, comparisons between these RCTs are problematic because they used different study designs,

inclusion criteria, and primary outcome measures. Three assessed outcome only at the end of BIO training; they did not assess maintenance of improvement[27, 30, 31].

In the most methodologically robust BIO RCT [15], 168 patients with at least weekly solid or liquid FI were screened to eliminate those who responded to conservative medical management during a four-week screening period. The remaining 108 patients were randomly assigned to receive either six sessions of BIO with pelvic floor exercises or pelvic floor exercises alone. In the intention-to-treat analysis, 76% of the BIO group reported adequate relief of their FI (not otherwise defined for them) three months following the end of treatment (approximately six months after onset of treatment) compared to 41% of the pelvic floor exercise group. Considering only patients who completed at least five sessions of BIO, 85% reported adequate relief of FI at six months. The average number of days per week with FI decreased from 3.2 at baseline to 0.8 after BIO. Complete continence was achieved by 44% of BIO treated patients compared to 21% of those treated with pelvic floor exercises alone. In a separate long-term study[33] 60 patients with refractory FI were assessed at 12 months after completion of BIO and showed persisting clinical improvements (63% were continent), and improvements in sphincter strength and rectal sensation.

The Pelvic Floor Disorders Network (PFDN) conducted a multisite study of the effects of BIO versus an educational handout, and oral loperamide versus placebo in a factorial design. Three hundred patients were enrolled across eight clinical sites. Dr. Whitehead served as a consultant on this study and Marie Gantz lead the PFDN Data Coordinating Center. A review of ClinicalTrials.gov identified one other ongoing RCT (NCT01882101) which compares BIO to percutaneous tibial nerve stimulation (PTNS), but no data have been reported yet. These two studies will not fill the knowledge gaps that the FIT Study is designed to address.

Two published RCTs compared pelvic floor physical therapy with manometry-assisted BIO to physical therapy alone in patients with FI. The first trial demonstrated that at 3 months follow-up BIO patients had greater reductions in scores on the Fecal Incontinence Severity Index (pre-treatment=33 and post-treatment=22, estimated SD ±2) compared to Pelvic Floor Exercises (PFE) patients *(F=6.82, p*=0.01, ANOVA).[12] Patients in the BIO group also tended to have fewer days/week with FI than patients in the PFE group (0.83+1.5 vs. 1.6+2.0 days/week of FI, mean and SD, *p*=0.08). Complete continence (no staining) was achieved by 20/45 (44%) of patients in the BIO group vs. 13/63 (21%) in the PFE group ($\chi 2=7.0$, *p*=0.008). This trial replicates the Heymen study[15] and provides additional support for manometric BIO; however, both this and the Heymen study have been criticized because all the subjects were recruited and treated in a single center, so generalizability across centers could not be assessed. A second study found that the addition of rectal balloon training and pelvic floor muscle training was no more effective than pelvic muscle training alone among patients with FI[18].

The only adverse event reported in any RCT of BIO for the treatment of FI was “skin soreness” in one patient[18, 24, 27]. Medicare reimbursement for pelvic floor rehabilitation for FI provided by a physical therapist is approximately $1,435 total for 6 sessions.

While BIO has been reported to increase anal squeeze pressure[15] and improve rectal sensation[34], the effects on anorectal sensorimotor functions vary considerably among studies[33, 35]. Moreover, the relationship between improvement in symptoms and anorectal functions has not been evaluated.

2.2.2. Perianal INJ of Dextranomer Bulking Agent: Two systematic reviews published in 2010[36, 37] concluded that there was no evidence for the efficacy of injectable bulking agents for the treatment of FI, but another review[38] which incorporated uncontrolled studies concluded that 56% of patients were treatment responders including 13% who achieved continence. Subsequent to these publications, Graf and colleagues[16, 39] reported a multisite RCT of the effects of dextranomer INJ versus sham (saline) injections in 206 patients. At six months follow-up, 53% of the dextranomer-INJ patients had at least a 50% decrease in FI compared to 21% of sham injected patients. At 12 months, the responder rate was sustained with 45% of the dextranomer INJ group achieving at least a 50% decrease in FI relative to baseline. Based on this multicenter RCT, dextranomer was approved by the FDA for treatment of FI.

In the only other controlled study, INJ were compared to BIO[18]. The 62 patients in the BIO group were instructed to practice at home 5 days per week for 6 months with a commercially available device that could also provide electrical stimulation, and half of the patients used electrical stimulation as an adjunctive

treatment. Patients were supervised by a physical therapist five to six times during this period. However, this report provided few details on how BIO training was done. The treatment protocol for INJ was similar to that used by Graf. Results showed that FI improved in both treatment groups (St. Mark's FI severity scores decreased from 12.9 to 8.3 in the INJ group and from 12.6 to 7.2 in the BIO group), but there were no differences between treatments.

In the Graf multisite study[16], anorectal physiology was not evaluated. In the controlled trial comparing BIO with INJ[18], the dextranomer INJ did not increase anal resting or squeeze pressure. Hence the mechanism by which dextranomer improves fecal continence is unknown.

Graf[16] reported there were 128 adverse events and two serious adverse events (AEs) in the 136 patients who received INJ. However, many of these were minor AEs related to changes in stool consistency. The incidence of more significant AEs, such as pain, fever, and/or abscess, was 9.6%. Other investigators have reported comparable rates of AEs in uncontrolled case series[40, 41]. Dextranomer treatment is not consistently reimbursed by third party payers but is estimated to cost approximately $7,408 if two injections are given [redacted]

2.2.3. Sacral Nerve Stimulation: SNS is performed in two steps: (1) During test stimulation, a temporary electrode is inserted with its tip near the sacral nerve and connected to an external stimulator for 1-2 weeks. However, screening procedures are evolving, with many surgeons now preferring to use barbed leads intended for permanent implant during the screening stage, reasoning that 70% to 90% of patients will improve enough to warrant a permanent implant, and for these patients, the permanent lead is already in place. In this study, we plan to use the tined lead to avoid the need for a second test if the PNE fails. (2) If FI frequency decreases by at least 50% during PNE, a battery-operated electrical stimulator is permanently implanted beneath the skin. An estimated 10% - 30% of patients fail to meet criteria for permanent implant. Publications on the effectiveness of SNS often report only the outcomes for patients receiving permanent implants, but this makes these outcomes not comparable to reports on BIO and INJ where the analysis sample includes all patients randomized to treatment (intent-to-treat analysis). Consequently, in the literature review below, we adjust for the number of patients failing test stimulation and report the intention-to-treat (ITT) outcomes for SNS.

Although SNS is regarded as standard of care for patients with severe FI who have failed enhanced medical treatment and is approved by the FDA for this indication, few RCTs[17, 42] have been published. Wexner[25] reported a large, uncontrolled multisite study, and this carefully done study was used for our sample size calculations. This study included 133 patients with at least two episodes of solid or liquid FI per week at baseline. After correction for patients who failed the test stimulation, the proportion achieving a 50% reduction by ITT analysis was 71.4% at six months and 66.2% at 12 months.

Tjandra[17] compared the effects of SNS to "optimal medical management" in 120 patients with at least weekly solid or liquid FI. The control intervention included pelvic floor exercises taught by digital rectal examination and loperamide if needed. Controls were seen approximately once per month in the first 6 months. By ITT analysis, 68% of SNS treated patients achieved at least a 50% reduction in FI by six months, and 42% achieved continence. Controls showed no improvement at all, which raises concerns about the credibility of the control condition for the patients randomized to control.

Thin[42] reported an underpowered RCT (described as a pilot study) which compared 19 patients treated with SNS to 17 treated with posterior tibial nerve stimulation (PTNS). No between-group statistical tests were reported but the trends favored SNS: 61% of SNS patients and 47% of PTNS patients met the responder criterion of a 50% reduction in FI episodes at 6 months. Leroi[26] published a randomized cross-over study comparing simulator-on to stimulator-off periods which is often cited in support of SNS; however, the 27 subjects in this study were likely unmasked because they could probably feel when the stimulator was on.

Tan[28] carried out a meta-analysis of available RCTs plus 32 reports on case series and concluded that SNS reduces incontinence episodes, improves ability to defer defecation, improves quality of life, and increases anal pressures. ClinicalTrials.gov identified one other ongoing cross-over study (NCT02163187) which is evaluating SNS in patients with FI following surgery for rectal cancer.

Wexner reported there were 13 treatment-related infections (AEs) including seven that required surgical intervention (serious adverse events, abbreviated SAE) in his series of 120 patients[29]. In his meta-analysis of 34 publications, Tan[28] estimated the complication rate as 15% with 3% requiring permanent explant (considered SAEs). Medicare reimbursement for SNS is approximately $18,450.

With SNS, improvement in FI frequency is associated with relatively minor effects on anorectal function[43]. One study observed that SNS but not sham stimulation increased the frequency of retrograde propagated sequences throughout the colon, which may be anticipated to delay colonic transit[44].

2.3. Expected impact of this FI comparative effectiveness trial: The proposed project will improve scientific knowledge, technical capability, and clinical practice as they relate to the treatment of FI. A critical barrier to progress in the treatment of FI is the lack of understanding regarding comparative effectiveness of currently approved treatment modalities and their pathophysiological basis. Our objectives are to address this significant gap in our knowledge by (1) comparing the effectiveness, safety, and cost of two treatments, BIO and INJ at 3, 6, 12, 18, and 24 months following the end of treatment; (2) identifying patient characteristics at baseline that predict response to each intervention; (3) investigating the mechanistic basis for treatment success by examining rectal sensory thresholds, rectal compliance, neurophysiological parameters, and stool consistency; (4) evaluating the response to treatment combinations selected by non-responders compared to the primary treatment assignment; and (5) assessing the rate of response to EMM, the durability of response, and patient characteristics that predict benefit from medical treatment. SNS will not be included as a randomized study treatment as it is a more invasive treatment and appears to negatively impact the willingness of patients to participant in the study. We will offer SNS to participants as an additional treatment choice when they are identified as non-responders to the randomized treatment at the 3-month follow-up assessment, thus allowing them the opportunity to choose as an additional treatment either SNS or the other intervention to which they were not initially randomized (either BIO or INJ). Participants who do not meet clinical criteria for receiving SNS, or who previously received and did not respond to SNS treatment will not be offered SNS as a treatment option at 3-month follow up.

When the aims of this project are achieved, the concepts, methods, technologies and treatments or preventive interventions related to the management of FI will be changed as a result of (1) development of a rational basis for recommending treatment with BIO or INJ; (2) demonstration of comparative effectiveness of each treatment modality; and (3) a new understanding of the effects of each treatment on bowel symptoms, and quality of life, especially regarding safety, tolerability, and adherence.

