MAYO CLINIC

Name and Clinic Number
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RESEARCH PARTICIPANT CONSENT AND PRIVACY AUTHORIZATION FORM

Study Title: Comparative effectiveness of biofeedback and injectable bulking agents for the treatment of fecal incontinence.

IRB#: 18-004651

Principal Investigator: Adil E. Bharucha and Colleagues

Please read this information carefully. It tells you important things about this research study. A member of our research team will talk to you about taking part in this research study. If you have questions at any time, please ask us.

Take your time to decide. Feel free to discuss the study with your family, friends, and healthcare provider before you make your decision.

To help you decide if you want to take part in this study, you should know:

- Taking part in this study is completely voluntary.
- You can choose not to participate.
- You are free to change your mind at any time if you choose to participate.
- Your decision won't cause any penalties or loss of benefits to which you're otherwise entitled.
- Your decision won't change the access to medical care you get at Mayo Clinic now or in the future if you choose not to participate or discontinue your participation.

For purposes of this form, Mayo Clinic refers to Mayo Clinic in Arizona, Florida and Rochester, Minnesota; Mayo Clinic Health System; and all owned and affiliated clinics, hospitals, and entities.

If you decide to take part in this research study, you will sign this consent form to show that you want to take part. We will give you a copy of this form to keep. A copy of this form will be put in your medical record.

If you are signing this consent form for someone else, "you" in the consent form refers to the participant.

CONTACT INFORMATION

You can contact …	At …	If you have questions about …
Principal Investigator(s): Dr. Adil E. Bharucha **Study Team Contact:** Kelly Feuerhak	**Phone:** (507) 284-2511 **Phone:** (507) 255-6802 **Institution Name and Address:** Mayo Clinic 200 First Street SW Rochester, MN 55905	▪ Study tests and procedures ▪ Research-related injuries or emergencies ▪ Any research-related concerns or complaints ▪ Withdrawing from the research study ▪ Materials you receive ▪ Research-related appointments
Mayo Clinic Institutional Review Board (IRB)	**Phone:** (507) 266-4000 **Toll-Free:** (866) 273-4681	▪ Rights of a research participant
Research Subject Advocate **(The RSA is independent of the Study Team)**	**Phone:** (507) 266-9372 **Toll-Free:** (866) 273-4681 **E-mail:** researchsubjectadvocate@mayo.edu	▪ Rights of a research participant ▪ Any research-related concerns or complaints ▪ Use of your Protected Health Information ▪ Stopping your authorization to use your Protected Health Information
Research Billing	**Rochester, MN:** (507) 266-5670	▪ Billing or insurance related to this research study

1. Information you should know

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Website will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Website at any time.

A description of this research study will be available on *mayoclinic.org.* This website will not include information that can identify you. You can search this website at any time.

2. What are some general things you should know about research studies?

This study is completely voluntary so you may refuse to join or withdraw your consent to be in the study, for any reason. Research studies are designed to obtain new knowledge that may help other people in the future. Being in a research study might not help you individually and there may be some risks.

If you decide not to participate in the study or leave the study before it is done, your relationship with the researcher, your healthcare provider, the Mayo Clinic, or the University of North Carolina-Chapel Hill will not be affected. You do not need to agree to be in the study to receive help for your problem. Details about this study are discussed below. It is important that you understand this information so that you can make an informed choice about being in this research study. You will be given a copy of this consent form. You should ask the researchers (names above) or staff members who may assist them, any questions you have about this study at any time.

3. What is the purpose of this study?

The purpose of this research study is to compare two treatments for fecal incontinence (also known as accidental bowel leakage) in men and women in terms of how well they work, how safe they are and how much they cost. The treatments are biofeedback therapy and dextranomer injections.

4. Are there any reasons you should not be in this study?

You should not be in this study if:

1. Your accidental bowel leakage (ABL) started within the last 6 months.
2. You have watery diarrhea not managed by diet or drugs.
3. You have Parkinson's disease, multiple sclerosis, severe diabetic neuropathy documented by EMG, spinal cord injury, spina bifida, or a neurodegenerative disorder.
4. You are currently receiving immunosuppression or chemotherapy. Immunosuppression medications are used to treat autoimmune diseases, such as psoriasis, lupus, rheumatoid arthritis, Crohn's disease, multiple sclerosis, and alopecia. Examples of immunosuppression

medication include Corticosteroids (prednisone, budesonide, prednisolone), Calcineurin inhibitors (cyclosporine, tacrolimus), mTOR inhibitors (sirolimus, everolimus), IMDH inhibitors (azathioprine, lefluomide, mycophenolate). Biologics (abatacept, adalimumab, anakinara, certolizumab, enanercept, golimumab, infliximab, ixekizumab, natalizumab, rituximab, secukinumab, tocilizumab, ustekinumab, vedolizumab), and monoclonial antibodies (basiliximab, daclizumab, muromonab). Chemotherapy medications are used for the treatment of cancer.

