Last Update: 10/26/2018

NCT02609607: Treating Anorectal Dysfunction in MS

PI: David J. Levinthal, MD, PhD

University of Pittsburgh **OSIRIS**

Section: Triage

Provide a short title for this study (200 characters or less)**:**

MS Bowel Study

T1.0 **Select the type of application:**
New Research Study

T2.0 **Is the proposed research study limited to the inclusion of deceased individuals?**
* No

T2.1 **Are any research activities being conducted at the VA Pittsburgh Healthcare System or with VA funds?**

* No

[reviewer notes¬]

T3.0 **What is the anticipated risk to the research participants?**

Greater Than Minimal Risk

Section: Cover Sheet

[reviewer notes¬]

CS1.0 **What is the reason for this submission?**

New Research Protocol Submission

CS1.1 **Has this research study been approved previously by the University of Pittsburgh IRB?**

* No

Section: Cover Sheet

CS1.1.1 Has this research study (or a substantially similar research study) been previously disapproved by the University of Pittsburgh IRB or, to your knowledge, by any other IRB?

* No

[reviewer notes¬]

CS2.0 Title of Research Study:

Treating Anorectal Dysfunction Associated with Multiple Sclerosis

CS2.0.1

Requested approval letter wording:

CS2.1 Research Protocol Abstract:

The majority of patients with multiple sclerosis (MS) suffer from constipation and/or fecal incontinence ("anorectal dysfunction"), and these difficulties are often ranked as negatively impactful on quality of life as impaired mobility. Despite the significant clinical burden of these symptoms, there remains very little research to support specific therapeutic options in managing anorectal dysfunction in MS patients. To address this gap in knowledge, we propose to establish the efficacy of a standardized, cost-effective, and easily implemented bowel regimen to treat anorectal dysfunction in patients with MS.

Specifically, this double-blind, randomized placebo controlled study will determine the impact of adding the regular administration of rectal suppository laxatives (e.g., a "timed rectal evacuation" strategy) on MS patients' subjective assessment of bowel symptoms. The "timed rectal evacuation" aspect of a bowel regimen has never been rigorously studied, but it could have a major clinical impact. In our study, patients with MS will receive oral laxatives or anti-diarrheal agents to normalize stool form (as indicated), and then be randomized to receive either placebo or bisacodyl 10 mg rectal suppositories administered every other day for 4 weeks. Patients also will undergo tests of anorectal function (per routine clinical practice) and standardized questionnaire assessments of bowel symptoms and their impact on quality of life. We will use this information to try to predict which groups of patients benefitted from the intervention. This proposal will significantly advance MS care and management by developing the evidence to support a simple and effective clinical treatment algorithm for anorectal dysfunction in the MS population.

CS2.2 Select the category that best describes your research:

[reviewer notes¬]

CS3.0 Name of the Principal Investigator:

David Levinthal

Note: Adjunct faculty of the University, including lecturers and instructors, are not permitted to serve as a PI or Faculty Mentor but may serve as co-investigators. Refer to Chapter 4 on the HRPO website for more information.

CS3.1 Affiliation of Principal Investigator:

UPitt faculty member

If you chose any of the **Pitt options**, please indicate the specific campus:
Main Campus - Pittsburgh

If you chose the UPitt faculty member option, provide the PI's **University Faculty Title**:
Asssistant Professor

CS3.2 **Address of Principal Investigator:**

M2 C-Wing PUH
200 Lothrop Street
Pittsburgh, PA 15213

CS3.3 **Recorded Primary Affiliation of the Principal Investigator:**

U of Pgh | School of Medicine | Systems Neuroscience Institute

CS3.4 **Identify the School, Department, Division or Center which is responsible for oversight of this research study:**

U of Pgh | School of Medicine | Medicine | Gastroenterology

CS3.5 **Telephone Number of Principal Investigator:**

412-303-0525

CS3.6 **Recorded Current E-mail Address of Principal Investigator to which all notifications will be sent:**

DLEVINTH@pitt.edu

CS3.7 **Fax Number:**

412-648-9378

CS3.8 **Does this study include any personnel from Carnegie Mellon University, and/or use any CMU resources or facilities (e.g., Scientific Imaging and Brain Research Center (SIBR)?**

* No

CS3.9 **Is this your first submission, as PI, to the Pitt IRB?**

* Yes

[reviewer notes¬]

CS4.0 **List of Co-Investigators:**

Last	First	Organization

There are no items to display

[reviewer notes¬]

CS5.0 **Name of Primary Research Coordinator:**

CS5.1 **Address of Primary Research Coordinator:**

CS5.2 **Telephone Number of Primary Research Coordinator:**

CS6.0 **Name of Secondary Research Coordinator:**

CS6.1 **Address of Secondary Research Coordinator:**

CS6.2 **Telephone Number of Secondary Research Coordinator:**

CS6.3 **Key Personnel/Support Staff (Only list those individuals who require access to OSIRIS):**

Last	First	Organization
Diable	Caitlin	UPMC | Physician Services Division | UPP | Other
Heyman	Rock	U of Pgh | School of Medicine | Neurology
O'Leary	Margie	UPMC | Other
ORIE	RYAN	UPMC | Other

[reviewer notes¬]

CS7.0 **Will this research study use any Clinical and Translational Research Center (CTRC) resources?**

No

[reviewer notes¬]

CS8.0 **Select the entity responsible for scientific review.**

Department Review - (a dean, department chair, division chief, or center head)
Note: **DoD funded studies** require departmental review

CS8.1 **Select the school, department or division which is responsible for scientific review of this submission.**

U of Pgh | School of Medicine | Medicine | Gastroenterology

[reviewer notes¬]

CS9.0 **Does this research study involve the administration of an investigational drug or an FDA-approved drug that will be used for research purposes?**

* Yes

CS9.1 Do you plan to utilize the Investigational Drug Service (IDS) to dispense the drug?

* Yes

CS10.0 Is this research study being conducted under a University of Pittsburgh-based, sponsor-investigator IND or IDE application?

* No

If YES, you are required to submit the IND or IDE application and all subsequent FDA correspondence through the Office for Investigator-Sponsored IND and IDE Support (O3IS). Refer to applicable University policies posted on the O3IS website (www.O3IS.pitt.edu).

[reviewer notes¬]

CS11.0 Use the 'Add' button to upload one or more of the following:

- **the sponsor protocol (including investigator initiated studies) and/or other brochures**
- **the multi-center protocol and consent form template, *if applicable***

Name Modified Date

Is this research study supported in whole or in part by industry? This includes the provision of products (drugs or devices).

* No

Is this a multi-centered study?

* No

[reviewer notes¬]

CS12.0 Does your research protocol involve the evaluation or use of procedures that emit ionizing radiation?

* No

CS13.0 Does this research study involve the deliberate transfer of recombinant or synthetic nucleic acid molecules into human subjects?

* No

Upload Appendix M of NIH Guidelines:

Name	Modified Date

CS14.0 Are you using UPMC facilities and/or UPMC patients during the conduct of your research study?

* Yes

If Yes, upload completed Research Fiscal Review Form:

Name	Modified Date
FRIAR - OSPARS Form -- LEVINTHAL 2015.docx	11/3/2015 3:01 PM

[reviewer notes¬]

CS15.0 Indicate the sites where research activities will be performed and/or private information will be obtained.