3.0 Study design:

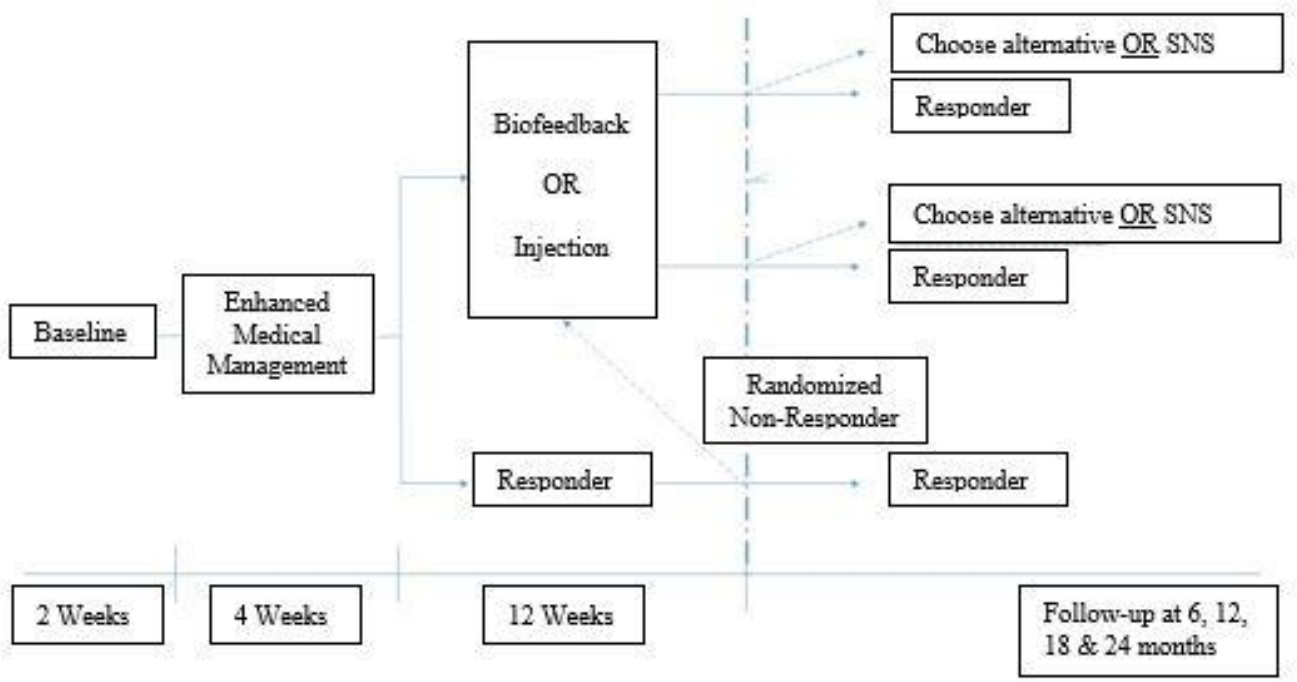
The overall study design, shown in Figure 1, is an unmasked, multisite, randomized, parallel group study comparing the effectiveness of two treatments for moderate to severe FI. This study design builds on the core recommendations of the NIDDK Workshop for design of an ideal comparative effectiveness RCT[3]. It is a parallel group design which has the following features:

1. *Baseline:* Patients will keep a daily symptom diary for two weeks prior to the Baseline visit to (a) document that they meet the minimum frequency required for inclusion in the study and (b) provide a reference value for assessing treatment response at the end of EMM and at 3, 6, 12, and 24 months follow-up points. Adverse events and cost will be reassessed at each in-person visit and at 3-, 6-, 12-, 18- and 24-month follow up assessments.
2. *Enhanced medical management:* All patients meeting inclusion criteria will first be treated with EMM for 4 weeks to identify those who really need a more expensive and more invasive treatment. The key components of treatment are patient education about the basic physiological mechanisms for defecation, diet and medication to normalize stool consistency, and pelvic floor exercises taught by printed instructions. (Section 6.1) Additional goals of the EMM protocol are (a) to ensure that patients randomized to INJ meet the accepted criteria by failing to respond to EMM, and (b) to document the efficacy and the durability of systematically applied, optimized EMM. This design is similar to the one used in the Heymen[15] RCT which provides the strongest evidence for the efficacy of BIO. We believe the exclusion of patients

who respond to the nonspecific treatment components that are included in the EMM protocol may make it easier to detect differential effects of BIO and INJ. Patients who are responders to EMM will be followed up 3 months later; those who remain responders will be continued on EMM and be followed for the remaining 24 months of the study. However, those who are no longer responders to EMM after 3 months will be invited to be randomized to BIO or INJ just like patients who failed EMM at the end of the initial run-in treatment, and all outcome measures will be assessed at 3 months from initiation of the treatment arm to which they are randomized. They will be pooled with other patients randomly assigned to the same treatment for the primary analyses and will be assessed at 6 months. Those subjects will participate for 27 months.

3. *Randomly assigned treatment:* The window for treatment to be initiated is 0 days – 4 weeks after randomization. Based on a randomization scheme implemented by the Data Coordinating Center, each patient will be randomly assigned to BIO or INJ and treated as follows:
   - BIO will consist of 5 required one-hour training sessions which should, ideally, be spaced at weekly intervals; however, the window between visits is 2 – 10 days to accommodate participants' schedules as long as no more than two visits occur in one calendar week. A 6th treatment session will be made available for patients if it is shown through anorectal manometry that they are having trouble understanding directions given during the first five sessions. These will occur in the 5-6 or so weeks following the initiation of treatment. Treatment approaches will include strength training in all patients, sensory training for patients with hyposensitivity, and/or urge-resistance training for patients with hypersensitivity to the sensations caused by rectal distention. Home exercises will be assigned to patients to practice these skills, and these will be guided by a brochure.
   - INJ will include a preparation for treatment and a treatment visit. Preparation will include the use of enemas and minimal restrictions on food intake. Prophylactic antibiotics should be started on the day of the procedure, per the treatment SOP. On the day of the procedure, a physician will inject 1 ml of dextranomer into each of 4 quadrants of the rectum proximal to the dentate line. Ten seconds will be allowed to pass before the injection needle is withdrawn to minimize drainage of the dextranomer. The patient will be scheduled to return in 6 weeks for possible repeat injection of a second 4 ml of dextranomer. At this second appointment, if FI has improved by 75% or more compared to baseline, the patient will be continued without a second injection. However, if the rate of FI is greater than 75% of baseline, the patient will be offered a second injection of dextranomer.
4. *Combination therapy:* The primary assessment of efficacy is at 3 months following the first treatment visit completed, and patients who have not achieved at least a 75% reduction in FI frequency compared to baseline will be classified as treatment failures; they will be invited to choose either the treatment to which they were not randomized or SNS as an adjunctive treatment for the remaining months of the study. One reason for offering non-responders an opportunity to try an additional treatment is to increase the likelihood that patients will consent to be randomized despite possibly having *a priori* preferences for one of the two treatments. The assumption that this will increase willingness to be enrolled was confirmed in the pilot feasibility survey we performed in 187 patients with FI representing the clinical sites: 57% of patients reported that the ability to receive the treatment of their choice if the assigned treatment was not effective, was important to their willingness to be randomized. Moreover, the estimated 46% of patients who do add a second treatment after the 3 months primary assessment will enable us to collect exploratory data on the possible benefits of combining these treatments. (None of the two investigational treatments can be discontinued.) Thus, the patients

Figure 1. Study Design



who add a second treatment and continue to be monitored up to 24 months will constitute a ***pragmatic clinical trial*** (i.e., the study design for these patients going forward emulates the clinical situation in which patients who have an unsatisfactory response to a treatment are offered a new treatment or an ancillary treatment). If SNS is selected as an adjunctive treatment it will be performed as follows:

- SNS will include insertion of a barbed stimulating electrode into the region of the S3-S4 nerve and connection to an external, battery-operated electrical stimulator for 10-14 days to test for reductions in FI. If the rate of FI decreases to at least 50% of the baseline rate, a permanent stimulator will be implanted beneath the skin. The patient will be scheduled to return in 4 weeks for an evaluation of the stimulator settings with adjustment if needed. If the initial 2-week test stimulation shows less than a 50% reduction in FI compared to baseline, SNS will be judged ineffective. The stimulator electrode may be removed at the patient's request or left in place.

5. *Primary outcomes include safety and cost as well as symptom reduction:* Very few studies have compared different treatments for FI (see Section 2.0), and these few have compared treatments based only on reductions in frequency of FI. Data on safety and cost as well as symptom reduction are needed to develop treatment algorithms and reimbursement policies. This study addresses this need by including number and type of adverse events and cost of care for two of the most frequently employed treatments for moderate to severe FI, in addition to reductions in FI. The primary outcomes will be assessed at 3 months following treatment initiation. The window for the 3-month follow-up assessment is 1 week before and 3 weeks after the anticipated due date.
6. *Long-term follow-up:* An intention-to-treat analysis of efficacy will be carried out at 6, 12 and 24 months. For these analyses, all patients randomized to the treatment will be included in the analysis. These follow-up assessments should occur within the following windows:

    - 6- and 12-month follow-up assessments - 1 week before and 3 weeks after the anticipated due date; and
    - 24-month assessment - 3 weeks before and 3 weeks after the anticipated due date.

    All treatments will continue to be active after the training period. The bulking agents injected in the INJ treatment will remain in place. For BIO, patients will be encouraged to continue to practice pelvic floor

exercises and enhanced awareness of rectal sensations following the initial training period. Patients who withdrew from the study or who fail treatment at 3 months will be evaluated as treatment failures in follow-up analyses of efficacy. Data will be collected from participants who switch to an alternative treatment at 3 months, but these data will not be considered in this analysis. Safety data will be collected at every visit and follow-up assessment. Patients who are responders at 3 months will continue to monitor symptoms for an additional 21 months (2 years total) whereas patients who are non-responders at 3 months will be retained as treatment failures in the long-term analysis of the comparative effectiveness of these two randomized treatments. For longitudinal assessments of safety, cost, and secondary outcomes such as quality of life and FI severity scales, statistical models will include data from follow up time points through 24 months.

7. *Adjust for Expectation of Benefit:* In a trial comparing behavioral and medical therapy, patients cannot be masked. The validated Credibility/Expectancy Questionnaire[45] was developed to assess the patient's expectation of benefit after initial exposure to treatment and was used in previous studies to determine whether there is equipoise between the active and control conditions in behavioral treatment trials[15]. In this study, which is unmasked from the patient perspective, we anticipate that many patients will not regard the treatments as equally credible; therefore, we will rely on randomization to balance the groups for average level of expectancy. We will also use the Credibility/Expectancy Questionnaire[45, 46] to assess individual differences in expectancy and will enter this into the analysis as a covariate to see whether it explains group differences in efficacy.

8. *Characterization of Enhanced Medical Treatment - Durability of improvement and predictors of response:* The primary purpose of treating all patients with an EMM run-in is to be able to exclude patients who do not require more costly interventions. However, we will take advantage of the opportunity provided by this run-in study to identify predictors of response to EMM and to assess the durability of improvements. EMM will not be "usual care" but will follow a written protocol that is intended to optimize EMM, which is why we label this enhanced medical management. Patients who are treatment responders at the end of the EMM run-in will be scheduled for 3-month follow-up, and those who are no longer treatment responders at 3 months follow up will be offered an opportunity to be randomized to one of the 2 treatments at this point. However, those who remain responders to EMM at 3 months follow up will continue to be followed for an additional 21 months. All patients, regardless of their outcomes at the end of EMM, will be encouraged to continue using the treatment approaches learned during the EMM phase. Participants, whether determined to be EMM responders or not, will be asked at the end of the 1-month EMM period and then also at the 3-; 6-; 12-; and 24-month follow-up assessments if they are continuing to adhere to these treatment approaches (pelvic floor exercises and medication).