5. You have had significant anal pain the last 6 months.
6. Your ABL occurs on average less than twice a week.
7. You only lose control of gas but can control stool.
8. You are unable to speak and understand English or Spanish.
9. You have been diagnosed with a serious mental health illness, including dementia, or are unable to understand all of the medical instructions.
10. You are pregnant or planning on becoming pregnant in the next two years.
11. You have had an obstetrical trauma in the past 6 months.
12. You are diagnosed with inflammatory bowel disease, such as Crohn's Disease or Ulcerative Colitis.
13. You have an intestinal stoma.
14. You have history of pelvic radiation within the previous 12 months or presence of active radiation proctitis.
15. You have something implanted in the anorectal region that could interfere with treatment.
16. You have an active anorectal condition in the past 6 months. This could include anal sores that cause pus to drain from openings in the anal canal or rectum, openings in the anal canal, infections in your body that originate from the anus or rectum, significant amounts of rectal or anal bleeding, inflammation of the rectum or anus, and small passages between your colon and vagina or your rectum and vagina, anal or rectal tumors, or other infections.
17. You have a history of having an ileoanal pouch; history of having an anal sphincteroplasty, rectopexy, or rectocele repair within the past 6 months; or history of having 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.
18. You failed a balloon expulsion test and are constipated most of the time.
19. You are allergic to hyaluronic acid-based products. These include skin care products for burns, bedsores, wounds, ulcers, and lip filler in plastic surgery. Brand names include Healon, Gelsyn-3, Hyalgan, Healon Ultimate Dual Pack, Provisc, ORTHOVISC, Euflexxa, GenVisc 850, Amvisc Plus, and Healon5.
20. You take blood-thinning medications (anticoagulants) and your physician believes it is unsafe for you to temporarily stop anticoagulants for any test procedures and treatments associated with the study.
21. You are unwilling to stop using medications, intended for the treatment of accidental bowel leakage, for the duration of the research study. Examples of these medications include herbal supplements, or prescribed medications for the purpose of modifying stool consistency, that

are not included in the approved medications list. The approved medications you can continue to use during the study includes: loperamide [example - Imodium], laxatives [example - MiraLax], fiber supplements [example - Citrucel], and bile acid binders [example – Questran/Welchol].

5. How many people will take part in this study?

This is a multi-site research study, which means there are sites other than Mayo Clinic that are also recruiting for this research study. If you decide to be in this study, you will be one of approximately 60 patients at Mayo Clinic who will be participating. There will be 285 participants among all the sites combined.

6. How long will you be in this research study?

Your total involvement in the study will last up to 30 months, including the follow up assessments. The study has two primary parts, treatment and follow-up. The treatment part of the study will last 3-5 months. After the treatment, we will ask you to complete assessments to see how well you are doing at 3, 6, 12, and 24 months after you start the treatment. You and your provider will decide if you will complete the 3-, 6-, 12- and 24-month assessments at home or will visit the clinic. You will need to visit the clinic for the 3-month assessment if you need to have some procedures. Additionally, we will call you over the telephone 18 months after start of treatment. If you did not respond adequately to the initial randomized treatment and chose a second treatment, three months will be added to your overall time in the study. You will come in for a second three-month visit, twelve weeks after your initial three-month visit. You would follow the remaining schedule of 6-, 12-, and 24-month clinic visits and 18-month phone call.

7. What will happen to you while you are in this research study?

There are five phases to this research study:

1. **Screening Visit**: In this visit, we will check to see if you are eligible to be in the study. You will be asked to complete questionnaires at this visit about your medical history and symptoms. Female participants will be asked to provide a urine sample for a pregnancy test. You will receive a brief medical exam to ensure you meet eligibility criteria. Depending on physician availability, the physical exam may be done at either the screening visit or the baseline visit.

   You will also receive a 14-day bowel symptom diary to take home and complete. We will provide you with a postage paid envelope to mail back the completed study diary and we will call you a few days after this visit to answer any questions you may have about filling out the diary correctly. It is very important to keep track of this diary and make daily entries. Once we receive and review the diary, we will notify you if you meet symptom-based criteria and will schedule your next visit over the phone. If you do not meet symptom-based criteria, your

participation in the research study will end. The screening visit is expected to last up to two hours.

2. **Baseline Visit**: You will be required to undergo a series of diagnostic tests to ensure you continue to meet eligibility criteria for the research study. These tests are considered part of standard medical care. The study will cover the costs of these tests and you or your insurance will not be charged, however you will not receive study-related compensation for standard of care tests. These include an endoanal ultrasound or pelvic floor MRI (you will undergo ultrasound or MRI, but not both, depending on the site), anorectal manometry, and balloon expulsion test. You will also undergo a procedure called the translumbosacral magnetic evoked potential test (TAMS), which is for research purposes only. To prepare for these test procedures, you will be administered up to two enemas to clear your rectum of stool. You will also receive training on enhanced medical management for the treatment of accidental bowel leakage at the end of this visit. The baseline visit is expected to last up to 8 hours. If you are unable to stay the entire duration of this visit, the enhanced medical management visit can be scheduled separately.

3. **Medical Management**: Enhanced Medical Management part of the research study will last 4 weeks. You will receive information from a health care provider within the study about educational, behavioral, and conservative medication interventions to control ABL. You will also complete a 28-day bowel diary for this section of the research study. It is very important to keep track of this diary and make daily entries. This visit is expected to last up to three hours. You and your provider will decide if you will visit the clinic, or if you will meet remotely by phone or over a computer. A health care provider will call you twice during this part of the research study, 3 days and 14 days after you start enhanced medical management. The purpose of these calls is to answer any questions you may have about the diary or questions about changes to the enhanced medical management program.

