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Effects of the Minnesota Medical Technologies Anal Insert Device in Fecal Incontinence

Protocol Number: IRB 18-004642

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Document History:

Protocol Version	Summary of Revisions Made
Protocol version 12FEB2019, Version 1.0	Not Applicable, Initial Release
Version 2.0	Entire Protocol. Administrative and clarification changes that included fixing typos, clarification of study procedures timing, clarification of Fitting Period assessment process, inclusion of change rationale to be included in protocol Summary of Revisions Made, clarify number of subjects who may participate in the [redacted], clarify process by which devices will be shipped to subjects, update abbreviations table, update location of protocol amendment summaries
Version 3.0	Study Design section 1.2, Schedule of Assessments section 1.3, and Overall Design section 4.1. Study site requested modification to provide the [redacted] and [redacted] at the screening visit after consent. The subject will complete the [redacted] then use the [redacted] at home. The subject will deliver, or send the [redacted] to the study site.
Version 4.0	• Updated Document History of changes table • Updated baseline and fitting sequence to ensure that a device remains in the body during anorectal manometry visit or the subject is to be withdrawn. Added allowance that if the 10mm size was not retained the subject would be assigned the 13mm device to confirm retention and comfort. If the 13mm size was retained in the body during

	ambulation, the subject would be allowed to immediately begin the fitting period using the 13mm device. Updated primary endpoint language to clarify this process and align with study flow.
Version 5.0	Added notes to Schedule of Assessments in section 1.3 which were inadvertently removed in version 2.
Version 6.0	Added an assessment of the ability of subject to retain the device to the screening visit.
Version 7.0	Increase subject participation number for the [redacted] from [redacted] to [redacted].

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STATEMENT OF COMPLIANCE

(1) [The trial will be carried out in accordance with the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies 21 CFR Parts 11, 50, 54, 56, and applicable sections of Part 812.

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether subjects previously enrolled will be required to re-consent.

PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Effects of the Minnesota Medical Technologies Anal Insert Device in Fecal Incontinence

Study Description: This is a prospective, open label study during which subjects with Fecal Incontinence (FI) will be recruited and enrolled into the treatment group. Subjects will participate in a 4-week baseline period in which information on fecal incontinence, bowel habits, and global measures will be collected.

Subjects meeting all inclusion and no exclusion criteria (including diary compliance, ≥ 4 FI episodes during the 4-week baseline period) will proceed to a up to 4-week fitting period where subjects will evaluate which of two device sizes (10mm or 13mm) is preferred. At the screening visit, the 10 mm, and, if necessary thereafter, the 13 mm device will be inserted into the rectum to determine if the device stays in situ while subjects are ambulating. Subjects who can retain the device will proceed to the baseline period. Subjects who can retain neither device size will be withdrawn from the study. After completion of the baseline period, those subjects who did not retain the 10 mm but did retain the 13 mm device will begin the fitting period with the 13 mm device. The sequence of events for the fitting period will be as follows:

1) Subjects who begin with the 10 mm device will use the device for a minimum of 2 weeks during the fitting period. Subjects will be asked to complete daily bowel diaries to determine the percent reduction in FI episodes, and subject comfort will be assessed using question #7 on the QUEST questionnaire. If greater than or equal to 75% reduction in FI episodes is observed during this fitting period, the subject will proceed immediately to the

treatment period and will continue using the 10mm device for the entire treatment period. If the reduction in FI episodes is less than 75%, and the QUEST score is 1-2 (indicating dissatisfaction with comfort), the subject will proceed immediately to the treatment period and will continue using the 10mm device for the entire treatment period. If the reduction in FI episodes is less than 75%, and the QUEST score is 3-5 (indicating satisfaction with comfort), the participant will use 13 mm devices for a minimum of 2 weeks as their fitting period and complete daily bowel diaries. At the end of this fitting period, the subject comfort will be reassessed with question #7 of the QUEST questionnaire. Subjects who report QUEST scores of 1-2 (indicating dissatisfaction with comfort) with the 13mm device will use the 10mm device for the entire treatment period. However, subjects who report QUEST scores of 3-5 (indicating satisfaction with comfort) at the end of the fitting period will proceed immediately to the treatment period and will continue using the size 13mm device for the entire treatment period.