3.1 Event Windows:

Event	Window for event
Screening	N/A
Baseline	To be completed no more than 6 weeks after ***Screening Visit.***
EMM – start	EMM should start 0 days – 4 weeks from the completion of the ***Baseline*** diary.
EMM - Check-in Calls	• Call 1: 3 – 5 business days after starting EMM • 14-day call: 2 business days before - 2 business days after the 14th day from the start of ***EMM***
Randomization in Medidata	***Randomization*** in Medidata EDC should occur 4 weeks - 6 weeks after the start of EMM. Note: • The ***Randomization Visit*** may occur anytime between the end of ***EMM*** and ***Treatment Initiation.***

	• *But*, all requirements for randomization eligibility must be completed before ***randomization*** in Medidata.
Treatment initiation (Time 0) for first randomized intervention (BIO, INJ)	Randomized treatment should start 0 days to 4 weeks after ***randomization*** in Medidata. Note: • If treatment is initiated on the same day as the ***Randomization Visit***, all randomization requirements (questionnaires and procedures) should be completed before ***treatment initiation***. • The ***Time 0*** date used to determine subsequent events dates in the Medidata EDC will be determined as follows: o Time 0 for BIO = Date of Train Session 1 o Time 0 for INJ = Date of the first injection o Time 0 for EMM responders = Date the randomization eligibility CFR is completed in Medidata (that is, date when participant is deemed to be ineligible for a randomized intervention as considered a responder to EMM). o For any participant who does not respond to EMM but who is also not randomized for any other reason, the ***Time 0*** used to determine the schedule for the follow-up assessments will also be the date on which the randomization eligibility CRF is completed in Medidata.
Biofeedback (BIO) therapy (5 x 1-hour visits, with an optional 6th)	Each ***Biofeedback*** Train session should be spaced with a minimum interval of 2 days and a maximum interval of 10 days from the previous session, with no more than two sessions in a calendar week. ***Preferred is one training session per week.***
Injection (INJ) – 6-week follow-up	1 week before – 2 weeks after the target date determined from ***Time 0***
3-month follow-up	1 week before – 3 weeks after the target date determined from ***Time 0***
6-month follow-up assessment	1 week before – 3 weeks after the target date determined from ***Time 0***
12-month follow-up assessment	1 week before – 3 weeks after the target date determined from ***Time 0***
18-month follow-up assessment	1 week before – 3 weeks after the target date determined from ***Time 0***
24-month follow-up assessment	3 weeks before – 3 weeks after the target date determined from ***Time 0***
Optional treatment - initiation	Optional additional treatment initiation should occur within 0 days to 4 weeks after the 3-month visit post randomization.
Note: • Event windows for follow-up assessments will continue to be determined from treatment initiation (***Time 0***) of the randomized intervention even when participants who fail that treatment select a second intervention. • The timeline for those participants who initially respond to ***EMM*** but are then randomized after they are determined to be treatment failures at the 3-month follow-up assessment will reset when they begin the randomized intervention. For these participants, the timeline for subsequent events will reset based on the ***Time 0*** of their randomized intervention. These participants will be active in the trial for an additional 3 months so that they are able to complete the 24 months of follow-up following the start of the randomized treatment.	

4.0 Outcome Measures

4.1 Primary Outcomes: There are three primary outcomes: efficacy, safety, and cost.

4.1.1 Efficacy: The primary efficacy analysis will be based on the proportion of responders in each treatment arm. A responder will be defined as an individual whose symptom diaries demonstrate at least a 75% reduction in the average weekly frequency of FI from baseline (prior to the EMM to the last two weeks of the treatment period preceding the 3-month post intervention follow up. The rationale for choosing a 75% reduction in the frequency of staining, solid and liquid stool incontinence as the primary outcome measure is that, both in focus groups and surveys we conducted, half of patients with FI reported that they did not consider a 50% reduction in FI episodes to be a satisfactory measure of treatment success; rather, they believed an improvement of 70-80% was necessary for a treatment to be considered successful[47].

The frequency of FI will be recorded on a paper diary. Patients will be asked to record (1) the time of each accidental bowel leakage (ABL), (2) the amount of leakage that occurred, (3) the rectal sensation that occurred prior to the event (no awareness, normal warning, or strong urge), and (4) the consistency of the leaked stool. Patients will also be asked to record (5) the time of any BM that occurred in the toilet even if this starts as an ABL and is finished by passing stool in the toilet, (6) the consistency of the BM using the Bristol Stool Form Scale, and (7) medications or other treatments employed. The primary outcome is based only on the number of FI events; however, the amount of stool lost and the type of sensation experienced before the leakage are needed to guide the BIO intervention, and the number and consistency of BMs and use of fiber or medications is used to guide the EMM intervention. Rather than use different diaries for each of these purposes, we will ask all subjects to use this paper diary throughout the intervention period and for two-week periods preceding all follow up assessments.

Previous studies have identified a number of limitations to paper diaries: (1) Missing data if subjects forget to complete the diary or if it is illegible. (2) Inaccurate data that may result if subjects forget to record events when they occur and then try to remember what happened at the end of the day or several days later. In previous studies[48], we provided patients with a pocket-sized paper diary to take with them throughout the day and asked them to transfer their symptom ratings from the paper diary to a website at the end of the day. If they failed to submit a report to the website within 12 hours, they were sent an email reminder or were telephoned. They were also reminded the next time they attempted to enter data, if the data for the previous day was missing, and they were given an opportunity to report on the previous day; however, they were not permitted to go back further than the previous 24 hours. They were also provided with bonus payments for not missing any diary reports. With this combination of techniques, we were able to obtain an average of 73 consecutive days of symptom diaries without interruption from 185 IBS patients varying in age from 18 to 84. However, there is concern that since advancing age is a risk factor for FI, the patients who enroll in this study will be older and less comfortable than young or middle-aged subjects with transferring data to the internet. Therefore, to avoid biasing enrollment against these older subjects, we decided to use paper diaries for this study. To ameliorate potential problems with missing or untimely data reporting we will (1) thoroughly train subjects in recording their diary information at enrollment, and (2) telephone subjects during the first two weeks that they keep the diary to ensure that they are able to record events on this paper diary when they occur.

To protect against experimenter bias, patients will be classified as responders or non-responders based on diary data entered into the electronic data capture (EDC) system at the end of EMM and at 3-, 6-, 12-, and 24-month follow-up. Once the diary data are entered, a calculation performed within the EDC system will determine which patients are non-responders eligible for randomization, and the same process will determine which patients are non-responders at 3 months so they can be offered alternative treatment.

4.1.2 Safety: Adverse events will be collected by participant interview and medical records review, as appropriate, at all clinic and follow-up assessments. Adverse events occurring in the period from the time that the participant is consented through the end of the participant's study involvement at the 24-month follow-up assessment should be documented (See ***Section 9.2***). Adverse events will be classified as Serious Adverse Events (SAEs) if conventional criteria are met [redacted] or simply as adverse events (AEs). AE

severity will be graded based on common terminology criteria for adverse events (CTCAE). Relationship to treatment will be assessed by the treating clinician and reviewed by the Medical Safety Monitor for the purpose of determining which events need to be reported to the IRB, DSMB and NIDDK in an expedited manner. At the end of the study, relationship to treatment will be evaluated by comparing the incidence of specific AEs between treatment groups. AEs will not be collected on the bowel diary, but patients will be encouraged to contact the study coordinator any time they notice a new symptom or side-effect.

4.1.3 Cost of care: A primary endpoint is cost for each treatment from the payer, patient, and societal perspectives. For the payer perspective, we will tabulate the numbers and types of treatment visits and multiply these by Medicare authorized reimbursement rates. Patient costs will be obtained from an *Out-of-Pocket Cost Questionnaire* developed to collect information on amounts patients pay for non-prescription medications and absorbent pads. Estimated costs from the societal perspective will be the sum of payer costs, patient costs, and patients' productivity losses associated with FI as evaluated by the *Work Productivity and Impairment questionnaire* (WPAI)[49]. The WPAI is a widely used measure of work absenteeism, impairment while at work, and interference with daily activities.

A secondary endpoint is an analysis of the cost-effectiveness of the two treatments. The metric used for comparing cost-effectiveness is the quality adjusted life years. This calculation requires a health-related quality of life index, i.e., a generic health related quality of life scale that may be used to compare the morbidity-related impact of different disease states. Harvie and colleagues[50] compared three of these health-related quality of life indices in a group of 200 women with fecal incontinence, urinary incontinence, and/or pelvic organ prolapse. The utility indices compared were the Health Utilities Index Mark 3 (HUI-3)[51], the Euro-Qol (EQ-5D)[52], and the Short Form 12 (SF-6)[53]. The HUI-3 and the EQ-5D were comparable in terms of their correlation with FI severity scales and their ability to discriminate between women with FI and those without. However, the EQ-5D is the only one that has previously been used to estimate cost-effectiveness for treatment of FI, and it was shown to be able to discriminate between SNS and another surgical treatment for FI[54].

4.1.3.1 EuroQol 5D (EQ-5D): The EQ-5D consists of 5 domains – mobility, self-care, usual activities, pain/discomfort, and anxiety/depression – with three possible responses indicative of severity of impact for each of the 5 single question corresponding to these 5 domains[55]. It shows good convergent validity with other standard measures of health utility such as the HUI-3[50], and is able to discriminate between different treatments for FI[54]. The EQ-5D is the most widely used health utilities instrument for assessing cost-effectiveness. This generic QoL measure will complement the disease-specific Fecal Incontinence Quality of Life Scale.

4.1.3.2 Work Productivity and Impairment (WPAI)[56]. The WPAI will be used to measure cost from a societal perspective. It is a widely used measure of work absenteeism, impairment while at work, and interference with daily activities. The WPAI can be given in two forms: one of which measures the impact of general health problems and a second which measures the impact of a specific health condition. The WPAI has been shown to have good convergent validity with other measures of work and activity impairment as well as test-retest reliability and discrimination between health states[49, 56]. It has not been used to measure the impact of FI on work productivity but has been used in studies of overactive bladder and urinary incontinence[57], and it is sensitive to the benefits of a drug on absenteeism and activity impairment in patients with irritable bowel syndrome[58].

4.1.3.3 The Out-of-Pocket Cost Questionnaire. This is a new questionnaire designed to collect information on the amounts patients pay for non-prescription medications and absorbent pads purchased for the self-management of FI. In an anonymous internet survey[59] of people with FI (half of whom had not discussed this problem with any physician), we asked how they coped with FI on their own; the first three responses in order of frequency were wearing pads, taking antidiarrheal medicines, and limiting food intake when they had to leave the house. This suggests that purchase of pads and medications for diarrhea or constipation may be significant sources of cost for patients.

4.2 Secondary endpoints:

4.2.1 Assessment of FI severity by the Fecal Incontinence Severity Scale (FISS) which is derived from the Fecal Incontinence and Constipation Assessment questionnaire[60]. This is a validated FI severity scale which incorporates the frequency of different types of stool loss (solid, liquid, staining and a combination), the circumstances surrounding FI (urgency, passive, combined, or neither), and volume of leakage. It is the only scale that incorporates the volume of leakage, which the NIDDK Workshop recommended be included when evaluating the severity of FI[61]. The originally published scale will be adapted for use as an outcome measure by changing the reporting period for symptoms to the past month rather than the past year. The psychometric properties of this instrument have been validated in community-based studies, and it has been used in a therapeutic trial[9, 61-63]. Symptom severity ranked by this

*Table 2: Measurements Table for FIT Study**

Schedule of assessments	Screening	Baseline	Randomize	3 mo	6 mo	12 mo	18 mo	24 mo
Socio-demographics and examination	X							
Bowel diary, including BSFS		X	X	X	X	X		X
Endoanal ultrasound		X**		X*** (INJ arm only)				
Balloon Evacuation Test (BET)		X**						
Anorectal manometry (ARM)		X**		X***				
Magnetic Evoked Potential (MEP)		X**		X***				
Fecal Incontinence Severity Scale (FISS)		X	X	X	X	X		X
Fecal Incontinence Quality of Life (FIQOL)		X	X	X	X	X		X
PHQ-12 Somatization scale			X	X	X	X		X
PROMIS Anxiety-7			X	X	X	X		X
PROMIS Depression-8			X	X	X	X		X
PROMIS Self-Efficacy Symptom Management			X	X	X	X		X
Assessment of AEs, SAEs		X	X	X	X	X	X	X
Cost (treatments, # of visits, out of pocket)		X	X	X	X	X	X	X
Work Productivity and Impairment (WPAI)		X	X	X	X	X	X	X
EuroQol 5D (EQ-5D)		X	X	X	X	X	X	X
Burden of Treatment Questionnaire		X	X	X	X	X	X	X
GI Symptom Questionnaire		X						
ABLe			X	X	X	X		X
Continence Rating			X	X	X	X		X

* Additionally, participants will complete the Credibility/ Expectancy Questionnaire (CEQ) each time that they start one of the four study interventions (EMM, BIO, INJ and SNS). So, all study participants will complete the CEQ when they start EMM and all randomized participants will complete the CEQ when they start BIO, INJ or SNS either as a randomized treatment or if they select BIO, INJ or SNS when they are identified as non-responders to the randomized treatment at the 3-month follow-up assessments.