4. **Randomization Visit**: You will be asked to return your bowel symptom diary and fill out questionnaires at the end of the 4 weeks. If you have greater than or equal to 75% reduction in accidental bowel leakage episodes at the end of 4 weeks, you will not be randomized to one of the two treatments but will be asked to continue with the instructions given for enhanced medical management. If you have less than 75% reduction in episodes, you will be assigned by chance to one of the two treatment options: biofeedback or dextranomer injections. Which of those options you receive will be determined randomly. You will be asked to complete a series of questionnaires. You will also be given a 14-day paper diary to complete at home prior to the 3-month assessment. You will need to start this diary 14 days prior to your next appointment. You and your provider will decide if you will complete the questionnaires at home or will visit the clinic. If you visit the clinic to complete the questionnaires, this visit is expected to last up to 90 minutes.

5. **Follow-Up Assessments**: You will be asked to complete assessments at 3, 6, 12, and 24 months after the first treatment visit to see how long the effects of the treatment last. You will also receive a phone call at 18 months.
   a. 3-Month Follow-up Assessment: If your ABL has not improved by at least 75% at the 3-month assessment, you will be invited to either the other study treatment (the one to which you were not randomly assigned) or sacral nerve stimulation. You will only be offered the chance of selecting the sacral nerve stimulation treatment as an optional treatment if you have not previously (prior to your participation in the study) been unsuccessfully treated with sacral nerve stimulation. If you were randomized into the dextranomer arm, you may be asked to complete a second endoanal ultrasound or pelvic floor MRI at the 3-month assessment. All participants, regardless of which treatment they have been undergoing, will be asked to complete questionnaires and to report any adverse events at this time as well. They may also be asked to undergo an anorectal manometry procedure and/or a magnetic evoke potential procedure. You and the research team will review your diary. If you come to the clinic at 6 months, the visit is expected to last up to 90 minutes. This visit may last up to three hours.
   b. 6-Month Follow-Up Assessment: If you receive a dextranomer injection at 3 months, you may be required to undergo an endoanal ultrasound or pelvic floor MRI procedure at 6 months. All participants will be asked to complete a series of questionnaires at 6 months and to report any adverse events. You and the research team will review your diary. You will be mailed a new 14-day paper diary to complete at home and asked to return it for this 6-month assessment. You will need to start this diary 14 days prior to your 6-month assessment date. If you come to the clinic at 6 months, the visit is expected to last up to 90 minutes.
   c. 12-Month Follow-Up Assessment: All participants will be asked to complete a series of questionnaires at 12 months and to report any adverse events. You and the research team will review your diary. You will be mailed a new 14-day paper diary to complete at home and return for this 12-month assessment. You will need to start this diary 14 days prior to the 12-month assessment. If you come to the clinic at 12 months, the visit is expected to last up to 90 minutes.
   d. 18-Month Follow-Up Telephone Call: All participants will be asked to report any adverse events.
   e. 24-Month Follow-Up Assessment (End of Study Assessment): All participants will be asked to complete a series of questionnaires at 24 months and to report any adverse events. You and the research team will review your diary. You will be mailed a new 14-day paper diary to complete at home and return for this 24-month assessment. You will need to start this diary 14 days prior to the 24-month assessment. If you come to the clinic at 24 months, the visit is expected to last up to 90 minutes. At the end of this assessment, your participation in the research study will end.

Description of the Diagnostic Tests

Anorectal Manometry (ARM): This test measures how well your pelvic floor and anorectal (anal and rectal) muscles function, and it measures your rectal sensations. A pencil-thick flexible probe with a balloon will be inserted into your rectum. You will be asked to perform several maneuvers, including squeeze and bearing down. You will also have rectal sensations assessed by distending the balloon in the rectum. After these maneuvers, the probe will be removed.

Balloon Evacuation Test (BET): A pencil-thick flexible tube with a balloon will be inserted into your rectum. We will fill the balloon with 50mL water and you will be asked to expel this balloon over a commode in a private bathroom stall.
Both of these tests (ARM and BET) will take up to one hour. The ARM and BET will be administered at the start of the study, either at your screening visit or baseline visit but if necessary, these tests can be administered any time in the study to prior to you starting a randomized study treatment. The ARM test may be administered again after treatment to assess for any changes, regardless of assigned treatment.

Translumbosacral Anorectal Magnetic Stimulation (TAMS): This test measures nerve conduction between the spinal cord and the rectum. You will be asked to initially lie in bed on your left side. Then we will place surface electrodes on your lower leg. A flexible pencil-thick probe will be inserted into the anus and rectum and taped into position. You will be asked to then lie on your stomach. Your lower back will be exposed and the stimulation sites will be marked. A magnetic coil (3-5 inches in diameter) will be placed at 4 locations over your lower back. At each location, your lower back will be stimulated by the coil up to 20 times. During the magnetic stimulation, we will record how long it takes for impulses to travel from your spinal cord to the rectum and anus. After these assessments, the probe and surface electrodes will be removed. This procedure may take approximately 30 minutes.

Anal Ultrasound: This test evaluates the appearance of the anal sphincters and for signs of injury. You will be asked to lie in bed on your left side. A rectal exam will be performed. An ultrasound probe will be gently inserted 5 centimeters into your rectum and pictures of your sphincters will be obtained. Thereafter, the probe will be removed. This procedure will take approximately 20 minutes. It is possible that this may not need to be repeated if you have had this test performed at some time in the previous 12 months.

Magnetic Resonance Imaging (MRI): At some clinical sites, a pelvic MRI may be substituted for the anal ultrasound. During the pelvic MRI, you will be placed in the lying position in the MR machine. A small probe approximately 1 inch in diameter will be placed in your rectum to take pictures of your anal sphincters (muscles). The probe will be removed and the rectum will be filled with ultrasound gel. MRI pictures will be taken while you are resting, while coughing, are while you squeeze the “cheeks” of your buttocks together, and try to defecate

(expel your rectal contents) on a disposable towel. It is very important to the study for you to expel all the ultrasound gel, even though you may be reluctant to do so. Thereafter, you will have the opportunity to use the toilet. MRI pictures will be obtained while you are asked to strain. You will be able to use the toilet to finish expelling the gel. The entire MRI exam will last about 1 hour. It is possible that this may not need to be repeated if you have had this test performed at some time in the previous 12 months.