2) Subjects who begin with the 13mm device will use the device for a minimum of two weeks during the fitting period. Thereafter, the subject will proceed to the treatment period and will continue using the 13mm device for the entire treatment period.

Following the fitting period, all subjects will then proceed to a 4-week treatment period in which information on fecal incontinence, bowel habits, and global measures will be collected.

After the treatment period, all individuals who withdraw for reasons other than personal preference (i.e., for medical reasons) and a minimum of 50% of all patients shall undergo an evaluation by anoscopy following the treatment period to assess for device related trauma.

The information on fecal incontinence, bowel habits, global measures and adverse events obtained during the bowel diary study (4-week baseline period and the 4-week treatment period) will be used to evaluate the safety and effectiveness of the study device. Adverse events will be collected from enrollment through study exit.

After completing baseline diaries, the following assessments will be performed for informational purposes: 1) All subjects who qualify for treatment with the Minnesota Medical Technologies Anal Insert will undergo a baseline anoscopy, [redacted] and [redacted]. 2) Up to [redacted] subjects who qualify for treatment with the Minnesota Medical Technologies Anal Insert will undergo [redacted] testing with the

study device in place [redacted]

Intended Use Statement

The Minnesota Medical Technologies Fecal Incontinence Insert is indicated for the management of accidental bowel leakage (ABL) or fecal incontinence. The rectal insert is designed for self-insertion to seal and help prevent the involuntary leakage of stool from the rectum.

Objectives:

1. Primary Effectiveness Endpoint: A relative percentage change in episodes of Accidental Bowel Leakage (ABL) determined by comparing treatment results to pre-treatment results from the baseline period as measured by daily diary recordings.

2. Exploratory:

- Evaluate the effects of the Minnesota Medical Technologies Anal Insert Device on [redacted].
- Evaluate if the effects of the Minnesota Medical Technologies Anal Insert Device on symptoms of FI [redacted] of the device to prevent leakage.
- Evaluate the [redacted] in subjects with FI.
- Investigate [redacted] associated with FI through [redacted] at baseline.

Endpoints:

1. Primary Effectiveness Endpoint: A relative percentage change in episodes of Accidental Bowel Leakage (ABL) determined by comparing treatment results to pre-treatment results from the baseline period as measured by daily diary. [Time Frame: Reduction in accidental bowel leakage from 4 week baseline period through 4 week treatment period (approximately Weeks 9-12, for four weeks after completion of fitting period).

Secondary Endpoints:

- A relative percentage change derived by comparing post-treatment Mayo Fecal Incontinence Severity Index (FISS) Scores to the pre-treatment (end of baseline period) FISS Scores.
- The proportion of subjects in whom the frequency of FI episodes during the treatment period is greater than or equal to 75% lower than frequency observed during baseline period.
- The proportion of subjects in whom, during treatment period, the device will reduce the number of days with FI by 50% as compared to

baseline.

- The proportion of subjects in whom the device will reduce the volume of FI during the treatment period as compared to baseline.
- The proportion of subjects in whom the anal insert device reduces the proportion of FI episodes which are associated with diarrhea.
- The proportion of subjects in whom the anal insert device reduces the number of episodes of passive and of urge FI.
- The proportion of subjects in whom the anal insert device improves the Quality of Life (QOL) related to FI during treatment as compared to baseline.
- The proportion of subjects in whom the anal insert device will affect the composition of stool leakage during treatment as compared to baseline.
- The proportion of subjects are satisfied with the anal insert device.
- The time for which a bowel movement can be deferred after the occurrence of urgency will be affected by the anal insert device.
- The proportion of complete bowel movements will be affected by the anal insert device during treatment as compared to baseline.
- Treatment with the anal insert device will affect anxiety and depression during treatment as compared to baseline.
- The anal insert device reduces the use of medications for FI during treatment as compared to baseline.

Exploratory Endpoints:

- Evaluate in up to [redacted] subjects the effects of the Minnesota Medical Technologies Anal Insert Device on [redacted].
- Evaluate if the effects of the Minnesota Medical Technologies Anal Insert Device on symptoms of FI [redacted] of the Minnesota Medical Technologies Anal Insert device to prevent anal leakage.
- Subjects [redacted] Minnesota Medical Technologies Anal Insert Device during [redacted].
- Evaluate the [redacted] in subjects with FI
- Investigate [redacted] associated with FI through [redacted] at baseline.