Choose all sites that apply and/or use **Other** to include sites not listed:

Sites:
UPMC

UPMC

Sites:
UPMC Presbyterian
UPMC Montefiore
Other UPMC Site- Specify below:

Kaufman Building (Department of Neurology outpatient suite)

If you selected **School**, **International** or **Other**, list the sites:

***For research being conducted at non Pitt or UPMC sites, upload a site permission letter granting the researcher permission to conduct their research at each external site:**
Name Modified Date

CS15.1 Have you, David Levinthal , verified that all members of the research team have the appropriate expertise, credentials, and if applicable, hospital privileges to perform those research procedures that are their responsibility as outlined in the IRB protocol?

* Yes

CS15.2 Describe the availability of resources and the adequacy of the facilities to conduct this study:

* Our study enrolls patient subjects that are already embedded within existing clinical care pathways at UPMC. Patients with multiple sclerosis (MS) already receive care in the Division of Neuroimmunology/MS in the Department of Neurology at UPMC, who maintains a large (2000+ patients) database of their MS patients with associated clinical data. Importantly, the registry also records information on patients' expressed

interest in participating in clinical research studies. During routine care, MS patients with anorectal dysfunction are already regularly referred to the Neurogastroenterology and Motility Group (PI and co-PI) within the Digestive Disorder Center at UPMC and undergo anorectal manometry testing and treatment in the DDC. We will use both routine care pathways and the MS database to recruit patients into the study (goal: 70 patients). We have contracted with Hieber's pharmacy and Falk Pharmacy to forumulate and distribute the study drug in a blinded fashion. We are currently in the process of identifying a study coordinator. The funding mechanism for this project has ample resources to support both of these efforts (study drug and coordinator). Thus, all of the resources that are required to conduct this study are easily available and fully adequate.

[reviewer notes¬]

CS16.0 Special Research Subject Populations:

Categories
None

[reviewer notes¬]

CS17.0 Does your research involve the experimental use of any type of human stem cell?

* No

[reviewer notes¬]

NIH Definition of a Clinical Trial

A research study[1] in which one or more human subjects[2] are prospectively assigned[3] to one or more interventions[4] (which may include placebo or other control) to evaluate the effects of those interventions on health related biomedical or behavioral outcomes.[5]

[1] See Common Rule definition of research at 45 CFR 46.102(d) .

[2] See Common Rule definition of human subject at 45 CFR 46.102(f) .

[3] The term "prospectively assigned" refers to a pre-defined process (e.g., randomization) specified in an approved protocol that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo, or other control) of a clinical trial.

[4] An intervention is defined as a manipulation of the subject or subject's environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints. Examples include: drugs/small molecules/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and, diagnostic strategies.

	Section: Cover Sheet

[5] Health-related biomedical or behavioral outcome is defined as the pre-specified goal(s) or condition(s) that reflect the effect of one or more interventions on human subjects' biomedical or behavioral status or quality of life. Examples include: positive or negative changes to physiological or biological parameters (e.g., improvement of lung capacity, gene expression); positive or negative changes to psychological or neurodevelopmental parameters (e.g., mood management intervention for smokers; reading comprehension and /or information retention); positive or negative changes to disease processes; positive or negative changes to health-related behaviors; and, positive or negative changes to quality of life.

CS18.0 * **Based on the above information, does this study meet the NIH definition of a clinical trial?**

Yes No

If Yes, click Save and then Click Here For Study Team's CITI Training Records . Please ensure all personnel's training is up to date

	Section: Section 1 - Objective, Aims, Background and Significance

[reviewer notes¬]

1.1 **Objective: What is the overall purpose of this research study?** (Limit response to 1-2 sentences.)
The goal of this proposal is to determine the impact of adding timed rectal evacuation as a treatment for anorectal dysfunction symptoms in patients with mild-to-moderate severe MS.

1.2 **Specific Aims: List the goals of the proposed study (e.g., describe the relevant hypotheses or the specific problems or issues that will be addressed by the study).**
MS-related disability and impaired quality of life is derived from both motor and non-motor symptoms associated with the disease. One of the most common, chronic non-motor symptoms in MS patients is anorectal dysfunction, broadly defined as the presence of chronic constipation and/or fecal incontinence. Anorectal dysfunction is experienced in some form by a majority of MS patients and is likely driven by subtle impairments in sensorimotor function that undermines patients' ability to sense rectal filling and/or appropriately coordinate pelvic muscles required for normal defecation. Collectively, because of the pervasive presence of common symptoms with a daily impact, anorectal dysfunction places a tremendous burden on MS patients and their caregivers. Yet, there is exceptionally little high quality evidence to suggest a specific therapeutic approach to MS patients with anorectal dysfunction. Thus, there is a compelling need to establish the evidence to support a safe, effective, and easily implemented treatment option for anorectal dysfunction in MS patients. As a first step to meeting this need, this proposal aims to determine the efficacy of timed rectal evacuation in an algorithm-based bowel regimen for treating anorectal dysfunction in patients with mild-to-moderate severity MS.

AIM 1: Determine the impact of timed rectal evacuation on anorectal dysfunction in MS patients

We will conduct a four week, single-center, randomized, double-blind placebo controlled clinical trial designed to assess the efficacy of timed rectal evacuation in improving the subjective global assessment of bowel symptoms in a cohort of patients with mild-to-moderate severity MS disease. Patients will be randomized 1:1 to administer either placebo or bisacodyl 10 mg rectal suppositories every other day during the 4 week trial. The primary endpoint will be the change in patients' rating of bowel symptom severity (10 point rating scale) at end of 4 weeks compared to baseline values. We will define an adequate treatment response as greater than a 30% reduction in symptom severity using an intention-to-treat analysis.

AIM 2: Determine the predictors of treatment response and impacts on quality of life

We plan to collect information on the patients' assessed severity of baseline and treatment-associated anorectal dysfunction, their impact on quality of life, as well as daily bowel diaries. Patients also will undergo anorectal sensory and manometric testing as a part of their routine clinical care. Enrolled patients that complete the study will be assessed for study medication compliance. All of these measures will be used to explore factors that are associated with treatment response. Changes in assessments of anorectal dysfunction-related quality of life will serve as key secondary end-points.

This proposal will significantly advance MS care and management by developing the evidence to support the adoption of a simple, safe, and cost-effective clinical treatment algorithm for anorectal dysfunction in the MS population. This paradigm for anorectal dysfunction management could be applicable to a majority of MS patients, and the treatment algorithm could be introduced to patients by nurses or mid-level clinical providers during points of routine MS patient care. Importantly, the treatment could be effectively accomplished by most patients and their caregivers at home. The findings of this investigation could also have a broader influence on care models for anorectal dysfunction associated with a range of other neurological illnesses, such as Parkinson's Disease, ALS, or stroke.

1.3 Background: Briefly describe previous findings or observations that provide the background leading to this proposal.

There is growing recognition that the factors driving multiple sclerosis (MS)-related disability extend beyond impairments in mobility to include both psychological and physical symptoms that negatively impact patients' quality of life. Anorectal dysfunction, broadly defined as the presence of chronic constipation and/or fecal incontinence, is a common symptom experienced by MS patients that is often ranked as negatively impactful on quality of life as impaired mobility. About 40% of MS patients suffer from chronic constipation, while ~25% of patients experience frequent episodes of fecal incontinence. Mixed forms of anorectal dysfunction are less common, occurring in at least 10-15% of MS patients, but pose a particular therapeutic challenge. Because of the daily impact of these common symptoms, anorectal dysfunction places a tremendous burden on MS patients and their caregivers.

Normal defecation patterns require precise conscious and unconscious sensorimotor functions to support the perception of rectal filling, to retain stool in the rectum without anal leakage, and to allow for volitional elimination of stool without difficulty. MS patients may be especially prone to developing anorectal dysfunction because even subtle impairments in sensation from the anorectum and/or the timing and efficacy of coordinated abdominal, pelvic floor, and anal muscle contractions are sufficient to generate symptoms. Regardless of subtle differences in the underlying mechanisms that lead to anorectal dysfunction in any one MS patient, an ideal therapeutic approach should be safe, flexible, straightforward, and effective enough to help most patients.