Description of the Treatments

Enhanced medical management: Everyone who meets eligibility criteria for the study will be treated with enhanced medical management for 4 weeks. The purpose is to determine whether patients really need more invasive and costly treatments or whether medical management is enough to improve their ABL. This medical management for ABL is enhanced compared to usual medical treatment in the following ways: You will be provided with a booklet that explains how your muscles work when you are having a bowel movement, as well as information about the effects of diet and medications for diarrhea or constipation. You will also be taught pelvic floor exercises to strengthen the anal sphincter muscles. Different medicines for controlling diarrhea or constipation may also be recommended. This treatment will be tailored to your symptoms based on your medical history.

If you have a satisfactory response to enhanced medical management (you have at least 75% fewer episodes of ABLs compared to baseline), you will not be randomized into one of the two treatment arms but will be asked to return in 3 months. If you don't improve or your symptoms become worse before the 3-month follow up, you will be randomized in one of the two treatments. Which treatment you are assigned to try will be determined by chance (like flipping a coin).

What is required of you for enhanced medical management: Enhanced medical management (EMM) requires that you meet with the provider over the course of four weeks. You and your provider will decide if you will visit the clinic, or if you will meet remotely by phone or over a computer. During the first meeting, the EMM therapist will explain how your muscles work to have a bowel movement and how to normalize stool consistency by making changes in your diet and adding different medications. You will also be taught and given printed instructions on how to perform pelvic floor exercises. We may recommend different medications to normalize stool consistency. If your stools are less firm or loose, we may recommend taking an over-the-counter anti-diarrheal drug, loperamide, also known as Imodium, start taking fiber supplements, or we may prescribe Welchol or Questran, which are medications that binds to bile salts to reduce episodes of diarrhea. If your stools are firmer, or you are constipated, we may recommend you take laxatives to soften stool consistency. The EMM therapist will call you twice during this part of the study, three and fourteen days after you finished EMM training, to ensure you are filling out the diary, to see

how you are doing with the medications, and to see if any changes need to be made to your treatment protocol. When you meet with the therapist at the end of the EMM treatment phase, your diary will be reviewed to see if you are eligible to be randomized into a treatment arm or if you will continue following the EMM treatment protocol without randomization.

Biofeedback therapy: Biofeedback allows you to see how your muscles are doing while you go through some exercises. Biofeedback therapy is provided with a soft plastic tube with tiny balloons that is inserted into your anus to measure pressure. These tiny balloons are used to measure the pressure when you squeeze your anus, and this pressure measurement is displayed on a computer screen to teach you how to squeeze more effectively. Another balloon will be filled with different amounts of air to help you learn to improve your rectal sensitivity. You will be taught how to squeeze the anal sphincter muscle at the lower end of the colon more effectively. Biofeedback therapy can also improve the sensation (feeling of contents) in the rectum: If your rectal sensation is reduced making it hard for you to know when to squeeze, it can increase your rectal sensation. If your rectal sensation is increased making you rush to the toilet, it can decrease your rectal sensation.

What is required of you for biofeedback: Biofeedback training requires five or six visits lasting one hour each. In between sessions, there will be homework assignments to practice the techniques. The training sessions will usually be scheduled once a week but may be scheduled up to twice a week as long as they occur at least two days apart. The entire course of treatment sessions can last up to 5 – 6 weeks. If the biofeedback provider sees that you would benefit from one more session, you may be able to attend an additional sixth session.

Anal injection of dextranomer: In this treatment, a doctor injects a small amount (4mL) of a special material under the lining of the anal canal that helps create a more effective barrier to bowel leakage. These injections are provided in two visits each lasting up to an hour. After this treatment, an anal ultrasound or pelvic MRI will be performed to determine whether the dextranomer remains in the anal canal.

What is required of you for dextranomer: This treatment does not require you to learn or practice new skills or limit your daily activities. Two or three outpatient visits to a doctor's office are required. You will be asked to take a Fleet's phosphate enema the night before and again the morning of the procedure to empty your rectum. You will also be asked to take an oral antibiotic for 2 days, starting on the day of the procedure, to minimize the risk of infections. An anoscope (hollow tube approximately 6 inches long) will be lubricated with an absorbable gel and inserted part way into the anal canal. Injections will be made through this hollow tube. The dextranomer liquid will be injected into the space under the lining of the anal canal in the front and back and on the left and right sides of the anal canal. Following these injections, you will be encouraged to use stool softeners such as docusate sodium until your first bowel movement and to use acetaminophen (Tylenol) as needed for injection site

discomfort. You should continue to follow the recommendations for medical management of your ABL. You will be asked to return 4 weeks after the initial injection to evaluate your response, and if you have achieved less than 75% reduction in ABLs, a second set of 4 injections will be given.