Study Population: Male and female subjects aged 18 years and older with a diagnosis of fecal

	incontinence who have failed conservative medical therapy (i.e., the use of bulking agents, anti-diarrheal agents (e.g., loperamide) and biofeedback therapy as appropriate) for FI.
Phase:	N/A
Description of Sites/Facilities Enrolling Subjects:	A single-site study at Mayo Clinic Rochester
Description of Study Intervention:	This Minnesota Medical Technologies Anal Insert Device is a non-sterile soft, flexible, liquid-filled anal insert meant for single use only (see Figures below). The device is self-inserted into the anal canal where the liquid-filled bulb of the device is designed to rest against, conform to, and provide a seal at the anorectal junction to prevent fecal discharge from the rectum. The liquid-filled shaft of the device is designed to conform to and fill the anal canal allowing the pressure from the internal and external anal sphincters to seal the canal. The device's external retainer flare is designed to rest against the outside of the anus and prevents migration of the insert into the anal canal and rectum. These mechanisms are designed to work together to prevent the involuntary leakage of fecal matter through the anal canal. The Minnesota Medical Technologies Anal Insert Device is depicted in **Figure 1** below. The profile drawing indicates the main parts of the device. The cross-section drawing shows the open lumen which allows for the insertion of the applicator. It also shows the liquid-filled (mineral oil) bulb. This liquid-filled feature extends from the bulb, along the length of the device shaft, and onto the external retainer. **Figure 1: Main Parts of The Minnesota Medical Technologies Anal Insert Device**

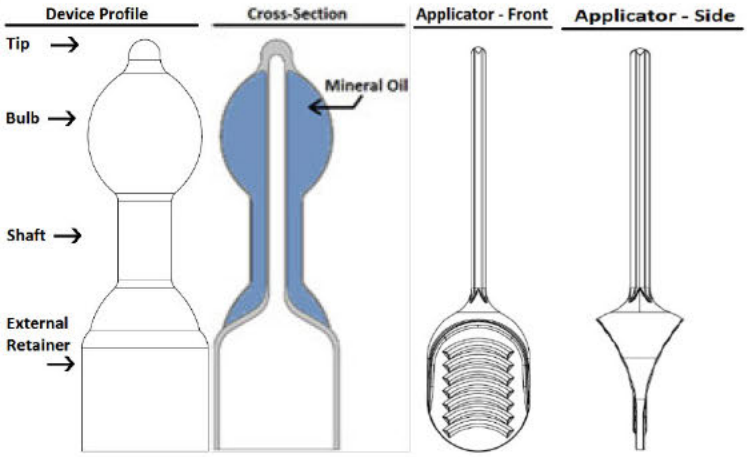
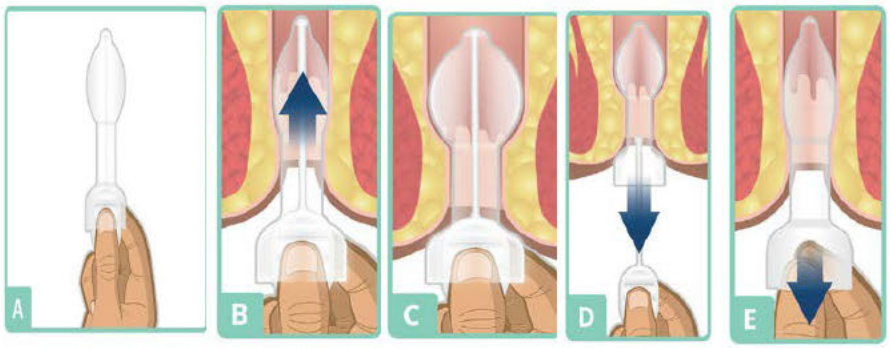


Figure 2 below illustrates the device with applicator and the insertion and removal process.

Figure 2: Minnesota Medical Technologies Anal Insert Device with applicator and the insertion /removal process.



Study Duration:

Overall study duration will be approximately 18 months. Individual subject participation in the study (screening period, baseline period, fitting period, treatment period and post-treatment repeat anoscopy, as applicable,) will be approximately 20 weeks.