1.4 Significance: Why is it important that this research be conducted? What gaps in existing information or knowledge is this research intended to fill?

Despite its significant burden on MS patients, there remains a paucity of published studies to provide strong evidence for any specific therapeutic option for anorectal dysfunction in this population. The few available studies are mostly small, uncontrolled trials, including studies focused on behavioral interventions and biofeedback, which demonstrated some limited benefit restricted to those with mild MS disease. This finding may not be surprising, as biofeedback requires intact central neural control over motor systems that are likely to be disrupted in MS patients with more advanced disease and more severe forms of anorectal dysfunction. Although abdominal massage may improve constipation in MS patients, this intervention is time consuming and difficult for MS patients with advanced disease to accomplish. Transanal irrigation in MS patients with anorectal dysfunction showed some promise of benefit in a substantial number of patients, but this approach requires specialized equipment, can be cumbersome for patients and caregivers to implement and poses some inherent risk of colonic perforation. Therefore, there is compelling need to establish evidence supporting a safe, effective, and easily implemented

	Section: Section 1 - Objective, Aims, Background and Significance

treatment option for anorectal dysfunction in MS patients.

One strategy often used in routine clinical practice to manage anorectal dysfunction is to normalize stool form while providing a means for "timed rectal evacuation" using a stimulant laxative rectal suppository. The benefit of this dual approach is to both minimize the difficulties with evacuation and to allow patients some flexibility in planning their schedule. With regular emptying of the distal colorectum, patients should be able to avoid rectal fecal impaction and minimize episodes of fecal incontinence. However, such a practical approach to anorectal dysfunction, particularly regarding the use of timed rectal evacuation, has not been subjected to rigorous clinical evaluation. The goal of this proposal is to determine the efficacy of timed rectal evacuation in an algorithm-based bowel regimen for treating anorectal dysfunction in patients with mild-to-moderately severe MS.

	Section: Section 2 - Research Design and Methods

[reviewer notes¬]

2.1 **Does this research study involve the *use* or evaluation of a drug, biological, or nutritional (e.g., herbal or dietary) supplement?**

* Yes

2.1.1 **Does this research study involve an evaluation of the safety and/or effectiveness of one or more marketed nutritional (e.g., herbal or dietary) supplements for the diagnosis, prevention, mitigation or treatment of a specific disease or condition or symptoms characteristic of a specfic disease or condition?**

* No

[reviewer notes¬]

2.1.2 **Does this research study involve the use or evaluation of one or more drugs or biologicals not currently approved by the FDA for general marketing?**

* No

[reviewer notes¬]

2.1.3 **Does this research involve the *use* or an evaluation of the effectiveness and/or safety of one or more drugs or biologicals currently approved by the FDA for general marketing?**

* Yes

2.1.3.1 **Are the FDA-approved drugs or biologicals being evaluated in this research study for a new clinical indication, different population, or route of administration and/or dosage level that is not currently specified in the FDA-approved product labeling?**

Drugs are often used **Off-Label** during routine practice. Before answering this question, review the FDA product labeling (http://labels.fda.gov) for the approved "Indications and Usage." If being used off-label, answer **Yes** to this question**.** You are required to provide

information and/or upload the package insert for each drug that is administered for research purposes.

* No

If you respond **YES**, an IND number or the FDA written concurrence of IND exemption may be required.

Upload information on FDA approved indications/doses and FDA exemption letter if applicable:

Name	Modified Date

[reviewer notes¬]

2.2 Will this research *use* or evaluate the safety and/or effectiveness of one or more devices?

* No

[reviewer notes¬]

2.3 Summarize the general classification (e.g., descriptive, experimental) and methodological design (e.g., observational, cross-sectional, longitudinal, randomized, open-label single-blind, double-blind, placebo-controlled, active treatment controlled, parallel arm, cross-over arm) of the proposed research study, as applicable.

Single-center, randomized, double-blind placebo controlled clinical trial

2.3.1 Does this research study involve a placebo-controlled arm?

* Yes

[reviewer notes¬]

2.3.1.1 Is there a commonly used diagnostic/treatment approach that is currently recognized as being effective for the proposed subjects' disease or condition, and that will be withheld from subjects assigned to the placebo arm of this research study?

No; subjects assigned to the placebo and experimental arms of the research study will continue to undergo a commonly used diagnostic/treatment approach

[reviewer notes¬]

2.4 Will any research subjects be withdrawn from known effective therapy for the purpose of participating in this research study?

* No

[reviewer notes¬]

2.5 Will screening procedures (i.e., procedures to determine research subject eligibility) be performed specifically for the purpose of this research study?

* Yes

2.5.1 List the screening procedures that will be performed for the purpose of this research study. Do NOT include the inclusion/exclusion criteria in this section as they will be addressed in section 3; questions 3.13 and 3.14.

There are two mechanisms in which patients will be effectively screened:

1) The study coordinator uses the data listed in the "UPMC Multiple Sclerosis and Related Disorders Registry" (PRO12010609) to identify prospective subjects. Patients have already consented to join this registry and this consent includes provision for information to be accessed by study personnel, with patients explicitly "opting in" to be contacted if they qualify for ongoing studies.

2) The care team at the UPMC MS Center (MDs, PAs, nurses, etc.) identify subjects interested in joining the study during the course of ongoing, routine clinical care encounters. Care team members would then provide the contact information of interested subjected to the study coordinator to arrange for the consent process and study initiation.

[reviewer notes¬]

2.6 Provide a detailed description of all research activities (e.g., all drugs or devices; psychosocial interventions or measures) that will be performed for the purpose of this research study.

This description of activities should be complete and of sufficient detail to permit an assessment of associated risks.

At a minimum the description should include:

- **all research activities**
- **personnel (by role) performing the procedures**
- **location of procedures**
- **duration of procedures**
- **timeline of study procedures**

RESEARCH PLAN: The goal of this proposal is to determine the efficacy of timed rectal evacuation as a treatment for anorectal dysfunction symptoms in patients with mild-to-moderate severe MS. The primary end-point of the randomized clinical trial is a greater than 30% improvement in patients' subjective global assessment of bowel symptom severity after 4 weeks. In secondary analyses, we will determine the factors predicting treatment response, as well as assess the impact of therapy on measures of global and anorectal dysfunction-related quality of life.

Study Design: This is a single-center, randomized, double-blind placebo controlled trial incorporated into routine clinical care for MS patients with anorectal dysfunction. Patients will be randomized to receive placebo or bisacodyl 10 mg rectal suppositories every other day for 4 weeks.

Study Population and enrollment: Patients at the University of Pittsburgh Medical Center (UPMC) MS Center with anorectal dysfunction will be recruited via either an existing registry, chart review, and/or ongoing care encounters. The UPMC MS Center currently cares for well over 2,000 patients. The study is adequately powered if enrollment reaches 56 patients (see Power Analysis below). To ensure adequate numbers in an intention-to-treat analysis, we will plan for a ~20% patient drop-out rate (thus, enrolling 70 patients in total). Normal clinical care pathways at UPMC naturally generate ~2-3 patient consultations per week for MS patients with anorectal dysfunction (total ~125 patients per year), and the pool of potential study candidates far exceeds that number. Therefore, enrollment of 70 patients appears quite feasible.