Sacral Nerve Stimulation: If it is determined at your 3-month follow-up assessment that you have not responded to the study treatment to which you were randomly assigned, sacral nerve stimulation will be one of the alternate treatments offered to you as long as you have not been unsuccessfully treatment with sacral nerve stimulation prior to your participation in the study. Sacral nerve stimulation improves bowel and bladder function by providing stimulation to nerves in the pelvis. Stimulating these nerves gives you better warning before passing stool and allows the rectal and anal muscles to work more effectively. This does *not* take control of your muscles directly, but simply helps them work better in order to prevent accidental bowel leakage. This stimulation is very faint and not painful. It involves two short, outpatient surgeries performed under intravenous (IV) sedation. During the first surgery, a small incision is made in the lower part of the back and a thin wire is placed next to the pelvic nerves with the help of x-ray guidance. This wire is connected to a small external battery that can be worn under your clothes and left in place for two weeks as a trial phase. There are 2 possible outcomes of this two-week trial period: (1) The electrical stimulation reduces bowel accidents by at least 50% (this occurs in up to 80-90% of patients). If this is the case, the stimulator is permanently implanted beneath the skin in your upper buttock through a second minor surgery so that it can continue to stimulate your bowels. Or (2) the accidental bowel leakage does not improve by at least 50% during the trial period. If this is the case, the wire is removed, and other treatments may be tried. If a permanent stimulator is implanted, a third visit will occur about one month later to assess surgical healing and to adjust the frequency and intensity of stimulation if needed. Adjustments in the stimulation settings may be made by you after consulting your surgeon.

What is required from you for sacral nerve stimulation: You will have two outpatient surgical procedures lasting 60-90 minutes each. You will receive intravenous sedation and numbing medication at the incision site for these procedures, but you will be awake enough to follow commands so that you can tell the surgeon if you feel the stimulation. After the wire implantation, you will be asked to limit your physical activities for the 2-week trial period so that the wire stays in place. The wire will be covered by a bandage for the trial period. If a stimulator is placed under your skin you will be asked to limit your physical activities for 2 weeks to allow the surgical incision (cut) to heal. After a permanent stimulator is implanted you will be taught basic information about the stimulator such as how to turn it on and off and check program settings. The costs of revisions and battery replacements will be billed to your insurance provider; they are not covered by the study.

8. What are the possible benefits from being in this research study?

Research is designed to benefit society by gaining new knowledge. You may receive a benefit from this study by receiving a treatment that has helped other people with accidental bowel leakage (fecal incontinence).

9. What are the possible risks or discomforts from being in this research study?

While the medications used in the enhanced medical management are generally safe, they may cause side effects.

Loperamide (brand name Imodium), if taken as directed by the package insert, is considered safe for purchase without a prescription. The most common side effect is constipation which can occur if you take too much Imodium. The physician or study nurse will help you adjust the dose to avoid this. Other rare side effects include nausea, vomiting, and urinary retention. Other very rare allergic reactions may include rash, other skin disorders, and difficulty breathing. If you experience any side effects, you should stop taking the Imodium and contact the study nurse or study doctor. On June 7, 2016 the FDA issued a Safety Alert for Human Medical Products stating that "…serious heart problems, including fatal arrhythmias, may result from using higher than the recommended dose or from abuse or misuse of loperamide to achieve a state of euphoria. The risk of these side-effects is increased by taking the following drugs at the same time: cimetidine or ranitidine (brand names Tagamet and Zantac) which are used to treat acid reflux, itraconazole or ketoconazole which are used to treat fungal infections, clarithromycin or erythromycin which are antibiotics, ritonavir which is used to treat HIV/AIDS, quinine which is used to treat malaria, quinidine which is used to treat cardiac arrhythmias, and gemfibrozil which is used to lower lipids. You should avoid taking these other drugs while taking loperamide, and you should not exceed the recommended dose of loperamide.

Fiber supplements such as Metamucil are considered safe and are approved by the FDA for sale without a prescription. The most common side effects include bloating and distention if fiber is added to your diet too quickly. We will increase the dosage slowly and decrease or stop it if you have bothersome side effects. You should drink water when you take fiber supplements.

Polyethylene glycol (brand name Miralax) is an FDA approved medication for the treatment of constipation and is available without a prescription. Side effects may include abdominal cramping, bloating, gas, nausea, diarrhea, and itching.

Colesevelam (brand name Welchol) is a FDA approved medication for the treatment of hyperlipidemia (high cholesterol) and to improve glycemic control (blood sugar) in adults

with type II diabetes. It has been researched and prescribed off label to help patients manage their diarrhea. Colesevelam is a bile acid sequestrate, which helps with patients who have bile acid malabsorption by binding to the bile acids and carrying them out of the intestine through stool. Bile acid malabsorption can be a cause of diarrhea. Common side effects of colesevelam include constipation, heartburn, nausea, headache, and pain or cramping in the abdomen or stomach. In clinical trials, approximately 3% of individuals with type II diabetes developed hypoglycemia or low blood sugar. Colesevelam can increase triglycerides, especially when used with insulin or sulfonylureas. This may cause hypertriglyceridemia and may increase risk for acute pancreatitis, but this risk is very rare. Colesevelam may decrease absorption of vitamin K, A, and E. Because of the size of the tablet, it may feel like you are having trouble swallowing the tablet, but this medication also comes in oral powder for suspension, which may solve this problem. You should take this medication with food and a drink. If you have a higher risk for a bowel obstruction, you should not take this medication. In clinical trials, colesevelam had drug interactions with oral contraceptives containing ethinyl estradiol and norethindrone. This may prevent your body from absorbing the medicine and may reduce the effectiveness of the oral contraceptive. If you are taking phenytoin, you should take this medication four hours before taking colesevelam to prevent drug interactions.