** The endoanal ultrasound, BET, ARM and MEP may be conducted at the randomization visit, if not done at Baseline. If an imaging study (US or MRI) was performed in the previous 12 months to assess the sphincters, then this need not be repeated at Baseline if the sphincters appeared normal and there has been no history of anorectal trauma, surgical procedures, or vaginal deliveries in the intervening period between the imaging exam and study participation.

***The endoanal ultrasound (INJ only), the ARM (all participants) and the MEP (all participants) may be performed at the 3-month follow-up assessment. Participants who complete **two** 3-month follow-up visits should only have the ARM and MEP performed at the first 3-month follow-up visit. This will only apply to participants who initially respond to EMM but are later identified as non-responders at the 3-month follow-up visit and are then randomized to BIO or INJ. They will complete another 3-month follow-up visit, this time three months after they have initiated one of the randomized treatments. NOTE: Participants who elect to receive INJ as an optional treatment may have an endoanal ultrasound at their follow-up visit following completion of that treatment (likely their 6-month follow-up visit).

scale is strongly correlated with the impact of FI on quality of life[63]. It will be given at baseline, end of EMM, 3, 6, 12, and 24 months (Table 2).

4.2.2 Fifty percent responder. To facilitate comparisons with previously published studies that have used a 50% responder definition[16, 25], we will also calculate the proportion of patients who have at least a 50% reduction in FI episodes. This will be calculated from diary data entered in the EDC system at the end of EMM and at 3-, 6-, 12-, and 24-month follow-up.

4.2.3 Continence rating. The proportion of patients in each treatment arm who are continent at each follow up will be reported as an additional secondary outcome of treatment efficacy. This will be calculated from diary data entered in the EDC system at the end of EMM, and at 3, 6, 12, and 24 months. Continence will be defined by three criteria: (1) Absence of FI episodes on the two-week bowel diary, (2) self-report by the patient using a questionnaire that they have had no ABLs for the last month, and (3) self-report that they "no longer have this problem" (question 1 below).

1. Have you had any ABLs in the last 30 days? Yes/No.
2. "How would you rate your response to this treatment? Please choose from the following: (a) Worse than before treatment. (b) About the same as before treatment. (c) Somewhat improved. (d) Much improved. (e) I no longer have this problem."

4.2.4 FI Quality of Life (FIQOL) scale[6]. This is a validated disease-specific quality of life scale which is commonly used in FI treatment trials. It will be given at baseline, end of EMM, and 3, 6, 12, and 24 months follow up (Table 2). The FIQOL contains 29 items and is scored for four subscales: Lifestyle, Coping/Behavior, Depression/Self-Perception, and Embarrassment[6]. It has good convergent validity with generic measures of health-related quality of life, good test-retest reliability, and ability to discriminate patients with FI from those with IBS.

4.2.5 PROMIS Anxiety Scale. PROMIS refers to the Patient Reported Outcomes Measurement Information System, which is a large collection of publicly available outcome measures available to clinical researchers. This library of validated patient reported outcome scales resulted from a collaboration between academic investigators and the National Institutes of Health. A team of PROMIS investigators consisting of experts in each domain (including anxiety) identified candidate items from existing questionnaires and wrote new items when necessary. This large item bank was then reviewed and revised if necessary, tested in focus groups of patients and non-patients to ensure domain coverage, and tested for understandability by cognitive interviews with individual items. Final edits were then made prior to field testing in large samples drawn from the population and from clinical samples. For each domain, a large bank of items was developed to be used as a pool of items for future test development, and subsets of items were selected for the development of computer adaptive testing (CAT) based on item response theory, and short paper forms of (typically) 4-8 items. Although there are no publications listed in PubMed for the use of the PROMIS Anxiety Scale in patients with FI, there are data on the psychometric properties of the scales in population samples and clinical samples with other disorders such as cancer and knee osteoarthritis. These sources show that the 7-item PROMIS anxiety scale correlated .97 with the 29 items in the full bank of anxiety items, showed an alpha reliability coefficient of .98 throughout most of the range for the scale, and a correlation of .96 with legacy measures of anxiety[64]. In clinical samples of patients with knee osteoarthritis[65] and multiple sclerosis[66], the correlations with legacy measures of anxiety were .71 and .95 respectively.

4.2.6 PROMIS Depression Scale. This scale was developed by the same process as the PROMIS Anxiety scale above. The 8-item short form PROMIS Depression scale correlates .96 with the whole bank of 28 depression items, has a reliability coefficient of .99 through most of the range of scores, and is correlated .83 with the CES-D depression scale[64]. In clinic samples with knee osteoarthritis[65] and multiple sclerosis[66], the correlations are .70 and .80 respectively.

4.2.7 PROMIS Self-Efficacy for Managing Symptoms Scale. This questionnaire was developed to assess the participant's willingness to engage in self-management skills, which is relevant to how patients perceive and react to the obligation to learn new skills and practice them when managing a symptom as compared to

accepting a treatment applied by a physician that does not require any responsibility for self-management. Although no validity data has been reported for the self-efficacy scale, this scale was selected because the items have face validity for FI (example: "I can keep my symptoms from interfering with relationships with friends and family." [49])

4.3 Moderator variables

4.3.1 PHQ12 (Somatization). This scale is derived from the Prime MD structured interview. It consists of the 15 most commonly reported symptoms in primary care practice. The subject is asked to rate how much they were bothered by each symptom in the last 1 months on a scale from 0="not bothered at all" to 2="bothered a lot". Total scores are 0-30, with cut-off points of 5, 10, and 15 dividing the responders into mild, medium, and high severity. The PHQ-15 is highly correlated with other measures of somatization[67], and it is a strong predictor of disability days, clinic visits, and scores on all subscales of the SF-20 health related quality of life scale[67, 68]. Cronbach's alpha is .80. The PHQ-15 includes 3 gastrointestinal symptoms, which could confound the interpretation of the impact of somatization in gastrointestinal (GI) disorders if the GI symptoms on the PHQ-15 are part of the diagnostic criteria for the GI disorder. Spiller has recommended eliminating these three items for GI studies, and he refers to this derived scale as the PHQ-12[69]. The cut-points dividing mild, medium, and high severity will be adjusted to 4, 8, and 12. We are using the PHQ-12 as a moderator variable because we have found somatization (measured by a different scale) to be a strong predictor of fecal incontinence severity. This is included as a moderator variable because recent unpublished studies show that somatization is a strong predictor of FI-specific quality of life.

4.3.2 Credibility/expectancy questionnaire (CEQ)[45]. A potential bias in trials where the treatment conditions cannot be masked is the patient's perception of the credibility and expectation of benefit associated with the treatments; these have been shown to influence the outcome of clinical trials. It is possible to assess the extent of this bias by asking patients to rate the intervention to which they are randomized for credibility and expectancy after their first exposure to the treatments. The CEQ consists of 6 items which are scored for two subscales: credibility and expectancy. This questionnaire has high internal consistency and good test-retest reliability[45]. It is recommended to be used in clinical trials of behavioral and surgical interventions where it is not possible to mask which treatment subjects are receiving and where a priori differences in credibility and expectancy could confound the interpretation of the trial results[70].

This questionnaire will be completed each time the participant starts one of the study interventions (EMM, BIO, INJ), as well as the optional treatment, SNS. So, all participants should complete the CEQ at least once – when they begin EMM. Randomized participants will complete it once or twice more – when they begin the randomized treatment (BIO, INJ) and then possibly again if they are identified as non-responders to the randomized treatment at the 3-month follow-up assessment and select the other treatment to which they were not originally randomized or SNS. The CEQ should always be administered at the treatment initiation visit but ***after*** the treatment has been initiated as follows:

- EMM – after the participant has completed the EMM treatment initiation session;
- BIO – after the participant has completed the TRAIN 1 session;
- INJ – after the participant has received the injection of bulking agent;
- SNS – after the participant has undergone the procedure to implant the temporary leads.

4.3.3 Sex. Because there are different risk-factors for FI in females vs. males[1], it is possible that the females and males will respond differently to these treatments. Randomization will be stratified by sex.

4.3.4 Subtype of FI: Passive vs. urge-related FI. Passive FI is defined as FI that occurs without any warning sensation, while urge FI is said to occur when the patient feels a warning sensation of rectal fullness or urgency prior to stool leakage but is unable to reach the toilet before leakage occurs. It has been suggested that dextranomer may be more effective in patients with passive FI as compared to urge FI[71]. Patients will be classified at baseline as passive FI if their symptom diary shows ≥50% of FI episodes occurring without warning and as urge FI if <50% occur without warning.

4.3.5 Bristol Stool Form Scale (BSFS) rating of stool consistency[72]. This is imbedded in the bowel diary. Measured at baseline, end of EMM, and at 3-, 6-, 12-, and 24-month follow-up (Table 2). The bowel diary form

includes validated pictures and descriptors of 7 different stool consistencies. For each 14-day bowel diary, we will compute the proportion of all BMs (including both continent and incontinent BMs) that are rated as BSFS types 1 or 2, and the proportion rated as BSFS types 6 or 7. The BSFS is a valid measure of stool form which correlates more strongly with whole gut transit time measured by the radio-opaque marker technique (r=.54) than with stool frequency (r=.35) or total stool output (r=.41). BSFS rating are also responsive to treatment with laxatives or antidiarrheal medications[72]. Another study[73] showed a significant correlation of r=.49 between the BSFS ratings of healthy volunteers and stool water content, and a stronger correlation of r=.70 between BSFS ratings made by GI experts and stool water. As might be expected from the classification of a continuous measure into discrete categories, there is moderate variability between raters in the discrimination of type 2 from type 3 and the discrimination of type 5 from type 6, but there is excellent discrimination overall between the three functional categories: hard stools of types 1-2, normal stools of types 3-5, and loose stools of types 6-7.

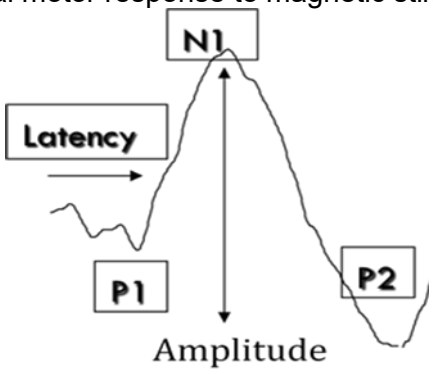
4.3.6 Anorectal manometry. Determine anal resting and anal squeeze pressures, sphincter squeeze endurance, rectal sensory thresholds (bag volume and intra-bag pressure at the first report of sensation, desire to defecate, urgency to defecate, and maximum tolerable volume), and rectal compliance. These parameters will be measured at baseline (but can be measured prior to randomization if not measured at Baseline) and may also be done at 3 months following initial treatment using the portable Medspira Anorectal manometry equipment, which can be used in the office and does not require a dedicated laboratory. This system includes a catheter, with 4 radially-oriented equidistant anal balloons and 1 rectal balloon, a wireless manometer, and a computer. The catheter is connected to the manometer that has pressure transducers and communicates wirelessly to the computer. The acquisition module display provides instructions that guide users conducting the study. The maneuvers used during portable manometry are identical to those in high-resolution manometry (HRM). Anorectal pressures and rectal sensation measured with portable manometry are significantly correlated with high-resolution manometry[74]. Participants who initially respond to EMM but are then randomized after they are identified as non-responders at the 3-month follow-up visit may have the ARM performed at the initial 3-month assessment but it should not be repeated at their second 3-month follow-up assessment if they are then randomized to BIO or INJ.

4.3.7 Motor evoked potentials (MEP) will be tested at the Baseline visit (but can be tested at any time before randomization). It may also be tested at 3-month follow-up in all treatment groups. However, participants who initially respond to EMM but are then randomized after they are identified as non-responders at the 3-month follow-up assessment will not have the MEP repeated at their second 3-month follow-up assessment, that is, at the follow-up 3 months after they initiated the randomized treatment. The MEP data will be collected at the Mayo Clinic and Augusta University. MEP data will not be collected at the University of North Carolina at Chapel Hill, the University of Alabama at Birmingham, and the University of Michigan.