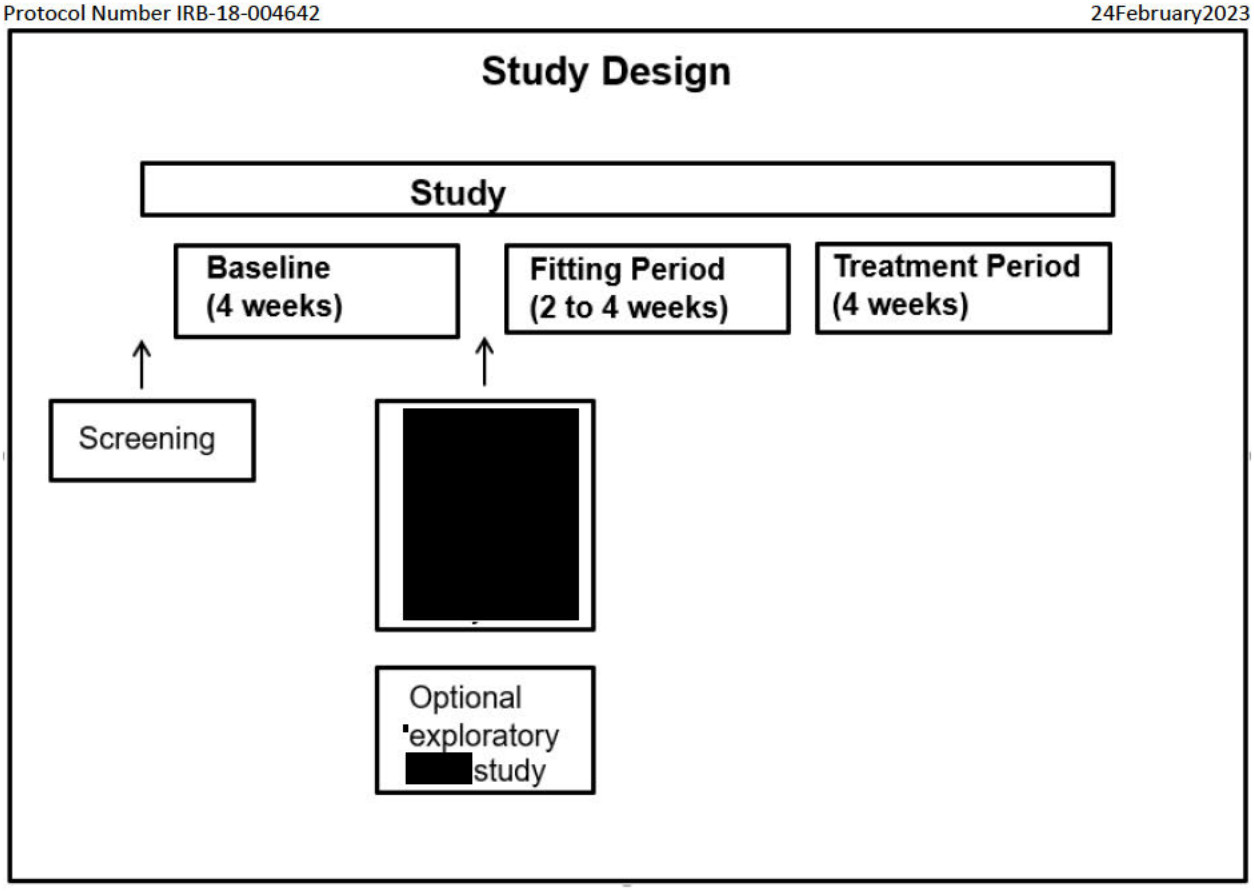
Study screening procedures will begin after the subject signs the informed consent form. The exception will be allowing subjects who had undergone anorectal manometry within six (6) months prior to signing informed consent. Subjects who underwent a technically adequate standard of care anorectal manometry at Mayo Clinic within six (6) months prior to signing consent will not be required to repeat anorectal manometry, and anorectal manometry results from the standard of care anorectal manometry testing performed within six (6) months prior to consent may

be used for study analysis. There will be a 4-week baseline period followed by an approximately 2 to 4-week fitting period, followed by a four (4) week treatment period. Subjects will also be contacted by telephone to encourage compliance and to assess adverse events. Individual study participation is anticipated to be complete 4 weeks after the last day the device is used. After the treatment period, all individuals who withdraw for reasons other than personal preference (i.e., for medical reasons) and a minimum of 50% of all patients shall undergo an evaluation by anoscopy following the treatment period to assess for device related trauma

While the protocol intends the fitting period to follow directly the baseline period, if needed for scheduling, there can be up to a 7-day interval between the completion of the baseline and initiation of the fitting period. In addition, all study procedures can be performed at ± 7 days to accommodate scheduling issues.