Cholestryamine (brand name Questran) is a FDA approved medication for the treatment of hypercholesterolemia (elevated low density lipoprotein [LDL] cholesterol. It has been researched and prescribed off label to help patients manage their diarrhea. Patients with complete biliary obstruction should not take this medication. Chronic use of cholestryamine resin may be associated with increased bleeding tendency due to hypoprothrombenemia associated with Vitamin K deficiency. Patients taking cholestryamine may develop constipation or worsen pre-existing constipation. Cholestraymine for oral suspension may delay or reduce the absorption of other medications, such as phenylbutazone, warfarin, thiazide diuretics, or propranolol, as well as tetracycline, penicillin G, phenobarbital, thyroid and throxine preparations, estrogens and progestins, and digitalis.

Biofeedback Therapy: Biofeedback is considered safe and side-effects are rarely reported. Soreness of anal muscles or fatigue may occur following a biofeedback session due to exercise. In rare instances, inserting a balloon catheter into the anus may cause a few drops of blood, especially if you have hemorrhoids. If this occurs, you should report it to the study physician. The risk of bleeding or injury is similar to using an enema or suppository.

Injectable Bulking Agent: Side-effects of treatment with dextranomer injections that have been reported in clinical research studies include infections at the site of injection which can progress to an abscess if untreated. Infections are largely preventable by taking antibiotics routinely for 2 days, starting on the day of the injection. Other adverse events include abdominal pain, anal fissures (tears in the lining of the anus), anal bleeding, anal

inflammation (pruritus), anal discomfort, back pain, chills, dermatitis (rash), device dislocation, dizziness, dyspareunia (pain during sex for women), injection site bruises (hematoma), painful defecation, urinary retention, and vaginal pain, or worsening symptoms of constipation, defecation urgency, diarrhea or accidental bowel leakage. Patients with bleeding diathesis or patients using anticoagulant or antiplatelet agents, as with any injections, may experience increased bleeding at injection sites. If you had an anal ultrasound or pelvic MRI within the last 12 months and have not had any health problems likely to change your sphincter pressure, the anal ultrasound or pelvic MRI may not be repeated at baseline. However, an anal ultrasound or pelvic MRI is required after the injection of dextranomer to determine whether the dextranomer remains in the walls of the anal canal.

Sacral Nerve Stimulation: About 15% of patients with a permanent stimulator experience pain or infection from the surgical placement of the stimulator beneath the skin. The stimulating electrode may have to be surgically removed due to infection in 3-5% of people. In rare cases, the wire may break or move and need to be replaced; this may occur after multiple falls or trauma to the surgical site. Pain at the surgical site, numbness and infection happen in more than 10% but less than 25% of patients and mostly happen in the first year. Diarrhea, constipation, back, pelvic, leg or buttock pain, skin irritation, fluid collection in the wound, urinary problems happen in less than 5% of patients and usually in the first year as well. The stimulator battery typically lasts 4-6 years and minor surgery is necessary to replace the battery. The surgery for battery replacement is outpatient and takes approximately 30 minutes to complete.

Embarrassment: Some questions on the study questionnaires may cause embarrassment due to the personal nature of the questions. You may skip any questions that make you feel uncomfortable. To protect confidentiality, your questionnaires will only be identified with a study ID number and kept in a locked cabinet. The list linking your information to your study ID number will be kept in a different secure location. In addition, there may be uncommon or previously unknown risks that might occur.
We are asking you to take a paper bowel diary with you to complete at home. There is a possibility that a friend/family member/co-worker/employer may see the diary. There is a risk for embarrassment and employment discrimination if this occurs. To minimize the risk of this happening, we will be printing the paper diaries smaller than an 8 ½ x 11 to fit into most pockets and purses.

Enema: You may experience the desire to defecate after taking an enema. Approximately 1% to 10% of individuals report experiencing bloating, nausea, abdominal pain, and/or diarrhea from the enema.

Anorectal Manometry: It is more likely that placement of the rectal probe may cause mild discomfort. If uncomfortable, the probe can be removed immediately. Very rarely, probe placement may cause bleeding or rectal perforation (less than one in a thousand cases). Should a rectal perforation occur, you may require hospitalization, antibiotics and surgery.

Translumbosacral Anorectal Magnetic Stimulation (TAMS): It is more likely that placement of the rectal probe may cause mild discomfort. If uncomfortable, the probe can be removed immediately. Very rarely, probe placement may cause bleeding or rectal perforation (less than one in a thousand cases). Should a rectal perforation occur, you may require hospitalization, antibiotics and surgery. It is less likely that magnetic stimulation may cause backache, skin discomfort or irritation, transient muscle twitching or pins and needles sensation in your back or legs. If uncomfortable, the test can be discontinued.
The provider may decide not to perform the TAMS test in patients with certain implantable devices, depending on the location of the device. If you have an implantable device, your provider will determine if it is safe for you to undergo the TAMS test. If it is determined that it is safe, then the device will be switched off prior to the TAMS study, and will be switched on after the study is completed. Previous experience at University of Iowa and Augusta University using this protocol for the TAMS test has been found to be safe in over 500 patients who have undergone this procedure.

Anal Ultrasound: It is more likely that placement of the rectal probe may cause mild discomfort. If uncomfortable, the probe can be removed immediately. Very rarely, probe placement may cause bleeding or rectal perforation (less than one in a thousand cases). Should a rectal perforation occur, you may require hospitalization, antibiotics and surgery.