This test uses a specially designed rectal probe with 2 pairs of bipolar steel ring electrodes, each 2 cm apart, mounted on a catheter (Gaeltec Ltd, Isle of Skye). The proximal pair will be located 8-10 cm from anus and the distal pair at 1-2 cm from anus. The electrodes are used to record the motor evoked potentials after magnetic stimulation. Magnetic stimulation of the lumbar (TLMS) and sacral (TSMS) nerve roots will be performed using a commercially available 90 mm coil magnetic stimulator (Magstim 200^2; MAGSTIM, Whitland, UK). The subject will lie prone. For the TLMS study, the coil will be placed on each side of the midline approximately 3-5 cm laterally and between L2 and L3 vertebra. The coil will be discharged with increasing frequency starting at 50% and up to a maximum output of 85% of the scale range for magnetic stimulation intensity. For the TSMS test, the sacrum will be palpated to identify the S2 and S3 vertebra. The coil will be placed on each side of the midline over the sacrum (S2-S3) and discharged up to a maximum of 85% magnetic stimulation intensity. The EMG responses from anterior tibialis muscle of one leg will also be recorded (as a control) using Ag/AgCl disc electrodes The MEP responses will be recorded into a 4-channel amplifier with a built in AD interface (Nihon Kohden, Japan) with filter settings of 5-2000 Hz and at a sampling rate of 4-8 kHz, fed into a computer for display and analysis. Figure 3 shows the whole system. An optimal response will be defined as an anal and rectal MEPs of >10μV and tibialis response of 100μV on at least 3/6 consecutive trials. A rest period of 5 minutes will be allowed between stimulations on each side. Five MEP responses will be obtained on each side and the average of the best three responses will be used to measure MEP response.

Measurements and Analysis: The latencies of wave forms (Figure 2) on both the TLMS and TSMS-induced MEP responses will be analyzed on both the right and left sides. The first and most prominent negative or positive deflection will be designated as the MEP response. We will measure the average latency for the left lumbo-rectal and lumbo-anal and the right lumbo-rectal and lumbo-anal MEPs. Similarly, the average latency for the left sacro-rectal and left sacro-anal and the right sacro-rectal and right sacro-anal MEP responses will be measured for a total of 8 measures. Each averaged response latency will be classified as abnormal if it is greater than the upper confidence interval reported previously for healthy controls; otherwise normal. Patients will be classified as having a neuropathy if ≥1 of 8 average latencies are abnormal. The validity of this test as a measure of pelvic nerve neuropathies was demonstrated in previous studies showing that these latencies differentiate patients with FI as a group from healthy controls (abnormally delayed latencies in 80% of patients with FI)[75], and abnormally delayed latencies are also found in patients with spinal cord injury (known neuropathy)[76]

Figure 2. Typical motor response to magnetic stimulation of the lumbar spine



4.3.8 Anorectal ultrasound or pelvic floor MRI. Measured at baseline (but if not done at Baseline, can still be measured up to and including at the time of the Randomization visit) in all subjects and may also be done at 3 months in dextranomer treated patients. Sites will report who performs and interprets the test, whether an anorectal ultrasound or a pelvic floor MRI was performed, the person performing the test and the person interpreting the study, the width of any defects in the internal and external anal sphincters and puborectalis muscles, and the minimum thickness of these muscles. For sites using anorectal ultrasound, BK probes that are 3 dimensional will be used, except for The University of Alabama at Birmingham where 2 dimensional BK probes will be used. Please see the Anorectal ultrasound/pelvic floor operating procedure manuals. If this was performed in the previous 12 months to assess the sphincters, then this need not be repeated at Baseline if the sphincters appeared normal and there has been no history of anorectal trauma, surgical procedures, or vaginal deliveries in the intervening period between the imaging exam and study participation.

4.3.9 Treatment Burden Scale. This questionnaire was developed to assist in understanding the burden of treatment, concerning time needed to complete the treatment, risk of new symptoms, adverse events or side effects, personal responsibility, and financial burden of the treatment.

5.0 Study population

The target study population are males and females aged 18 or older who have moderate to severe FI, defined as a minimum average frequency of staining, solid or liquid FI events at least 2/week using the baseline bowel diary. Patients will be recruited by a variety of methods: Direct referrals from clinicians, patients with a diagnosis of FI in their medical record (ICD 10 diagnosis code R15), registries of research participants with FI who have participated in previous studies of FI treatment, and advertisements in newsletters, newspapers, on websites, or flyers posted in medical or surgical clinics. Information on how the patient learned about the study will be collected at their screening visit.

5.1 Inclusion/ Exclusion criteria

Inclusion Criteria	Exclusion Criteria
Physician diagnosis of FI (R15) for the past 6 months or longer. We will recruit some subjects by advertisement who may not have consulted a physician, and this diagnosis may be made by the study physician.	Dementia will be assessed using the Six-Item Screener to Identify Cognitive Impairment. The subject is asked to remember 3 words (apple, table, penny), which may be repeated up to 3 times. This is followed by 3 questions on the year, month, and day of the week. Finally, the subject is asked to recall the three words. Three or more errors has a sensitivity of 88.7% and specificity of 88.0% compared to clinical diagnosis and is not different from the Mini Mental State Exam. [Callahan, CM et al. Six-Item Screener to Identify Cognitive Impairment among Potential Subjects for Clinical Research. Medical Care 2002;40:771-81.]
Able to ambulate independently on level surfaces. Patient may use assistive devices other than parallel bars.	Obstetrical injuries including third and fourth degree tears in the anal sphincter within 6 months.
Average ≥2 solid, liquid, or staining FI episodes per week by self-report and during the two-week baseline	Pregnant or planning pregnancy in next 2 years
Meets criteria for dextranomer treatment except an internal anal sphincter defect of 180 degrees or less is acceptable.	Internal anal sphincter separation >180 degrees on ultrasound or magnetic resonance imaging
Required for randomization: Less than 75% reduction in the number of FI episodes after 4 weeks of EMM.	Spinal cord injury or spina bifida
Age >=18 years	Congenital malformation of anorectum
	Complete rectal prolapse or grade III/IV hemorrhoids
	History of ileoanal pouch; history of anal sphincteroplasty, rectopexy, or rectocele repair within the past 6 months; or history of pelvic surgery with synthetic graft and suspected graft erosion into the anus, rectum, or skin or if the graft ends less than approximately 1" above the upper limit of the anal canal.
	Established diagnosis of inflammatory bowel disease
	Intestinal stoma present
	History of pelvic radiation within previous 12 months or presence of active radiation proctitis.
	Patients who cannot expel the rectal balloon during the balloon expulsion test and who have constipation most of the time.
	Anatomic limitations to placement of dextranomer injections.
	Presence of existing implant in the anorectal region
	Allergy to hyaluronic acid-based products
	Active anorectal conditions in the last 6 months including abscess, fissures, sepsis, significant bleeding, proctitis, colovaginal and rectovaginal fistulas, anorectal tumors, or other infections.
	If the patient's physician believes it is unsafe for the patient to temporarily stop anticoagulants for any test procedures and treatments associated with the study.
	Patients who have 4 or more days with 4 or more bowel movements classed as a 6 or 7 on the Bristol Stool Scale per day in either (any) week during the Baseline will be excluded.
	Patients with Parkinson's disease, multiple sclerosis, severe diabetic neuropathy documented by EMG, and neurodegenerative disorder.
	Patients currently receiving immunotherapy or chemotherapy
	Significant anal pain in the last 6 months.
	If the patient is unwilling to stop using over-the-counter medications, herbal supplements, or prescribed medications for the purpose of modifying stool consistency, that are not included in the approved medications list (loperamide, laxatives, fiber supplements, and Questran are approved medications), for the duration of the research study.

Medical history will be documented to test for predictors of response.

5.2 Sample Size Estimates

5.2.1. Primary Efficacy Outcome

Sample-size calculations are based on the number of patients required to detect a difference of 20% in the proportion of responders because we consider this to be the Minimum Clinically Important Difference (MCID) between groups following treatment. Table 3 shows the sample data used in these calculations, which comes from published pivotal trials for dextranomer and biofeedback. Conservatively assuming an average response rate of 50% across the groups, an alpha of .05 and power of 80% we would need at least 97 patients per group to test for differences of this magnitude between 2 treatment groups. Since the planned analysis will use an intention to treat (ITT) approach in which all participants will have a defined efficacy outcome regardless of study completion, this sample size was not inflated to account for potential drop out.

The data in Table 3 suggest that we have an excellent chance of detecting a difference of 20% and of showing that BIO is superior to INJ in the proposed trial. We should also be able to show significant differences between BIO and the other two treatments for adverse events, estimated cost of care, percent continent, and impact of FI on quality of life (Table 4).

Table 3: Preliminary Data for Sample Size Calculations

Efficacy Outcome Measure	***BIO Heymen[15]***	***INJ Graf[16]***	***Sample size required per group***
Baseline: FI days per week	3.4 (SD=2.1)	4.8	--
≥50% decrease (%)	93%	53%	28
≥75% decrease (%)	78%	32%	28
Continent (%)	44%	5.9%	29

Table 4: Preliminary Data on Other Outcome Measures

Outcome Measure	**BIO Heymen[15]**	**INJ Graf[16]**	**Sample size required per group**
[1]Adverse events (% subjects)	0%	9.6%	74
[2]Estimated cost ($)	$1,435	$7,408	--
[3]% Change in quality of life impact	11.9% (SD = 21.5)	27.3%	32
[3]St Mark's Score or FISI, Average % decrease	36% (SD = 45.8)	17.9%	102

[1]There were 128 AEs in 136 patients, but some were relatively minor. We list only the estimated rate of pain, fever, and abscess (13 events in 136 patients). Sample size calculations are for tests of proportions with alpha = .05 and beta = .80.
[2]Costs are estimated from published Medicare reimbursement tables are not compared statistically.
[3]Continuous outcomes for quality of life and FI severity calculations assume alpha = .05 and beta = .80.

It is anticipated that up to 15% of participants enrolled in the study will drop out (with no further follow up). before completing enhanced medical treatment. If the number who drop out exceeds 15%, additional subject will be recruited and enrolled into the study, but prior research suggests that 15% is a reasonable estimate. Another 15-20% are expected to achieve a 75% reduction in FI during EMM and will need to be replaced Thus,

we anticipate that approximately 285 participants will need to begin EMM treatment in order for 194 to complete the run-in phase and be randomized to BIO or INJ (97 per group). The participant flow diagram is shown in Figure 3.

5.2.2. Primary Safety Outcome

For the primary safety outcome, we will use Fisher's exact tests to compare the percentage of participants in the two randomized treatment groups who experience an adverse event (AE) of pelvic pain of grade II or greater severity, treatment site infection, or a serious adverse event (SAE) requiring hospitalization between randomization and the 3-month assessment. For this analysis, participants who are missing safety data will be excluded from analysis, but we assume that 78 in the BIO group and 92 in the INJ group will be available for evaluation at 3 months and that those numbers represent the minimum number of participants who will be included in the primary safety analysis. Based on previous studies, we expect the percentages of participants with a qualifying AE or SAE to be approximately 9.8% (9/92) in the INJ group, and 0% (0/78) in the BIO group. The anticipated sample size will provide 83% power to detect a pairwise difference between percentages of 0 and 10% at an alpha of 0.05.

5.2.3. Primary Cost Outcome

Analysis of Cost from the Payer Perspective. To perform power calculations for the difference in 3 month treatment costs, we used cost estimates for treatment provided in Bernstein[77] and described below. As standard deviations were not provided in the text, we assumed a standard deviation of 0.5 (UB-LB). Sample sizes are based on the number of participants in each treatment group who are expected to be evaluated at the primary endpoint.

- BIO treatment was estimated at $265.45 ($212.36-318.55) per month. Treatment cost in Table 5 is provided for 3 months.
- Physician and device costs (ranges) for INJ treatment was: $281.03 ($224.82-337.23) and $4,900 ($2,940-6,860). We assumed two injections per participant in the first 3 months, and summed them to produce the treatment cost in the table.