Subject Duration: The study will consist of a screening visit, a 4-week baseline period, an assessment visit, a 2 to 4-week fitting period, and a 4-week (28-days) treatment period. Allowing for additional days to accommodate scheduling, including repeat anoscopy, if required, the subject participation duration is expected to be approximately 20 weeks.

1.2 SCHEMA



Study sequence is shown above.

1. Subjects will sign informed consent. At the screening visit, the 10 mm, and, if necessary thereafter, the 13 mm device will be inserted into the rectum to determine if the device stays in situ while subjects are ambulating. Subjects who can retain neither device size will be withdrawn from the study. Subjects who can retain the device will proceed to the baseline period. Subjects will be asked to keep a symptom diary for the 4-week baseline period and complete questionnaires to ascertain if they have FI symptoms of sufficient severity to be considered for treatment. Subjects will be provided with [redacted] and a [redacted] for use at home during the baseline period.

2. Subjects will return home and record every bowel movement and episode of fecal incontinence in a daily diary for 4 weeks. Subjects will be asked to mail diaries and questionnaires to the study site every week. Subjects will complete the [redacted], then [redacted] using the [redacted]. Subjects will be asked to deliver, or send the [redacted] to the study site [redacted]. If the diaries and questionnaires are not returned during this baseline period, patients will be contacted.

3. Subjects who have completed the 4-week baseline period and meet criteria for treatment and do not meet any exclusion criteria, will return to the clinic to have assessments (i.e., baseline anoscopy,

[redacted], [redacted] (if not already performed as within six (6) months of consent), and [redacted]).

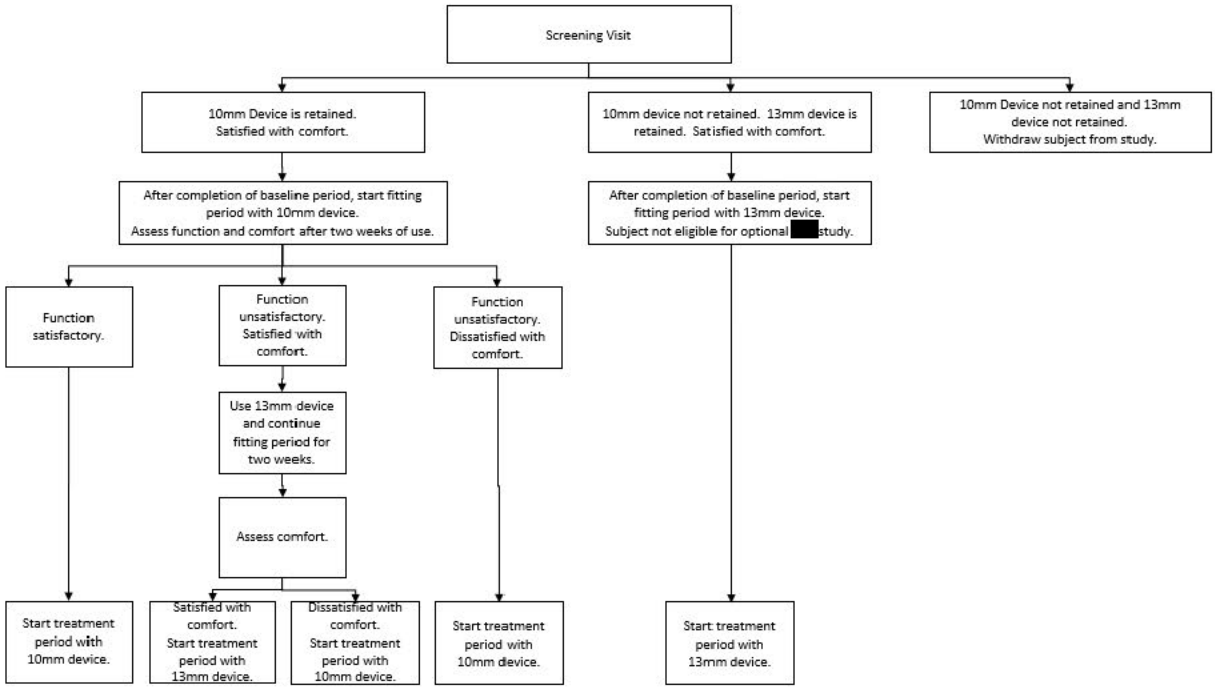
[redacted] sub-study subjects (up to [redacted] subjects who agree to [redacted] sub-study) will also have [redacted] evaluate the effects of the Minnesota Medical Technologies Anal Insert Device on [redacted], and to evaluate [redacted] Participants will be enrolled in this sub-study until up to [redacted] participants have completed [redacted] sub-study. In the event a subject does not wish to participate in [redacted] sub-study, but they do wish to participate in the treatment study, they may do so. If they do not wish to participate in the treatment study, their participation in the trial will be terminated and they will exit the study.