Magnetic Resonance Imaging: No significant side effects are expected from the pelvic MRI exam. Rare but potential complications include rectal perforation (a tear in the wall of the rectum that creates a hole). This risk of this complication is much lower than 1 in 1000 procedures. A rectal perforation may require surgery. Some people can feel claustrophobic in the MRI scanner.

10. What alternative do you have if you choose not to participate in this research study?

You do not have to be in this research study in order to receive treatment for ABL. All the procedures in this research study are available with referral from a physician. The other procedures or treatments that are available include the standard medical care provided by your physician.

11. What if we learn new findings or information during the study?

You will be given any new information gained during the course of the study that might affect your willingness to continue your participation.

12. How will your privacy and the confidentiality of your records be protected?

Mayo Clinic is committed to protecting the confidentiality of information obtained about you in connection with this research study.

During this research, information about your health will be collected. Under Federal law called the Privacy Rule, health information is private. However, there are exceptions to this rule, and you should know who may be able to see, use and share your health information for research and why they may need to do so. Information about you and your health cannot be used in this research study without your written permission. If you sign this form, it will provide that permission. For confidentiality, your questionnaires and other data will be identified with only a random study ID number and will be kept in a locked cabinet. A copy of this consent form will go into your medical record. This will allow the doctors caring for you to know what study medications or tests you may be receiving as a part of the study and know how to take care of you if you have other health problems or needs during the study.

Health information may be collected about you from:

- Past, present and future medical records.
- Research procedures, including research office visits, tests, interviews and questionnaires.

Why will this information be used and/or given to others?

- To do the research.
- To report the results.
- To see if the research was done correctly.

If the results of this study are made public, information that identifies you will not be used.

Who may use or share your health information?

- Mayo Clinic research staff involved in this study.
- UNC-Chapel Hill

With whom may your health information be shared?

- The Mayo Clinic Institutional Review Board that oversees the research.
- Other Mayo Clinic physicians involved in your clinical care. Researchers involved in this study at other institutions.

- Federal and State agencies (such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health and other United States agencies) or government agencies in other countries that oversee or review research.
- The sponsor(s) of this study and the people or groups it hires to help perform this research.
- A group that oversees the data (study information) and safety of this research.

Is your health information protected after it has been shared with others?

Mayo Clinic asks anyone who receives your health information from us to protect your privacy; however, once your information is shared outside Mayo Clinic, we cannot promise that it will remain private and it may no longer be protected by the Privacy Rule.

Your Privacy Rights

You do not have to sign this form, but if you do not, you cannot take part in this research study.

If you cancel your permission to use or share your health information, your participation in this study will end and no more information about you will be collected; however, information already collected about you in the study may continue to be used.

If you choose not to take part or if you withdraw from this study, it will not harm your relationship with your own doctors or with Mayo Clinic.

You can cancel your permission to use or share your health information at any time by sending a letter to the address below:

Mayo Clinic
Office for Human Research Protection
ATTN: Notice of Revocation of Authorization
201 Building 4-60
200 1st Street SW
Rochester, MN 55905

Alternatively, you may cancel your permission by emailing the Mayo Clinic Research Subject Advocate at: researchsubjectadvocate@mayo.edu.

Please be sure to include in your letter or email:

- The name of the Principal Investigator,
- The study IRB number and /or study name, and
- Your contact information.

Your permission lasts forever, unless you cancel it.

13. What if you are injured from your participation in this research study?

Where to get help: If you think you have suffered a research-related injury, you should promptly notify the Principal Investigator listed in the Contact Information at the beginning of this form. Mayo Clinic will offer care for research-related injuries, including first aid, emergency treatment and follow-up care as needed.

Who will pay for the treatment of research related injuries: All research involves a chance that something bad might happen to you. This may include the risk of personal injury. In spite of all safety measures, you might develop a reaction or injury from being in this study. If such problems occur, the researchers will help you get medical care, but any costs for the medical care will be billed to you and/or your insurance company. None of the sites in this research study has not set aside funds to pay you for any such reactions or injuries, or for the related medical care. However, by signing this form, you do not give up any of your legal rights.

14. Are there reasons you might leave this research study early?

You can withdraw from this study at any time, without penalty. The investigators also have the right to stop your participation at any time. This may be because you experienced unexpected reactions, failed to follow instructions, or the entire study has been stopped. You will be compensated for the time and effort you put forth during the research study.

15. Will you be paid for taking part in this research study?

1. You will be compensated $50 for each medical test that is for research purposes only and is not part of standard medical care for ABL.
    a. The anorecal manometry and endoanal ultrasound [or pelvic floor MRI] at the baseline visit are considered part of standard medical care
    b. The anorecal manometry at the 3 month visit, magnetic evoke potential procedures at baseline and the 3 month assessment, and the endoanal ultrasound [or pelvic floor MRI] for the dextranomer patients at the three month visit would be considered medical tests for research purposes.
    The maximum compensation for research-related diagnostic tests in the biofeedback arm is $150. The maximum compensation for research related-diagnostic tests in the dextranomer arm is $200.

2. You will be compensated $30 for completion of each of six bowel diaries (Baseline, Medical Management, 3-, 6-, 12-, and 24-month assessments). To receive full compensation for each bowel diary, you cannot miss more than 2 days per diary. It is very important to keep track of this diary and make daily entries. The maximum compensation for completing all bowel diaries is $180.