Table 5. Assumptions underlying power analysis for medical costs of FIT treatments for 3 months

	Treatment Cost	Sample Size	Standard Deviation
BIO	$796	103	160
INJ	$10,363	123	4,032

Performing analysis with an alpha of 0.05 results in a power of 1.0 given that the differences in expected treatment costs are so large.

Analysis of Cost from the Societal Perspective. To perform power calculations for the difference in 3-month societal costs, we added treatment cost estimates provided in Table 5 to 3 month medical and productivity costs associated with FI, adjusted by treatment. Medical and productivity FI costs were taken from Xu[78]. Given lack of data on the extent to which each treatment may impact medical and productivity costs of FI, we incorporated the assumptions outlined below (Table 6). Annual direct and indirect medical costs are estimated to be $2,562, and annual productivity costs are estimated at $1,549. We multiplied these costs by 0.25 to estimate 3-month costs.

- BIO was assumed to reduce FI medical costs by 25%, and productivity costs by 0%.
- INJ was assumed to reduce FI medical costs by 50% and productivity costs by 25%.

Table 6. Assumptions underlying power analysis for societal costs of FIT treatments for 3 months

	Societal Cost	Sample Size	Standard Deviation
BIO	$1,664	103	2,138
INJ	$10,973	123	5,448

Performing analysis with an alpha of 0.05 results in a power of 1.0 given the large, expected difference in societal costs between the treatments.

5.3. Secondary Aim to Evaluate Treatment Combinations

A secondary aim of the study is to evaluate treatment-order combinations after participants are allowed to cross over into other study arms. At the 3-month assessment, non-responders to randomized treatment can choose to initiate an additional treatment. This is a pragmatic approach reflecting the reality that patients in clinical care who are not happy with their initial FI treatment may choose to try another treatment. Table 7 shows the number of 3-month non-responders in each randomization group who are expected to be followed to 6, 12 and 24 months with the assumption of 15% attrition (loss to follow up or missing outcomes for other reasons) between the 3- and 12-month assessments and an additional 15% attrition between the 12- and 24-month assessments. Since non-responders can choose to try the other study treatment or SNS after 3 months, we estimate that between 5 and 50 participants will be in each of the possible treatment-order combinations at 6, 12 and 24 months. We will estimate 95% confidence intervals for the number of responders in each treatment-order combination at each time point. Table 8 shows 95% confidence intervals for a range of group sizes and responder percentages; confidence intervals are estimated using a Wilson Score interval[79] recommended for small sample sizes.

Table 7. Randomized treatment non-responders and estimated number followed at 6, 12 and 24 months

Randomized treatment	Non-responders at 3 months	Followed to 6 months	Followed to 12 months	Followed to 24 months
BIO	17	17	15	13
INJ	63	60	53	45

Table 8. 95% Confidence intervals for observed responder (or non-responder) percentages of 50-90% and treatment-order combination group sizes of 5-50 participants

Number of participants	Responder (or non-responder) percentage				
	50%	60%	70%	80%	90%
5		23-88%		38-96%	
10	24-76%	31-83%	40-89%	49-94%	60-98%
20	30-70%	39-78%	48-85%	58-92%	70-97%
30	33-67%	42-75%	52-83%	63-90%	74-97%
40	35-65%	45-74%	55-82%	65-90%	77-96%
50	37-63%	46-72%	56-81%	67-89%	79-96%

5.4 Estimated patient flow for this study

Figure 3 shows the estimated flow of patients through this study and identifies our assumptions regarding attrition. We estimate we will need to screen 855 patients because 2/3 will be ineligible or unwilling to be randomized. This leaves 285 to be recruited into the EMM protocol. Based on the Heymen study[15], we assume

15% attrition during this treatment phase and also assume that 20% (n=57) will be responders to EMM and therefore not eligible for randomization. This will leave 194 to be randomized (97 per group).

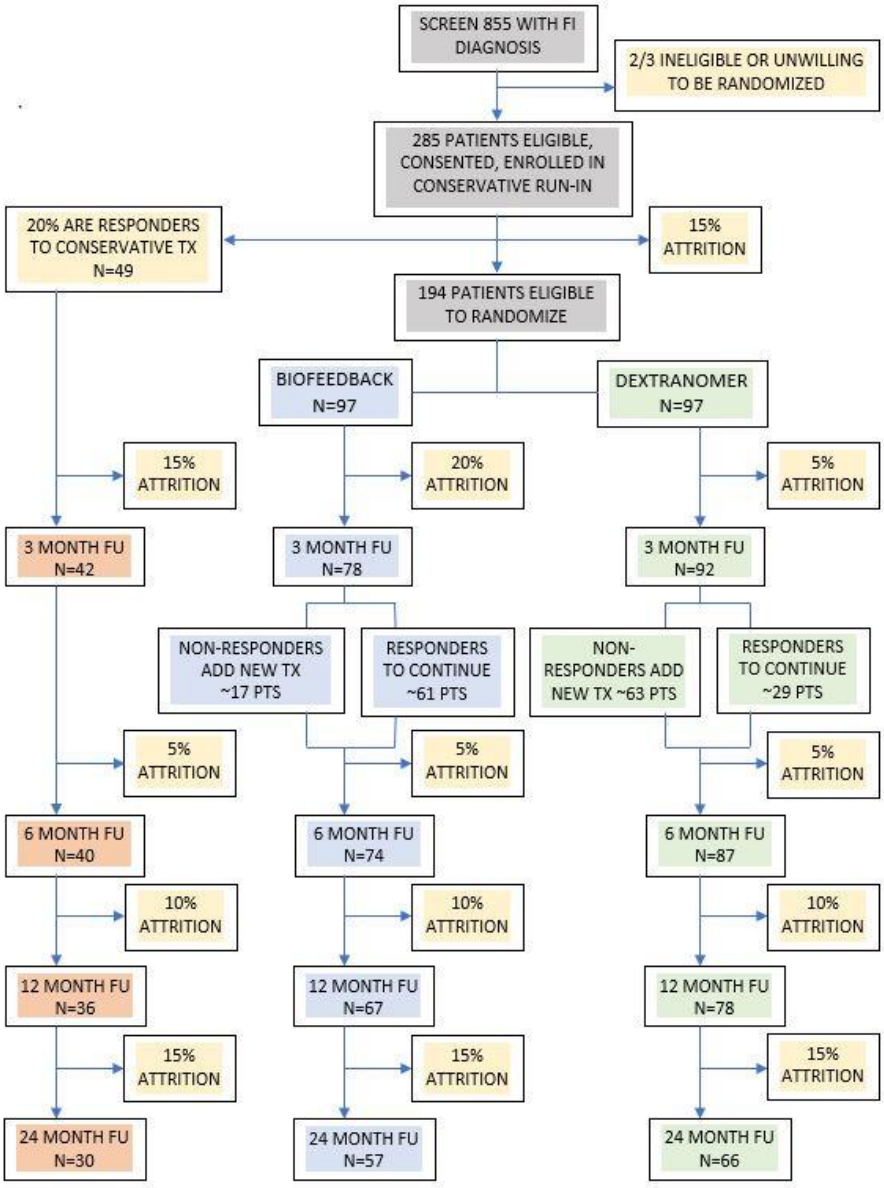
Figure 3 shows that we expect 78 from the BIO group to complete the 3-month assessment after allowing for attrition of 20% and we expect 92 from the INJ group to complete the 3-month assessment. (We assume attrition will be no greater than 5% for the INJ group because this is a low-burden treatment and also because patients will want to be screened for AEs related to INJ.) However, the statistical analysis will be by intent to treat (ITT) and will include all 194 randomized to treatment; patients who are lost to follow up prior to 3 months will be considered treatment failures. The number of patients we expect to be responders to each of the treatments at the 3-month assessment is based on the pivotal trials shown in Table 1. We separated them in this way in Figure 3 to be able to estimate the numbers of non-responders who are likely to choose an additional treatment option after 3 months. The expected number of non-responders eligible for an additional therapy at 3 months is 63 for the INJ arm[16] and 17 for the biofeedback arm[15]. Assuming equal probability of choosing either of the 2 available options as an added or alternative treatment, we could expect 40 patients to choose the SNS treatment, 32 to choose BIO, and 9 to choose INJ. For the primary analyses of follow up at 6, 12 and 24 months, these non-responders will be retained in the ITT analysis as non-responders to their primary assignment at randomization. However, when we perform exploratory analyses of treatment combinations, these subjects will be treated as distinct groups and compared to patients who received monotherapy for the duration of the study. These comparisons (Aim D) are exploratory because there is insufficient power to test for significance. The left column of boxes in Figure 3 shows how we intend to follow up the responders to EMM.

5.5 Feasibility Survey

In Year 1 of the U34 planning grant, we conducted two feasibility surveys to inform us whether sufficient numbers of subjects would be willing to be randomized to a 3-arm treatment study. In the first survey, we recruited 164 individuals through an internet registry who reported experiencing FI at least twice each month. The anonymous internet survey gave brief descriptions of BIO, SNS, and INJ including published reports of their effectiveness, safety, and cost. These subjects were then asked to rate the effectiveness and safety of each treatment on a 0-10 scale from “definitely not” to “yes, definitely”. They rated their willingness to undergo each treatment on a 0-10 scale from “definitely not” to “yes, definitely”. The 164 respondents to this survey included 112 females (68% of total sample), average age was 43 years, and average FISS severity score was 8 with 119 (73%) scoring in the moderate to severe range of FI severity. When asked to rate their willingness to enroll in a study in which they would be randomly assigned to one of these three treatments, 32% rated their willingness as 8 or greater on the 0-10 scale. When asked about each treatment separately they were significantly more willing to try BIO than INJ, and significantly more willing to try INJ than SNS. They rated these three treatments as equally effective but BIO was perceived as significantly safer than INJ, and INJ was perceived as significantly safer than SNS. Concerns expressed about the safety of SNS included infection risk, use of electricity, and possible nerve damage.

The second feasibility survey was carried out in the 4 clinical settings where this study would take place. From 40 to 51 patients with established diagnoses of FI participated at each site (total n=187). The proportion who would be willing to be randomized with a confidence rating of at least 8/10 was 40%. Patients who were unwilling to be randomized to this three-arm study most commonly listed safety concerns (62%) or unequal costs as reasons for their reluctance to be randomized. The data from these two surveys suggest that approximately 32% to 40% of eligible patients would be willing to be randomized. This is consistent with our assumption (see Figure 3) that 1 in 3 patients screened will be eligible and willing to be randomized.

Figure 3: Expected Patient Flow



6.0 Details of Interventions

Detailed procedure manuals were developed for each intervention (including the conservative run-in treatment) by separate protocol committees and are given below in subsequent Appendices. Adherence to these treatment protocols will be monitored as detailed in the procedure manuals.

6.1 Enhanced medical management

The key components of treatment are patient education about the basic physiological mechanisms for defecation, diet and medication to normalize stool consistency, and pelvic floor exercises taught by printed instructions. This treatment will be tailored to the underlying bowel disturbance as evaluated by a 2-week baseline bowel diary and described Manual of Procedures.

We have previous experience with the design and testing of EMM. In an RCT of BIO[15], we developed a protocol for a conservative run-in prior to implementation of the BIO or pelvic floor exercise protocol. This conservative treatment protocol included educating patients about the basic physiology of continence and defecation by showing them videos of defecography examinations, teaching them to normalize stool consistency by adding fiber to their diet or taking antidiarrheal or laxative medications if needed, and teaching

them to use a daily symptom diary to chart their progress. By the end of this 4-week intervention, there was an average 60% reduction in frequency of FI, and 22% of patients reported adequate relief.

Subsequently, with the support of grant R01 HS018695 we enhanced the EMM protocol by giving it to a series of small groups of patients with FI and asking them for feedback on what they found helpful or difficult, and what suggestions they had for improvement. Then with the assistance of two consultants who were nurses with expertise on FI (Christine Norton and Diane Newman), we developed a pamphlet for explaining each step in the program to patients and a series of training videos to teach nurses how to provide this intervention. These data were adapted by Dr. Bharucha into a Standard Operating Procedure for EMM.