Study flow: A schematic of the study flow is shown in the attached figure. All patient encounters, referrals, and tests are integrated into the flow of routine clinical care at UPMC. Recruited patients will meet with the study coordinator in an in-person meeting to discuss the details of the study and obtain informed consent (Kaufman Building MS Clinic). At that time (Phase 1), additional measures of baseline bowel symptom severity and bowel-related quality of life (QOL) will be obtained by standardized questionnaires (see below). The study coordinator will provide patients with instructions on maintaining a daily bowel diary (see Study Measures below), and then initiate referrals for anorectal function testing in the DDC and a later follow-up appointment with the PI/Co-PI ("NeuroGI"). The consent process, baseline questionnaires, and instructions on bowel diary are unlikely to take more than 1 hour of time.

During the next 2-4 weeks after study entry, patients will complete the baseline daily bowel diary.

During Phase 2, patients will meet the PI / Co-PI in the UPMC Digestive Disorders Center (DDC) for anorectal function testing (anorectal sensory and High Resolution Anorectal Manometry (HRAM) testing), which typically takes about 45 minutes. This is a one time, routine test that is performed in patients with anorectal dysfunction. It involves the transanal placement of a thin manometry catheter with inflatable balloon into the rectum. The patients' threshold to first sensation of rectal filling, urgency, and pain, basal anal resting pressure, voluntary anal squeeze pressure, and the rectal-anal inhibitory reflex (RAIR) to rectal distention and during simulated strain, as well as the ability to evacuate a 50 cc volume rectal balloon within one minute are all recorded variables and constitute normal components of such testing. The PI/Co-PI will meet with patients in the DDC GI lab around the time of the anorectal testing, and based on the clinical assessment of dominant bowel symptoms, provide patients with guidance on baseline interventions (either laxative or anti-diarrheal use). For example, the use of oral therapies is predicated on patients' typical stool form (using the Bristol Stool Scale 1-7) – the goal is to achieve a typical bowel movement of a 3-5 in consistency. Patients with Bristol 1-2 stools (hard) will use 8.5 – 42 grams of PEG-3350 laxative per day, while those with Bristol 6-7 (loose) will use 0.5 – 4 grams of loperamide per day, titrated to the goal. At the end of Phase 2 visit, patients will be given instructions on study medication use and will obtain the study drug (double-blinded; study drug "blister" packets would have been previously randomized by the pharmacy and delivered to the DDC). Patients will be encouraged to continue daily bowel diaries for the ensuing 4 weeks of the study trial period. Phase 2, including the physiological testing assessment and meeting with the PI/Co-PI, should take about 1.5 hours in total.

During the next 4 weeks, patients will use recommended oral therapies in addition to the every other day use of the rectal suppository study medication. They will record events in their daily bowel diary.

Finally in Phase 3, after the 4 week study period, patients will meet with the study coordinator to collect unused study medication and completed bowel diaries, and then undergo final reassessments of bowel dysfunction severity and QOL measures. This process could take up to 1 hour. After the questionnaires are completed, patients and the PI/Co-PI will be debriefed (i.e. study arm allocation will be revealed) before having a routine followup clinic visit (continuity of care).

PERSONNEL:

1) The study coordinator will identify and screen potential study subjects (by accessing the "UPMC Multiple Sclerosis and Related Disorders Registry" (PRO12010609) to identify prospective subjects), coordinate the informed consent process with the PI/Co-PI, collect intake questionnaires, and provide instruction on bowel diaries (Phase 1). The coordinator will schedule referrals for anorectal function testing and follow-up DDC visit , and contact patients during the 4-week trial period to verify compliance. Finally, the coordinator will collect bowel diaries and remaining medications at study end, administer study exit questionnaires, and then debrief subjects and the PI/Co-PI once the blind is broken (Phase 3).

2) DDC GI nursing staff routinely performs HRAM studies and will do so in this study. The PI/Co-PI will be involved in clinical care and recommendations both during Phase 2 and Phase 3 (and beyond).

3) MS Physicians will be involved in initial identification of potential subjects and all MS-related continuity of care.

4) Falk Pharmacy serves UPMC for clinical trials, and staff will ensure the 1:1 randomization and distribution of either twenty placebo or biscodyl 10 mg rectal suppositories (used every other day over 4 weeks during the study period). Falk Pharmacy staff is experienced in running clinical trials and maintaining double-blind study conditions between subjects and investigators. Patients will receive a slight excess number of suppositories in order to assess study medication compliance at trial end.

STUDY MEASURES: We plan to obtain the following information from all enrolled patients:
1) Primary Patient-Reported Outcome Measure: "Using a scale of 1 to 10 (1 being no problem and 10 being maximally impactful symptoms), how would you rate the severity of your bowel symptoms over the past 2 weeks?"
2) Daily Bowel Diaries – patients will record the consistency (Bristol Stool Scale, 1-7), number of bowel movements (BM), and occurrence of any fecal incontinence (FI) episodes each day. This data will be used to abstract BM and FI weekly frequency, as well as the mean change in stool consistency during the study period.
3) Patient Assessment of Constipation Symptom Questionnaire (PAC-SYM)
4) Fecal Incontinence Severity Index (FISI)
5) Patient Assessment of Constipation QOL (PAC-QOL)
6) Rockwood Fecal Incontinence Quality of Life Scale (FIQL)
7) SF-36 health status questionnaire
8) Study Medication Compliance
9) Anorectal Sensory and High Resolution Anorectal Manometry Testing: First sensation of rectal filling, urgency, and pain, basal anal resting pressure, voluntary anal squeeze pressure, and the rectal-anal inhibitory reflex (RAIR) to rectal distention and simulated strain, as well as the ability to evacuate a 50 cc volume rectal balloon within one minute.

2.6.1 Will blood samples be obtained as part of this research study?

* No

*If submitting a protocol for expedited review, it should be clear that the planned blood draws are within the parameters described here: http://www.hhs.gov/ohrp/policy/expedited98.html (see Expedited Research Category #2)

If **Yes**, address the frequency, volume per withdrawal, the total volume per visit, and the qualifications of the individual performing the procedure:

	Section: Section 2 - Research Design and Methods

Study Flow Chart:

Name	Modified Date
STUDY DIAGRAM - UPDATED 10-26-15.pdf	10/26/2015 11:13 AM

[reviewer notes¬]

2.7 **Will follow-up procedures be performed specifically for research purposes? Follow-up procedures may include phone calls, interviews, biomedical tests or other monitoring procedures.**

* No

[reviewer notes¬]

2.8 **Does this research study involve the use of any questionnaires, interview or survey instruments?**

* Yes

Upload a copy of all materials except for the SCID or KSADS which are on file at the IRB. The use of all instruments must be addressed in question 2.6 and/or question 2.7 (except for an exempt submission where they should be addressed on the appropriate uploaded exempt form).

Name	Modified Date
Primary Endpoint - PAC-SYM and FISI Questionnaires.pdf	11/3/2015 3:24 PM
SF-36 QUESTIONNAIRE in PDF.pdf	11/3/2015 3:24 PM
FIQL .pdf	11/3/2015 3:24 PM
PAC-QOL.pdf	11/3/2015 3:23 PM
Bowel Diary Pages.pdf	11/3/2015 3:35 PM

Previously the name and publisher for commercially available materials were listed in the textbox below but effective 9/1/2015, all materials (except for the SCID and KSADS) must be uploaded using the Add button above.
Each of these questionnaires (PAC-SYM, FISI, PAC-QOL, FIQL, SF-36) are open access.