	Biofeedback	Dextranomer
Standard Medical Care at Baseline	Anorecal Manometry Endoanal Ultrasound/MRI	Anorecal Manometry Endoanal Ultrasound/MRI
Research Procedures Baseline	Magnetic Evoke Potential ($50)	Magnetic Evoke Potential ($50)
Research Procedures 3-month visit	Magnetic Evoke Potential *($50)** Anorecal Manometry *($50)**	Magnetic Evoke Potential *($50)** Endoanal Ultrasound or pelvic floor MRI *($50)** Anorecal Manometry *($50)**
Research Diaries	$180	$180
Total	$330 ($100 for optional procedures)	$380 ($150 for optional procedures)

* Optional procedures

3. You will be compensated for the travel required for each in-person visit based on the distance you have to travel to the clinic. There will be three levels of travel reimbursement: $50 per visit if you live up to 50 miles from the clinic; $100 per visit if you live between 50 and 87 miles from the clinic; and if you live more than 87 miles for the clinic, you will be reimbursed at a rate of 57.5 cents per mile traveled, up to a maximum of $300. If you live more than 50 miles from the clinic and you need to stay overnight in a hotel, you will be paid an additional $100. The clinic will not book or pay for your hotel accommodations directly. Your total compensation will be based on the number of test procedures and the number of visits and distance you have to travel.
4. You will be compensated for medications recommended during the enhanced medical management period and subsequent follow–up periods. If any of the following medications were suggested and you are actively taking them, you will be compensated based on the following list: Loperamide: $5.00 per month, Questran: $126 per month, Fiber supplements: $10 per month, and Laxatives: $10 per month.

16. What tests or procedures will you need to pay for if you take part in this research study?

During the medical treatment phase, you may be required to purchase over the counter medications. You will be reimbursed after the fact for the costs of these medications based on the reimbursement rate cited in the previous section. The cost of the Anorectal Manometry and anal ultrasound or pelvic MRI performed as part of standard medical care at the beginning of the study will not be covered by the NIH research grant. Patients who are assigned by chance to the biofeedback and dextranomer injection treatment groups will not have to pay anything for research related costs for these treatments; these costs will be paid by the NIH research grant.

Sacral Nerve Stimulation (SNS) for the treatment of accidental bowel leakage (ABL), also known as fecal incontinence, is a FDA-approved treatment that is covered by Medicare, TRICARE, and many private and employee sponsored health insurances. However, the rate at which each covers the costs of this procedure varies, so we cannot identify a specific dollar amount that you will be responsible for paying.

We have set aside up to $3,074 from the NIH grant to reimburse you for any out-of-pocket expenses incurred during treatment for SNS regardless of your health insurance coverage. There is a possibility that your provider deductibles, co-payments, and co-insurance charges will exceed $3,074, and you would be responsible for any remaining balance. Costs for other types of health care may not reduce the amount owed for SNS.

If you have insurance please consult your insurance provider directly to identify coverage for SNS, or otherwise please reference the SNS Insurance Coverage handout for additional information.

Patients assigned by chance to the SNS group will be responsible for submitting the facility fees and professional charges to their insurance company. If you do not have insurance, these charges will be billed to you directly.

Though these treatments are routinely performed in clinic, there is a possibility you may need additional care or a surgical procedure beyond what is covered in this research study. These will likely result in additional costs to you and your insurance provider and you will be responsible for these costs.

17. What is a Certificate of Confidentiality?

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of Federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this

research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.
The Certificate of Confidentiality does not prevent the researchers from disclosing voluntarily, without your consent, information that would identify you as a participant in the research project under the following circumstances: intent to hurt self or others.

18. Who is funding this study?

This research is sponsored by the National Institutes of Health (NIH) and National Institutes of Diabetes, Digestive and Kidney Diseases (NIDDK) (Sponsors). This means that the research team is being paid by the sponsor for doing the study. Jan Busby-Whitehead, the principal investigator on this study, is a faculty member in the School of Medicine and the Division of Geriatric Medicine at UNC Chapel Hill, and has been provided with gifts of equipment and software from Medspira and Solesta Injection Kits from Palette Life Sciences Inc. These gifts will be used in conducting the research in this study.
If you would like more information, please ask the researchers listed on the first page of this form.

19. Information Regarding Conflict of Interest:

One or more of the investigators associated with this project and Mayo Clinic have a financial interest in technology used in the research and that the investigator(s) and Mayo Clinic may stand to gain financially from the successful outcome of the research. This research has been reviewed by the Mayo Clinic Conflict of Interest Review Board and is being conducted in compliance with Mayo Clinic Conflict of Interest policies.

Both the Mayo Clinic Conflict of Interest Review Board and the Institutional Review Board have reviewed the financial interest for one or more of the investigators and/or Mayo Clinic related to this research and they have determined that this financial interest poses no additional significant risk to the welfare of participants in this research project or to the integrity of the research.

Additional information is available to any interested study participant regarding the details of this financial interest and how it is being managed by contacting the study coordinator or the Office of Conflict of Interest Review at 507-284-0075.

20. What if you have questions about this study?

You have the right to ask, and have answered, any questions you may have about this research. If you have questions, or if a research-related injury occurs, you should contact the researchers listed on the first page of this form. A description of this clinical trial will be available on www.clinicaltrials.gov, as required by U.S. Law. This website will not include information that

can identify you. At most, the website will include a summary of the results. You can search this website at any time.

ENROLLMENT AND PERMISSION SIGNATURES

Your signature documents your permission to take part in this research.

Printed Name Date (mm/dd/yyyy) Time (hh:mm am/pm)

Signature

Person Obtaining Consent

- I have explained the research study to the participant.
- I have answered all questions about this research study to the best of my ability.

Printed Name Date (mm/dd/yyyy) Time (hh:mm am/pm)

Signature