6.2 BIO training

The BIO protocol developed for the PFDN by Whitehead and other experts on BIO for FI[80] provided the foundation for the Biofeedback Manual of Procedures. An important feature of this BIO protocol is its ability to adapt to the individual patient's needs: The most common physiological deficits that cause FI are (1) weakness of the external anal sphincter, (2) loss of the ability to sense weak distentions of the rectum caused by the movement of stool into the rectum, and (3) strong urges associated with rectal contractions that overwhelm the patient's ability to retain stool in the rectum long enough to reach the toilet. We developed separate BIO procedures specific to each of these deficits: (1) strength training for sphincter weakness, (2) sensory discrimination training to improve the ability to detect weak rectal distentions, and (3) urge resistance training. Each component is described briefly below:

a. Strength training: The patient is provided with visual feedback of anal canal pressure and rectal pressure, shown as two line tracings on a graph. The interventionist explains that the sphincter should be able to squeeze with enough strength to increase anal canal pressure to at least 100 mmHg. Then over a series of 20-second trials, the interventionist sets intermediate goals that are beyond the patient's average ability but which can be achieved at least 25% of the time. The interventionist sets a target line on the screen for the patient to aim for, and as performance improves, this target is moved up. Once the patient demonstrates improvement in the maximum anal canal squeeze pressure, the interventionist asks the patient to focus on the rectal balloon pressure and to avoid increases in rectal pressure when squeezing the external sphincter. Rectal pressure is caused by contraction of the abdominal wall muscles, which many patients are in the habit of doing although this actually increases the likelihood of FI. Lastly, when the patient is making progress on strengthening the sphincter squeeze and isolating it from inappropriate abdominal wall contractions, the interventionist will ask them to practice increasing the duration of their anal squeeze response by keeping the anal pressure tracing above the target pressure for progressively longer periods.

b. Sensory training: No visual feedback is provided to the patient during sensory training; instead they are asked to focus on internal sensations to learn to recognize weaker distentions. The interventionist rapidly inflates the rectal balloon using a hand-held syringe and holds the air in the balloon for 5-seconds before withdrawing it. The patient is asked to squeeze when they feel any sensation in their rectum and to also report their perception verbally to the interventionist. The first distention is with 50 ml of air which most patients can detect. If the patient detected and responded to the 50 ml distention, the next distention is 10 ml less. This is repeated until the patient begins to make errors; the last distention to which they responded correctly is the sensory threshold. At this point the interventionist switches to a discrimination training protocol in which some distentions are at the sensory threshold and some 5 ml less than this with the sequence being made unpredictable to the patient. The interventionist provides verbal encouragement during training to help the patient gradually improve their sensory threshold.

c. Urge resistance training: Some patients with FI have strong urge sensations associated with rectal contractions, and they are unable to make it to the toilet. These urge sensations may be precipitated by anxiety about the possibility of having an accident (commonly experienced when they are trying to open the door of their house after returning from a shopping trip). Urge resistance training is based on the principles of systematic desensitization of a feared situation. The interventionist first inflates the rectal balloon to

identify the threshold for a strong urge. She (or he) then deflates the rectal balloon by 30 ml to reduce the intensity of the urge sensation and has the patient use deep breathing to relax. She then re-inflates the rectal balloon slowly while encouraging the patient to use relaxation to inhibit the urge sensation. Three to four such ramp distentions are used in the training session. It is usually possible to see an improvement in the tolerance for rectal distention within a session.

Which of these three BIO protocols are used, alone or in combination, depends on the patient's deficits. To guide the BIO therapist, a brief anorectal manometry test to assess sphincter squeeze responses and sensory thresholds is performed at the beginning of each BIO session. The patient's symptom diary is also used to determine what type of training to focus on during BIO: the occurrence of FI without awareness suggests the need for sensory discrimination training while the occurrence of strong urges before FI suggests a need for urge resistance training. Strength training is provided in every BIO training session, but the interventionist may place greater emphasis on maximum squeeze, squeeze duration, or avoidance of abdominal wall contractions based on the initial anorectal manometry assessment.

BIO training and anorectal manometric testing will use the Medspira Anorectal Manometry system and MCompass software (Minneapolis, MN). The PFDN worked closely with software engineers at Medspira to tailor the software to the needs of BIO therapy and to incorporate on-screen prompts to assist the BIO interventionist in following the protocol.

We have also developed a program for training the BIO interventionists and monitoring their adherence to protocol. The key elements are these: (1) we recruit physical therapists or nurses with prior experience in muscle retraining, (2) these candidates are asked to review a series of training slides and videos and to pass built-in quizzes, and (3) they are trained one-on-one with a live patient surrogate and then evaluated (certified) with a live patient surrogate by Dr. Whitehead.

6.3 INJ of dextranomer: This protocol is a modified version of the protocol used by Graf to ensure consistency across sites and safety of patients[16]. Patients are treated prophylactically with oral antibiotics to minimize injection site infections. One ml of NASHA dextranomer is injected through an anoscope into each quadrant of the submucosa (4 ml total) approximately 5 mm above the dentate line. After each INJ, the needle is left in place for 10 seconds to avoid backward leakage of contrast through the injection channel. Following the INJ patients are counselled to use stool softeners (docusate sodium) until the first bowel movement and to use paracetamol as needed for INJ site discomfort. Prophylactic antibiotics will be administered for 2 days starting on the day of injection. Six weeks after initial INJ, patients return for evaluation, and if the patient has achieved less than 75% reduction in FI, a second INJ is given.

6.4 Comparison of elements of BIO and INJ:

Table 9 shows the elements of the two treatments compared to each other.

	Enhanced Medical Management	**Biofeedback**	**Injection**
Preparation	None	None	Diet restrictions; enemas; and antibiotics per the procedure SOP
Number of visits	2 visit + 2 phone calls	5-6 visits	2 visits
Visit duration	60 min 1st visit; 15 min phone calls (Day 3; Day 14); 30 min last visit	60 min	45 min
Visit frequency	1st and last visits (start of treatment and after treatment program has ended)	Up to 2 visits per week, spaced 2-10 days apart for first 5-6 weeks or so	0 and 6 weeks
Procedure	Daily sphincter exercises, meds to normalize bowel habits	Learn how to improve strength and rectal sensation	Bulking agent injected into rectal wall to narrow opening
Expected Adverse Events	None	None	Pain at injection site, bleeding, infection

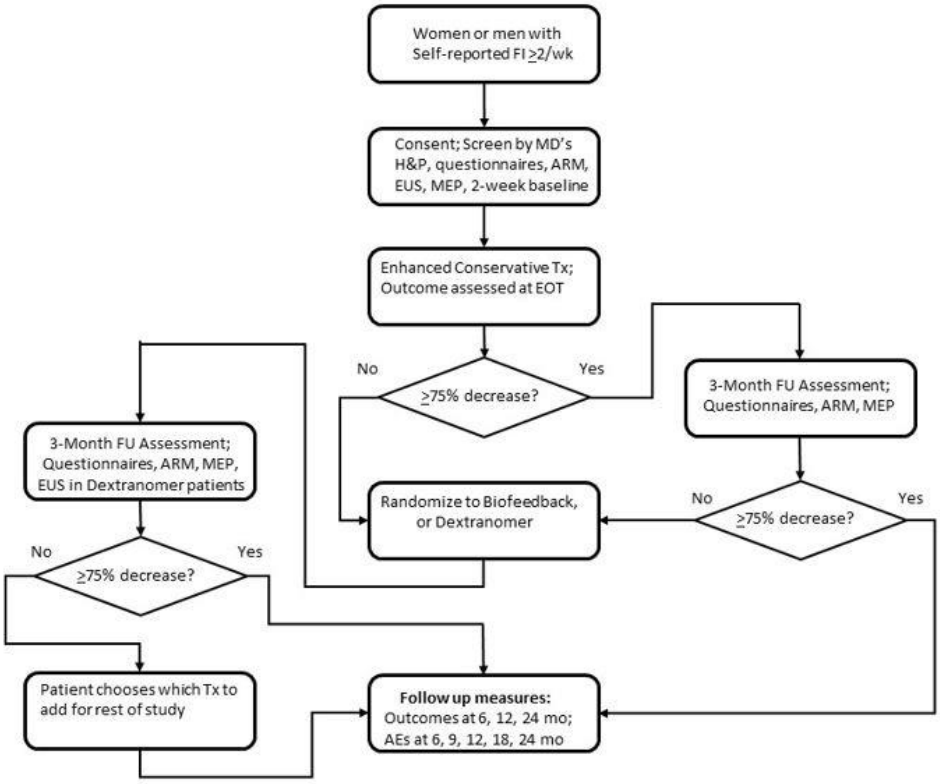
7.0 Randomization and Masking

7.1 Randomization

Enrollment in the study will be defined as satisfying all eligibility criteria and signing informed consent (see Section 9.4). Randomization to the two interventions being compared BIO and INJ) will not occur until patients have completed EMM and been classified as a non-responder based on showing a less than 75% reduction in the average frequency of solid, liquid, and/or staining FI events compared to the two-week baseline. See Figure 4 for Decision Tree governing patient flow through the study.

Randomization will occur in a ratio of 1:1 with an equal chance of being randomized to each treatment group. Randomization will be performed using randomly permuted blocks, with block sizes known only to the DCC, and will be stratified by clinical site and sex (male and female). For each participant, the web-based electronic data capture system will determine the treatment allocation from a static randomization table. Personnel at the clinical sites will not have access to the randomization table in order to minimize the risk of selection bias.

Figure 4: Decision Tree



7.2 Masking

7.2.1 *Masking of patients to treatment assignment*. Patients will be aware of the treatment to which they are assigned and the nature of alternative treatment to which they were not assigned. Should subjects have an *a priori* preference for one of the treatments, their expectation of benefit could be biased based on whether they were randomized to their preferred treatment. However, random assignment to the two treatments should balance the number of people with a positive expectancy in each treatment group. Moreover, we will assess individual differences in expectation of benefit by administering the Credibility/Expectancy Questionnaire at baseline and immediately after randomization. The expectancy scores will be entered into the analysis as a covariate to see if treatment group differences in efficacy are explained by expectancy, and to correct for this bias in the outcome assessment if present.

7.2.2 *Masking of investigators and study staff to treatment assignment*. The investigators and study staff will be unmasked with respect to the treatment assignment at randomization, raising the possibility of investigator bias. However, this investigator bias will be reduced or eliminated by (1) having separate protocol committees develop each protocol and separate study teams administer the intervention; and (2) masking the assessment of outcome measures to the investigators and study staff as explained below.

7.2.3 *Masking of outcome assessment*. Please refer to Table 2 for a list of measures and when they are assessed. Treatment response will be calculated from patient bowel diary data entered in the EDC system. The research assistant who enters the data into the electronic data capture system on the study website will be responsible for checking the diaries for completeness and interpretability to be sure the data can be entered into the EDC system and may contact subjects to clarify data entries if necessary. Patient reported outcome questionnaires will be completed by participants in the clinic using tablet computers or at home via links sent by email. For the small minority of patients who are unable or unwilling to complete these questionnaires electronically, paper versions of these questionnaires will be

available.

8.0 Statistical Considerations

8.1 Analysis of Primary Endpoints

Assessment of Randomized Treatment Response at 3 Months (Primary Efficacy Analysis). To test the efficacy of randomized treatment assignment, a generalized linear model with a logit link will be constructed to predict treatment response at 3 months post-randomization. Treatment group and the stratification factors of clinical site and sex will be included in the model as categorical independent variables. An ITT approach will be used in which participants will be analyzed based on their assigned treatment group regardless of actual treatment received. Participants without a valid bowel diary at 3 months due to drop out or other reasons will be classified as non-responders. Using this model, we will test the null hypothesis that the proportion of responders is the same in the two treatment groups at 3 months following randomization using an alpha of 0.05. Sensitivity analyses will be conducted to assess the impact of classifying participants with missing data as non-responders.