[reviewer notes¬]

2.9 **If subjects are also patients, will any clinical procedures that are being used for their conventional medical care also be used for research purposes?**

* yes

If **Yes,** describe the clinical procedures (and, if applicable, their frequency) that will be used for research purposes:
Anorectal function testing (anorectal sensory function and high resolution anorectal manometry [HRAM]) is commonly used for to help patients with anorectal dysfunction. The testing is typically performed once.

	Section: Section 2 - Research Design and Methods

2.10 The blood sample question was moved to 2.6.1.

[reviewer notes¬]

2.11 **What is the total duration of the subject's participation in this research study across all visits, including follow-up surveillance?**

* Up to 8 weeks

[reviewer notes¬]

2.12 **Does this research study involve any type of planned deception?**
If Yes, you are required to request an alteration of the informed consent process (question 4.7)

* No

[reviewer notes¬]

2.13 **Does this research study involve the use of UPMC/Pitt protected health information that will be de-identified by an IRB approved "honest broker" system?**

* No

[reviewer notes¬]

2.14 **Will protected health information from a UPMC/Pitt HIPAA covered entity be accessed for research purposes or will research data be placed in the UPMC/Pitt medical record?**

* Yes

If you answer **Yes**, you are required to submit this study to the Research Informatics Office, Health Record Research Request (R3). Per UPMC Policy HS-RS0005, all research projects that access or involve UPMC electronic protected health information (e-PHI) must be submitted to R3, with the exception of clinical trials that are contracted through the UPMC Office of Sponsored Programs and Research Support (OSPARS).

Complete the R3 intake form available at http://rio.pitt.edu/services. An R3 representative will conduct a review. You will be notified once your R3 review is complete or if anything further is needed.

Describe the medical record information that will be collected from the UPMC/Pitt HIPAA covered entity and/or the research-derived information that will be placed in the medical records.

Basic Demographic information (age, sex, marital status, smoking and alcohol use, etc.)

MS-related information (duration of diagnosis, disease subtype, symptom assessment, current medication use)

Past medical history (particularly in regard to abdominal or anorectal surgeries, presence of inflammatory bowel disease, or recent infectious colitis)

2.14.1 Will protected health information from a non-UPMC/Pitt HIPAA covered entity be obtained for research purposes or will research data be placed in the non-UPMC/Pitt medical record?

* No

I, David Levinthal **, certify that any member of my research team accessing, reviewing and/or recording information from medical records have completed the CITI Privacy & Information Security course or, if completed within the past year, the Internet-Based Studies in Education and Research (ISER) HIPAA for Researchers (Formerly RPF Module 6). The HIPAA certificates must be available for review if audited but do not need to be uploaded into this OSIRIS application.**

* Yes

2.14.2 Are you requesting a waiver of the requirement to obtain written HIPAA authorization for the collection of the PHI?

* No

[reviewer notes¬]

2.15 Does this research study involve the long-term storage (banking) of biological specimens?

* No

[reviewer notes¬]

2.16 Will research participants be asked to provide information about their family members or acquaintances?

* No

[reviewer notes¬]

2.17 What are the main outcome variables that will be evaluated in this study?

PRIMARY END POINT: The primary end-point of the randomized clinical trial is a greater than 30% improvement in patients' subjective global assessment of bowel symptom severity after 4 weeks based on the answer to the following question: "Using a scale of 1 to 10 (1 being no problem and 10 being maximally impactful symptoms), how would you rate the severity of your bowel symptoms over the past 2 weeks?"

SECONDARY END POINTS:
1) Daily Bowel Diaries – patients will record the consistency (Bristol Stool Scale, 1-7), number of bowel movements (BM), and occurrence of any fecal incontinence (FI) episodes each day. This data will be used to abstract BM and FI weekly frequency, as well as the mean change in stool consistency during the study period.

2) Patient Assessment of Constipation Symptom Questionnaire (PAC-SYM)
3) Fecal Incontinence Severity Index (FISI)
4) Patient Assessment of Constipation QOL (PAC-QOL)
5) Rockwood Fecal Incontinence Quality of Life Scale (FIQL)
6) SF-36 health status questionnaire
7) Study Medication Compliance
8) Anorectal Sensory and High Resolution Anorectal Manometry Testing: First sensation of rectal filling, urgency, and pain, basal anal resting pressure, voluntary anal squeeze pressure, and the rectal-anal inhibitory reflex (RAIR) to rectal distention and simulated strain, as well as the ability to evacuate a 50 cc volume rectal balloon within one minute.

2.18 Describe the statistical approaches that will be used to analyze the study data.

* Addressed below:

Categorical data will be analyzed using Fisher's Exact tests for differences in proportions. Continuous data will be analyzed using Student's t-tests to detect differences in group means, with Bonferroni correction for multiple comparisons. We will use logistic regression to determine the factors that predict treatment responses.
A $p<0.05$ will be used as the threshold for statistical significance in all cases.

POWER ANALYSIS/SAMPLE SIZE: It is generally regarded that a 3-point reduction represents a clinically meaningful change using such a 10 point scale, and similar research studies using patient-reported outcomes have reported standard deviations ranging around ~2.5 points. However, we do not have baseline data to estimate variance, and thus we took a conservative estimate with an expected standard deviation of 4 points. Given these assumptions, we will need 28 patients in each study arm to detect at least a 30% reduction in symptom severity, with a power of 0.80, alpha=$P<0.05$ in a two-tailed analysis.

[reviewer notes¬]

2.19 Will this research be conducted in (a) a foreign country and/or (b) at a site (e.g., Navajo Nation) where the cultural background of the subject population differs substantially from that of Pittsburgh and its surrounding communities?

* No

Note that copies of training records, licenses, certificates should be maintained in the study regulatory binder and are subject to audit by the Research Conduct and Compliance Office (RCCO).

In addition, individuals planning to conduct human subject research outside the United States must complete an optional module on the CITI training website: International Studies. Click here to access the instruction sheet for accessing optional CITI modules.

[reviewer notes¬]

2.21 Will this research study be conducted within a nursing home located in Pennsylvania?

* No

Section: Section 2 - Research Design and Methods

Section: Section 3 - Human Subjects

[reviewer notes¬]

Section 3 - Human Subjects

3.1 **What is the age range of the subject population?**

18-80

3.2 **What is their gender?**

* Both males and females

Provide a justification if single gender selected:

3.3 **Will any racial or ethnic subgroups be explicitly excluded from participation?**

* No

If **Yes**, identify subgroups and provide a justification:

3.4 **For studies conducted in the U.S., do you expect that all subjects will be able to comprehend English?**

* Yes

[reviewer notes¬]

3.5 **Participation of Children: Will children less than 18 years of age be studied?**

* No

If **No**, provide a justification for excluding children:
Multiple sclerosis does not typically manifest in childhood. Childhood MS may represent a variant of the disease not generalizable to the typical adult MS population.

[reviewer notes¬]

3.6 **Does this research study involve prisoners, or is it anticipated that the research study may involve prisoners?**

* No

[reviewer notes¬]

3.7 **Will pregnant women be knowingly and purposely included in this research study?**

* No

[reviewer notes¬]

3.8 **Does this research study involve neonates of uncertain viability or nonviable neonates?**

* No

[reviewer notes¬]

3.9 **Fetal Tissues: Does this research involve the use of fetal tissues or organs?**

* No

[reviewer notes¬]
--->

3.10 **What is the total number of subjects to be studied at this site, including subjects to be screened for eligibility?**

Note: The number below is calculated by summing the data entered in question 3.11. Any additions or changes to the values entered in 3.11 will be reflected in 3.10.

* 400

3.11 **Identify each of the disease or condition specific subgroups (include healthy volunteers, if applicable) that will be studied.**

Click on the "Add" button and specify for each subgroup:

1) how many subjects will undergo research related procedures at this site; and

2) if applicable, how many subjects will be required to undergo screening procedures (e.g., blood work, EKG, x-rays, etc.) to establish eligibility. Do Not include subjects who will undergo preliminary telephone screening.

*

	Subgroup	Number to undergo research procedures	Number to undergo screening procedures
View	MS patients	70	400

3.12 **Provide a statistical justification for the total number of subjects to be enrolled into this research study at the multicenter sites or this site.**

* Described below:

The primary outcome measure is the group mean difference in subjective severity ratings of bowel symptoms using a 10 point scale. It is generally regarded that a 3-point reduction represents a clinically meaningful change using such a scale, and similar

research studies using patient-reported outcomes have reported standard deviations ranging around ~2.5 points on a 10 point scale. However, we do not have baseline data in this population to estimate variance, and thus we took a conservative estimate with an expected standard deviation of 4 points. Given these assumptions, we will need 28 patients in each study arm to detect at least a 3 point reduction in symptom severity, with a power of 0.80, alpha=P<0.05 in a two-tailed analysis.

Thus, the study is adequately powered if enrollment reaches 56 patients. However, to ensure adequate numbers in an intention-to-treat analysis, we will plan for a ~20% patient drop-out rate. Therefore, we will aim to enroll 70 patients in total.

[reviewer notes¬]

3.13 **Inclusion Criteria: List the specific criteria for inclusion of potential subjects.**

MS patients with mild to moderately severe disease (MSIS-29 Physical domain scores <61 or an equivalent EDSS < 6.5) aged 18-80, of any gender, disease subtype, duration of illness, or with any current use of disease modifying therapy and who also have anorectal dysfunction (chronic constipation and/or fecal incontinence) are eligible. MSIS-29 and EDSS scores are determined in the course of routine MS care at UPMC.

3.14 **Exclusion Criteria: List the specific criteria for exclusion of potential subjects from participation.**

MS patients with severe disease, as assessed by MSIS-29 Physical domain scores greater than 61 or an equivalent EDSS of greater than 6.5), aged <18 or >80, or patients with surgically altered anorectal anatomy (i.e. proctectomy/partial colectomy, ostomy creation), active enteric infection (i.e. Clostidium Difficile), or inflammatory bowel disease (i.e. ulcerative proctitis) will be excluded.

3.15 **Will HIV serostatus be evaluated specifically for the purpose of participation in this research study?**

* No

If **Yes**, provide a justification:

[reviewer notes¬]

4.1 Select all recruitment methods to be used to identify potential subjects:
Research Registry
Other Strategies: Described below

Research Registry

List the IRB approval number and title for each registry source:
PRO12010609: "UPMC Multiple Sclerosis and Related Disorders Registry"

Section: Section 4 - Recruitment and Informed Consent Procedures

4.2 **Provide a detailed description of your recruitment methods, including identifying and initiating contact with participants:**

Patients at the University of Pittsburgh Medical Center (UPMC) MS Center with anorectal dysfunction will be recruited via two possible mechanisms: 1) via an existing MS research registry of patients who have previously expressed a willingness to participate in research projects and/or 2) during the course of ongoing, routine clinical care encounters at the UPMC MS Center.

Patients identified by method 1 or 2 will be contacted either in person or by phone during business hours by our study coordinator. We may send an email announcement of the study to the patients on the MS research registry.

The UPMC MS Center currently cares for well over 2,000 patients and generates ~125 outpatient consultations per year to the NeuroGI group (PI/Co-PI) to help co-manage MS patients with anorectal dysfunction. We should not have difficulty meeting our target enrollment for the study.

Note: Questions jump from 4.2 to 4.6 as questions 4.3-4.5 have been removed and the information is now captured in 4.1

[reviewer notes¬]

4.6 **Are you requesting a waiver to document informed consent for any or all participants, for any or all procedures? (e.g., a verbal or computerized consent script will be used, but the subjects will not be required to sign a written informed consent document.** ***This is not a waiver to obtain consent.***

* No

[reviewer notes¬]

4.7 **Are you requesting a waiver to obtain informed consent or an alteration of the informed consent process for any of the following?**

* No

4.7.1 **If Yes, select the reason(s) for your request:**

There are no items to display

General Requirements: The Federal Policy **[45 CFR 46.116 (d)]** specifies in order for a waiver of consent to be approved, the request must meet four criteria. For each request, you will be asked to provide a justification addressing how each of these criterion is met.

[reviewer notes¬]

4.8 Are you requesting an exception to the requirement to obtain informed consent for research involving the evaluation of an 'emergency' procedure?

Note: This exception allows research on life-threatening conditions for which available treatments are unproven or unsatisfactory and where it is not possible to obtain informed consent.

* No

[reviewer notes¬]

4.9 Upload all consent documents for watermarking:

Draft Consent Forms for editing:

Name	Modified Date
Consent Form	10/26/2018 10:02 AM

Approved Consent Form(s):

Name	Modified Date
Consent Form	10/26/2018 10:02 AM

[reviewer notes¬]

4.10 Will all potential adult subjects be capable of providing direct consent for study participation?

*
Yes

[reviewer notes¬]

4.11 At what point will you obtain the informed consent of potential research subjects or their authorized representative?

After performing certain of the screening procedures, but prior to performing any of the research interventions/interactions

4.11.1 Address why you feel that it is acceptable to defer obtaining written informed consent until after the screening procedures have been performed.

Study flow will be optimized by making an assessment of inclusion and exclusion criteria before approaching patients; there is no benefit to obtaining written informed consent in an individual not eligible for the study, and there wasted time and effort (for both patient and investigative team) in doing so. There is no appreciable harm (i.e. HIPPA will be preserved) if our study coordinator pre-screened patients with upcoming appointments to

the UPMC MS center. Lastly, the most substantial screening will be performed using an already IRB-approved MS patient registry designed specifically for this purpose (PRO12010609, "UPMC Multiple Sclerosis and Related Disorders Registry").

4.11.2 Taking into account the nature of the study and subject population, indicate how the research team will ensure that subjects have sufficient time to decide whether to participate in this study. In addition, describe the steps that will be taken to minimize the possibility of coercion or undue influence.

The patients enrolled via the MS patient registry or those identified by screening the list of patients with upcoming MS clinic visits will have several days to even weeks before deciding to participate in the study. Patients identified by MS care physicians during the course of routine care are already referred to the PI/Co-PI. These referrals could trigger an inquiry into their interest in study participation. Due to the schedules of the PI/Co-PI, these consultations often are scheduled at least 6-8 weeks prior to being seen. Thus, there should be ample time for participants to consider their decision to enroll in the study. Our study coordinator will contact patients by phone and present the study paradigm in a non-judgmental way, emphasizing that the decision to enroll will in no way influence their access to care. Additionally, at the point of first contact, patients will not have direct interaction with the PI / Co-PI, and thus there is no clear way that the PI/Co-PI could exert coercion on potential study candidates at that early point.