Assessment of Safety. The primary safety outcome is the percentage of participants in each randomized treatment group who experience an adverse event (AE) of pelvic pain of grade II or greater severity, treatment site infection, or a serious adverse event (SAE) requiring hospitalization between randomization and the 3 month assessment. Because the proportion of participants with one of these events is expected to be small, Fisher's exact tests will be used to compare the percentage of participants with a qualifying adverse event. The difference between the two treatment groups will be evaluated for significance using an alpha of 0.05. Participants who are missing safety data due to drop out or other reasons will be excluded from this analysis.

Cost of Care Analysis. Mean and median costs per participant will be estimated for each of the two treatment groups and from the perspectives of payers, patients, and society. We will analyze whether differences in costs through 3-month follow up across the intervention arms and perspectives are statistically significant using parametric t-tests or using non-parametric bootstrapping methods. We will evaluate differences between the two treatment groups using an alpha of <0.05.

8.2 Analysis of Secondary Efficacy Endpoints

Assessment of Efficacy through 24 months. Treatment response (≥75% reduction in weekly FI episodes) at time points through 24 months will be analyzed using a longitudinal extension of the model used for the primary efficacy analysis. Month of assessment, and interaction between month and other predictors, will be included in the model, and the correlation between measures assessed on the same participant over time will be modeled using an appropriate covariance structure. Participants classified as non-responders at 3 months will continue to be considered non-responders at subsequent time points. Participants with missing responses will be classified as non-responders, but sensitivity analyses will be conducted to assess the impact of this assumption.

Assessment of Safety through 24 months. The percentage of participants reporting AEs of pelvic pain of grade II or greater severity, treatment site infection, or an SAE requiring hospitalization by 6, 12, 18, and 24 months will be estimated with 95% confidence intervals using the Wilson Score interval method. Separate estimates will be produced for the groups of participants treated with each of the two therapies alone, and for participants in each of the treatment-order combinations. Confidence intervals will be compared descriptively.

Assessment of Cost of Care through 24 months. The median costs per participant from the perspectives of payers, patients, and society through 24 months will be estimated for each of the treatment groups, including the treatment combinations, using methods described for the primary cost of care endpoint. No formal hypothesis testing will be done, and p-values will be presented for informational purposes only.

Assessment of FI Severity. General linear modeling will be used to analyze change from baseline to 3 months in FI severity as assessed by the Fecal Incontinence Severity Scale (FISS). Independent variables in the model will include randomized treatment group, clinical site, and sex. Missing outcomes will be assumed missing at random for the purpose of this analysis, but sensitivity analyses will be conducted to test the robustness of the results to this assumption. The model will be used to estimate 95% confidence intervals for the change from baseline to 3 months in FISS score in each of the randomized treatment groups. In addition, longitudinal general linear modeling will be used to analyze change from baseline to 6, 12, and 24 months in FISS score. In addition to the independent variables used in the 3-month analysis, the model will include fixed effects for time and the interaction between treatment and time. The model will account for the lack of independence between multiple measures assessed over time on the same study participant by modeling the within-participant covariance structure. For the 6- to 24-month time points, 95% confidence intervals for change from baseline in FISS score will be estimated for responders in each randomized treatment group, as determined at 3 months, and separate estimates will be produced for groups of non-responders who select into each treatment combination. In this analysis, no formal hypothesis testing will be done, and confidence intervals will be compared descriptively.

Fifty Percent Responder Rate. The proportion of participants who have at least a 50% reduction in FI episodes will be modeled using the same methods described for the primary efficacy outcome. However, no formal hypothesis testing will be done, and p-values will be presented for informational purposes only. This will be analyzed for each follow-up assessment through 24 months.

Continence Rate. The proportion of participants who are continent at each follow up time point will be modeled using the same methods described for the primary efficacy outcome. No formal hypothesis testing will be done, and p-values will be presented for informational purposes only. This will be analyzed for each follow-up assessment through 24 months.

Assessment of Disease-Specific Quality of Life. Change from baseline to 3 months, and to 6 through 24 months in the FI Quality of Life (FIQOL) scale will be analyzed using methods described for the analysis of FI severity.

Assessment of Anxiety, Depression, and Self-Efficacy for Managing Symptoms. Change from baseline to 3 months, and to 6 through 24 months in these Patient Reported Outcomes Measurement Information System (PROMIS) scales will be analyzed using methods described for assessment of FI severity.

8.3 Analysis of Secondary Aims

Identify predictors of treatment response to each intervention. Generalized linear modeling will be used to identify baseline variables which are significant independent predictors of responder status at 3 months. Candidate independent variables in these models include (a) demographic variables (e.g., sex, age, race, ethnicity, education); (b) clinical history variables (e.g., FI frequency, volume, duration, and association with urgency and diarrhea); and (c) baseline pelvic floor physiology (e.g., anal canal resting pressure, squeeze pressure, duration of squeeze, rectal sensory threshold for first sensation and urgency, maximum tolerable volume, structural integrity of anal sphincters assessed by ultrasound, and integrity of the pelvic floor innervation by trans-sacral and trans-lumbar magnetic evoked potentials) and other moderator variables described in the protocol. Differences in predictors of response among the treatment groups will be assessed by evaluating interaction terms for the predictors and treatment group. Secondary analyses evaluating predictors of treatment response at other time points and predictors of other secondary outcomes will be conducted using similar methods.

Investigate the mechanistic basis for treatment success for each intervention. General linear modeling will be used to identify measures associated with change from baseline to 3 months in FI frequency. The independent variables to be tested are anal squeeze pressures, rectal sensory thresholds, rectal maximum tolerable volume, trans-lumbar and trans-anal magnetic evoked potential, stool consistency measure by the Bristol Stool Form Scale, and adherence to protocol. Differences in predictors among the treatment groups will be assessed by evaluating interaction terms for the predictors and treatment group.

Evaluate treatment combinations. To assess the effectiveness of allowing non-responders to choose an additional treatment at 3 months, we will estimate 95% confidence intervals for the number of responders in each treatment-order combination at 6, 12, and 24 months using a Wilson Score interval[79]. Confidence intervals will be compared descriptively.

Assess the efficacy and durability of enhanced medical treatment and identify patient characteristics that predict treatment response. The proportion of responders will be calculated at the end of EMM and at 3-, 6-, 12-, and 24-month follow-up. A longitudinal generalized linear model will be constructed to predict treatment response based on time and clinical site; the model will account for the lack of independence between multiple measures assessed over time on the same study participant by modeling the within-participant covariance structure. Participants who are non-responders to EMM at 3 months will continue to be classified as non-responders at 6, 12, and 24 months. Participants without a valid bowel diary will be classified as non-responders at that time point, and those who initiate off-study treatment for FI after EMM will be classified as non-responders at each subsequent visit/assessment. Using this model, we will compare response rates at the end of EMM to response rates at 3, 6, 12, and 24 months. We will also calculate 95% confidence intervals for the percentage of participants reporting AEs during EMM. Costs of EMM will be estimated and compared to costs of the other study interventions using methods described for cost of care analysis. The predictors of response to EMM at baseline, 3, 6, 12, and 24 months will be explored using generalized linear modeling.

Cost- Effectiveness Analysis. We will estimate the impact of each intervention on quality-adjusted life-years (QALYs). QALYs are summary measures of morbidity and mortality that typically range from 0 to 1 over a full year, where 1 represents perfect health. QALY estimates will be obtained from the EQ-5D; annual QALY measures will be calculated. We will assess the average cost per QALY gained for each intervention and the incremental cost per QALY gained by comparing the interventions ordered from lowest to highest QALY gains (i.e., comparing the intervention with medium effectiveness to the intervention with lowest effectiveness and the intervention with highest effectiveness to the intervention with medium effectiveness).

8.4 Interim Analysis

Interim analyses for safety will take place at regular intervals corresponding to the timing of Data and Safety Monitoring Board (DSMB) meetings. For each meeting, the DCC will prepare confidential reports for the DSMB summarizing AEs and SAEs, with statistical comparisons of event rates between treatment groups. Based on the data presented, the DSMB may recommend stopping the study for safety concerns, but there are no formal stopping guidelines for safety for this study.

The percent of treatment responders in each randomized treatment group will also be presented to the DSMB, but no formal interim analyses for efficacy are planned. The primary reason for this is that an interim analysis would be very unlikely to reveal an adequately strong signal in favor of one of the treatment groups for all three of the primary outcomes, and in that case, stopping the study early would prevent some of the primary study questions from being answered. In addition, if the study was stopped early, the smaller sample size that would result would reduce the precision with which we could estimate efficacy among participants who add a supplemental treatment.

9.0 Data and Safety Monitoring and Informed Consent

9.1 Data and Safety Monitoring Board

The protocol will be approved by the DSMB prior to initiation of participant recruitment. The DSMB will also review study data at regularly scheduled meetings either in person or by teleconference. Reports prepared by the DCC for these meetings will include AE and SAE summaries by treatment group and individual SAE narratives. They will also include data on participant recruitment, visit/assessment completion, and adherence to protocol. The DSMB will provide recommendations to NIDDK regarding continuing the study or stopping the study for safety or futility.

9.2 Reporting of Adverse Events

All adverse events that occur from the time that the participant is consented through the 3-month follow up visit will be recorded on designated CRFs. Following the 3-month follow up assessment and through the 24-month follow-up assessment, the research coordinators will record only AEs of grade II or higher; however, any AE, regardless of severity/grade, should be reported through the 24-month follow-up visit if it is possibly related to the randomized or optional study treatments. Failure of the study interventions to adequately control fecal incontinence symptoms (failure of efficacy) will be captured by the study endpoints and will not be recorded as an adverse event.

9.3 Reporting of Serious Adverse Events

Each clinical investigator is responsible for reporting serious adverse events (SAEs) to the IRB at their institution per local IRB requirements, and to the DCC within 24 hours of when the clinical site is notified of the event. In accordance with GCP, an adverse event is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. An adverse event is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.

Reporting of Unanticipated Adverse Device Effect

Unanticipated adverse device effect means 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 was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. A sponsor who conducts an evaluation of an unanticipated adverse device effect shall report the results of such evaluation to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect.

Additionally, 21CFR803.1 requires reporting of any required intervention to prevent permanent impairment or damage (applies to devices). This should be reported if the investigator suspects that the use of a medical product may have resulted in a condition which required medical or surgical intervention to preclude permanent impairment or damage to a patient.

Once the SAE is reported to the DCC, it is reviewed by the medical safety monitor (MSM). An SAE summary report is sent to the DSMB and NIDDK (the sponsor). The SAE review process will be documented by the DCC.

Any serious adverse events (SAEs) that are deemed related and unexpected will be submitted in a safety report to the DSMB, NIDDK, and all participating investigators. Clinical sites will follow local IRB guidelines for submission of any unexpected and related SAEs that occur at either their own site or at other study sites.

9.4 Informed Consent

Patients who are candidates for study participation will be approached for enrollment. Written informed consent will be obtained in accordance with IRB Guidelines. A common template for informed consent will be used by all clinical sites, with modifications allowed to meet the necessary requirements of their institutional human subjects committees.

A participant may be prematurely withdrawn from the trial and/or discontinue study treatment as a result of the following:

- At their own request or at the request of their legally acceptable representative.
- If in the investigator's opinion, continuation in the trial would be detrimental to the well-being of the participant.
- If the patient is diagnosed with a condition which is excluded per protocol.
- At the specific request of the sponsor or termination of the study by the sponsor.
- Participant becomes pregnant.

In the event that a participant withdraws consent before completing the study per protocol, attempts will be made to collect the most recently applicable information and follow AEs/SAEs to resolution. If a participant discontinues treatment but does not withdraw consent, all attempts will be made to continue follow up of the participant per protocol.

10.0 Data Management and Data Sharing

10.1 Data Sharing

Study data will be provided to the Repository so that it can be shared in accordance with NIDDK data sharing policies. Publicly released data will satisfy HIPAA and other applicable requirements for protecting participant identity. The informed consent form will include language regarding data sharing.

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