[reviewer notes¬]

4.12 Describe the process that you will employ to ensure the subjects are fully informed about this research study.

* Addressed below:

This description must include the following elements:

- who from the research team will be involved in the consent process (both the discussion and documentation);
- person who will provide consent or permission;
- information communicated; and
- any waiting period between informing the prospective participant about the study and obtaining consent

In addition, address the following if applicable based on your subject population:

- process for child assent and parental permission
  - continued participation if a child subject turns 18 during participation
- process for obtaining proxy consent and assent for decisionally impaired subjects
  - continued participation if subject regains capacity to consent

Most of our participants are likely to be identified via the "UPMC Multiple Sclerosis and Related Disorders Registry" or by screening individuals with MS upcoming clinic visits. A potential participant who is deemed eligible via these screening procedures may be contacted and then sent the consent form for review prior to the study visit if they are interested. Thus, the potential participant will be given substantial time (days to weeks) to review the consent form and have an opportunity to contact study staff with any questions prior to enrollment. Our study coordinator will again provide a detailed review of the study with special focus on the potential benefits and risks of the study, and all of the potential subject's questions should be answered at the time of the consenting. The subject will be reminded that participation is voluntary and that if s/he does not want to participate, then refusal will not impact subsequent care. If the subject is still interested in participating,

Section: Section 4 - Recruitment and Informed Consent Procedures

then one of the investigators (PI/Co-PI) will obtain informed consent and sign the Certification of Informed Consent. A copy of the consent form will be given to the subject.

4.13 Are you requesting an exception to either IRB policy related to the informed consent process?

- For studies involving a drug, device or surgical procedures, a *licensed physician who is a listed investigator* is required to obtain the written informed consent unless an exception to this policy has been approved by the IRB
- For all other studies, a *listed* investigator is required to obtain consent (Note: In order to request an exception to this policy, the study must be minimal risk)

* No

If **Yes**, provide a justification and describe the qualifications of the individual who will obtain consent:

4.14 Will you inform research subjects about the outcome of this research study following its completion?

* Yes

If **Yes**, describe the process to inform subjects of the results:
Patients and the PI/Co-PI will be debriefed after Phase 3 by the study coordinator. They will then be seen by the PI/Co-PI in a standard follow up clinic visit. The debriefing is a necessary part of the patient's continuity of care, as it may direct changes in patient management (i.e. if a patient did not have a clinical improvement in the placebo arm, they may be offered study medication or its equivalent). As a patient reported outcome is the primary outcome measure, the "results" of the study should be self-evident to patients.

Section: Section 5 - Potential Risks and Benefits

[reviewer notes¬]

5.1 Describe potential risks (physical, psychological, social, legal, economic or other) associated with screening procedures, research interventions/interactions, and follow-up/monitoring procedures performed specifically for this study:

*

View

Research Activity:	Bowel Diary
Common Risks:	*No Value Entered*
Infrequent Risks:	All efforts will be made to keep the information secure. However, there is a small chance of a breach in confidentiality with any medical record keeping.
Other Risks:	*No Value Entered*

View

Research Activity:	Medical Record Review
Common Risks:	*No Value Entered*
Infrequent Risks:	There is a small chance of a breach in confidentiality with any medical record review, either by Care Team staff as a part of routine care, or by the study coordinator in the process of

		accessing information from the "UPMC Multiple Sclerosis and Related Disorders Registry" (PRO12010609).
	Other Risks:	*No Value Entered*

View	**Research Activity:**	Research Intervention
	Common Risks:	The study medication, bisacodyl 10 mg rectal suppository, is available over-the-counter for routine use for constipation. Side effects of bisacodyl rectal suppositories include stomach discomfort, nausea, faintness, rectal burning, mild cramps, and diarrhea but these are potential issues are uncommon. There are no side effects to taking placebo, but patients could have a risk of continued bowel dysfunction if they do not receive the study drug.
	Infrequent Risks:	*No Value Entered*
	Other Risks:	*No Value Entered*

View	**Research Activity:**	Screening and Enrollment
	Common Risks:	Minimal risk of patient's concern that participation is expected or that their care would be impacted by opting out.
	Infrequent Risks:	*No Value Entered*
	Other Risks:	*No Value Entered*

View	**Research Activity:**	Study Survey Data
	Common Risks:	*No Value Entered*
	Infrequent Risks:	All efforts will be made to keep the information secure. However, there is a small chance of a breach in confidentiality with any medical record keeping.
	Other Risks:	*No Value Entered*

5.1.1 Describe the steps that will be taken to prevent or to minimize the severity of the potential risks:

The study coordinator will contact patients to make sure that they are not having any problems during the study period. Patients will be encouraged to contact study staff regarding any concerns during the study period at any time.

Our study coordinator will emphasize that participation is completely voluntary, that patients can always opt out even once enrolled, and that their decision to participate or not will have no impact on care decisions.

5.2 What steps will be taken in the event that a clinically significant, unexpected disease or condition is identified during the conduct of the study?

* **Not Applicable**

5.3 All the risk questions (screening, intervention/interaction, follow-up) have been merged into one question (5.1).

[reviewer notes¬]

Section: Section 5 - Potential Risks and Benefits

5.4 **Do any of the research procedures pose a physical or clinically significant psychological risk to women who are or may be pregnant or to a fetus?**

* No

[reviewer notes¬]

5.5 **Do any of the research procedures pose a potential risk of causing genetic mutations that could lead to birth defects?**

* No

[reviewer notes¬]

5.6 **Are there any alternative procedures or courses of treatment which may be of benefit to the subject if they choose not to participate in this study?**

* No

If **Yes**, describe in detail:

[reviewer notes¬]

5.7 **Describe the specific endpoints (e.g., adverse reactions/events, failure to demonstrate effectiveness, disease progression) or other circumstances (e.g., subject's failure to follow study procedures) that will result in discontinuing a subject's participation?**

* Not applicable - There are no anticipated circumstances that would lead to discontinuing a subject's participation in this research study.

[reviewer notes¬]

5.8 **Will any individuals <u>other</u> than the investigators/research staff involved in the conduct of this research study and authorized representatives of the University Research Conduct and Compliance Office (RCCO) be permitted access to research data/documents (including medical record information) associated with the conduct of this research study?**

* No

5.9 **Has or will a Federal Certificate of Confidentiality be obtained for this research study?**

* No

5.10 **Question has been moved to 5.17**

5.11 **Question has been moved to 5.16**

[reviewer notes¬]

5.12 Does participation in this research study offer the potential for direct benefit to the research subjects?

Yes - Describe the direct benefit that subjects may receive as a result of study participation. Indicate if all, or only certain, of the subjects may derive this potential benefit.

Describe the benefit:
Most patients are likely to see some subjective improvement in bowel function (even those in the placebo arm), since all patients will be will be recommended to use some intervention to alter stool form (i.e. laxatives or anti-diarrheals). The study participants assigned to the active medication arm may derive subjectively greater improvement in bowel related symptoms (the primary hypothesis).

5.13 Describe the data and safety monitoring plan associated with this study. If the research study involves multiple sites, the plan must address both a local and central review process.

The Principal Investigator, Dr. Levinthal, will meet with Klaus Bielefeldt (Co-PI) every 8 weeks to evaluate the progress of the research study, including assessment of data quality and subject recruitment.

Data and Safety will be further monitored by a joint meeting every 6 months between the PI, Co-PI, and Margie O'Leary, a nurse manager of the UPMC MS Clinic who oversees clinical trials for the group. This group will be responsible for the following: 1) reviewing the data accumulated from the ongoing study; 2) advising the principal investigator or study sponsor of necessary changes to elements of the study that affect subject safety; 3) determining whether there has been any change to the risk-to-benefit assessment during the course of the study; and 4) determining whether the study should continue as designed. They will also review, on an ad hoc basis, any serious adverse events (SAE) that are directly related to the study medication as given according the study protocol. The results of the DSMB meetings will be submitted to the IRB at the time of the annual renewal.

[reviewer notes¬]

Section 5 - Potential Risks and Benefits of Study Participation

5.14 What precautions will be used to ensure subject privacy is respected? (e.g. the research intervention will be conducted in a private room; the collection of sensitive information about subjects is limited to the amount necessary to achieve the aims of the research, so that no unneeded sensitive information is being collected, drapes or other barriers will be used for subjects who are required to disrobe)

The interactions between patients and the study coordinator/study staff (informed consent, study questionnaires) will be conducted in a private room, likely within the MS Clinic on initial study entry and in the DDC at study close.

Enrolled patients undergoing anorectal manometry testing will have the testing performed in a private room in the DDC GI Lab, adjacent to a private bathroom / changing area.

5.15 What precautions will be used to maintain the confidentiality of identifiable information? (e.g., paper-based records will be kept in a secure location and only be accessible to personnel involved in the study, computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords, prior to

Section: Section 5 - Potential Risks and Benefits

access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information, whenever feasible, identifiers will be removed from study-related information, precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys, audio and/or video recordings of subjects will be transcribed and then destroyed to eliminate audible identification of subjects)

All paper-based records (informed consent forms, study questionnaires and daily bowel diaries) will be kept in a secure location and only be accessible to personnel involved in the conduct and analysis of the study.

Electronic files used in the analysis will contain only de-identified data.

5.16 If the subject withdraws from the study, describe what, if anything, will happen to the subject's research data or biological specimens.

If the subject withdraws from the study after having passed Phase 1 (i.e. baseline measures of bowel dysfunction and quality of life), we would keep the data for an "intention-to-treat" analysis (with the assumption of an non-response). If a subject has not completed Phase 1, then the research data will be destroyed.

5.17 Following the required data retention period, describe the procedures utilized to protect subject confidentiality. (e.g., destruction of research records; removal of identifiers; destruction of linkage code information; secured long-term retention)

We will destroy primary research records with any identifiers, but may opt to retain de-identified electronic data on a secured server for future re-analysis. Per University of Pittsburgh guidelines, research records will be archived for a minimum of seven years after final reporting or publication of a project.

Section: Section 6 - Costs and Payments

[reviewer notes¬]

6.1 Will research subjects or their insurance providers be charged for any of the procedures (e.g., screening procedures, research procedures, follow-up procedures) performed for the purpose of this research study?
*

Yes; charges will be billed only for procedures performed as part of the subject's routine clinical care as addressed in question 2.9

[reviewer notes¬]

6.2 Will subjects be compensated in any way for their participation in this research study?

* No

Section: Section 7 - Qualifications and Source(s) of Support

[reviewer notes¬]

Section: Section 7 - Qualifications and Source(s) of Support

7.1 Summarize the qualifications and expertise of the principal investigator and listed co-investigators to perform the procedures outlined in this research study.

The PI (Levinthal) is an MD, PhD adult neurogastroenterologist with expertise in GI motility disorders, particularly those arising in patients with underlying neurological illness. He has already conducted clinical studies investigating the prevalence and associations of GI disorders in the MS population at UPMC.

Key personnel includes Rock Heyman, an MD and the Director of the Neuroinflammation / MS Division in the Department of Neurology at UPMC. He is in charge of clinical operations of the MS clinic and has extensive experience running clinical trials involving the MS population.

The PI (Levinthal) has the appropriate privileges to perform and evaluate all proposed clinical procedures (including the anorectal function testing).

[reviewer notes¬]

7.2 Indicate all sources of support for this research study.

*

Selections
Foundation: Upload a copy of the research plan that was submitted to the agency

If **Federal** support, provide the sponsor information:

Federal sponsor	Grant Title	Grant number	Awardee institution	Federal grant application

For projects not supported by a federal grant, upload the research plan that was submitted for funding:

Name	Modified Date
PilotResearch_Guidelines_ApplicationForm June 2015 - LEVINTHAL .pdf	10/26/2015 1:13 PM

If **Industry** support, provide the sponsor information and level of support:

If **Foundation** support, provide the sponsor information:
Consortium of Multiple Sclerosis Centers (CMSC)

If **Other** support, provide the support information and level of support:

[reviewer notes¬]

7.3 Is this study funded in part or whole by a PHS Agency?

* No

Section: Section 7 - Qualifications and Source(s) of Support

Does any investigator* involved in this study (select all that apply):

	Name
☐	**A.** Have equity in a **publicly-traded entity** that either sponsors** this research or owns the technology being evaluated or developed that exceeds a **5% ownership interest** or a current value of **$10,000**?
☐	**B.** Have equity in a **non-publicly-traded entity** that either sponsors this research or owns the technology being evaluated or developed?
☐	**C.** Receive salary, consulting fees, honoraria, royalties or other remuneration from an entity that either sponsors this research or owns the technology being evaluated or developed that is expected to exceed **$10,000** during the past or next 12 months?
☐	**D.** Have rights as either the author or inventor of **intellectual property** being evaluated or developed in this research that is the subject of an issued patent or has been optioned or licensed to an entity?
☐	**E.** Have an officer or management position**** with a **Licensed Start-up Company** overseen by the COI Committee that either sponsors this research or owns the technology being evaluated or developed?
☐	**F.** Receive compensation of any amount when the value of the compensation would be affected by the outcome of this research, such as compensation that is explicitly greater for a favorable outcome than for an unfavorable outcome or compensation in the form of an equity interest in the entity that either sponsors this research or owns the technology being evaluated or developed?
☑	**None of the above options apply and there are no other financial conflicts of interest in the conduct of this research.**

***Investigator** means the PI, co-investigators, and any other member of the study team, regardless of title, who participates in the design, conduct, or reporting of this research, as well as his/her spouse, registered domestic partner, dependents, or other members of his/her household. **The PI is responsible for ensuring that s/he and all other relevant members of the study team review the above questions describing Significant Financial Interests.**

****through the provision of funds, drugs, devices, or other support for this research

*****Such as serving on the Board of Directors or Board of Managers or a position that carries a fiduciary responsibility to the company (e.g., CEO, CFO, CTO, or CMO).

Section: Supporting Documentation

[reviewer notes¬]

Supporting Documentation Section

References and Other Attachments

Additional documents:

Name	Modified Date	Version
FRIAR - OSPARS Form -- LEVINTHAL 2015.docx	10/27/2015 5:38 PM	0.01

Please use the Add button to the left to upload additional documents if needed.

Section: Supporting Documentation

[reviewer notes¬]

ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world.

"Applicable clinical trials" are required **by federal law** to be registered in ClinicalTrials.gov.

Applicable Clinical Trials (ACTs) are studies that meet the following criteria:

- The study is an interventional study AND
- The study intervention is a drug, biologic, medical device, radiation or genetic AND
- The Study is not Phase 0 or 1 AND
- The study has at least one site in the United States or is conducted under an investigational new drug application or investigational device exemption

NIH Policy

Effective January 18, 2017, revised NIH Policy requires that all clinical trials funded in whole or in part by the NIH be registered and results information posted on ClinicalTrials.gov.

As defined by the NIH, a clinical trial is:

A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health related biomedical or behavioral outcomes.

The NIH Policy extends beyond the Food and Drug Administration Amendment Act (FDAAA 801) requirements in that it requires registration and results reporting of:

- clinical trials of behavioral, surgical and other types of health and medical interventions
- phase 1 studies of drugs and biological products
- small feasibility studies of device products

Failure to submit all required registration and results information requested on ClinicalTrials.gov can jeopardize University grant funding, the future funding of the grantee and subject the University of Pittsburgh to future monetary penalties.

In addition, to promote transparency of the clinical trials process, the International Committee of Medical Journal Editors (ICMJE) has established a policy requiring the entry of clinical trials in a public registry, such as ClinicalTrials.gov, prior to subject enrollment as a condition of consideration for publication of the trial results.

* **Based on the above information, will this study be registered in ClinicalTrials.gov?**