4. Eligible subjects will proceed to the fitting period which will last up to 4 weeks.
Subjects who did not retain the 10 mm but did retain the 13 mm device at the screening visit will begin the fitting period with the 13 mm device. The sequence of events for the fitting period will be as follows:

1) Subjects who begin with the 10 mm device will use the device for a minimum of 2 weeks during the fitting period. Subjects will be asked to complete daily bowel diaries to determine the percent reduction in FI episodes, and subject comfort will be assessed using question #7 on the QUEST questionnaire. (a) If greater than or equal to 75% reduction in FI episodes is observed during this fitting period, the subject will proceed immediately to the treatment period and will continue using the 10mm device for the entire treatment period. (b) If the reduction in FI episodes is less than 75%, and the QUEST score is 1-2 (indicating dissatisfaction with comfort), the subject will proceed immediately to the treatment period and will continue using the 10mm device for the entire treatment period. (c) If the reduction in FI episodes is less than 75%, and the QUEST score is 3-5 (indicating satisfaction with comfort), the participant will use 13 mm devices for the remaining 2 weeks of their fitting period and complete daily bowel diaries.
2) At the end of this fitting period, the subject comfort will be reassessed with question #7 of the QUEST questionnaire. Subjects who report QUEST scores of 1-2 (indicating dissatisfaction with comfort) with the 13mm device will use the 10mm device for the entire treatment period. However, subjects who report QUEST scores of 3-5 (indicating satisfaction with comfort) at the end of the fitting period will proceed immediately to the treatment period and will continue using the size 13mm device for the entire treatment period.
3) Subjects who begin with the 13mm device will use the device for a minimum of two weeks during the fitting period. Thereafter, the subject will proceed to the treatment period and will continue using the 13mm device for the entire treatment period.

Subjects will be contacted at least twice per month during the fitting period. Attempts will be made to space these calls at an interval of 7 days.

This sequence is shown in the following flow diagram:



5. Subjects proceed to the 4-week treatment period, use the Minnesota Medical Technologies Anal Insert Devices, and record every bowel movement and episode of fecal incontinence in a daily diary for 4 weeks. Subjects will be asked to complete questionnaires on a weekly basis and also complete additional questionnaires once at the end of the treatment period. Subjects will be asked to mail bowel diaries and questionnaires to the study site every week.

6. Subjects will be contacted (i.e., by telephone or text or e mail) to ask about their experience with using study devices, to remind them to complete study questionnaires, to assess safety, and to answer other subject questions, as applicable. The schedule for contacting subjects can be adjusted on a per subject basis, but the guidance is that subjects will be initially contacted three (3) days and at 1-2 weeks after the treatment period begins. Thereafter, subjects will be contacted at least twice monthly to inquire about any adverse events, especially pain or bleeding with device use and any change in medications and as necessary if they do not return bowel diaries or questionnaires. Up to 3 attempts to contact subjects will be made for each assessment, and contact attempts will be documented.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Schedule of Assessments

	Screening visit	Baseline Period (weeks 1-4)	[redacted] Sub-Study, as applicable	Fitting Period (up to four weeks after baseline)	Treatment Period* (approximately weeks 9-12)
Day (target) on which this event occurs or *begins*)	0	*Day 1*[1]	Day 28[2]	*Approx. day 29*[3]	*Approx. day 57*[3]
Window of days for start of this event	up to six months prior to consent for anorectal manometry	Day 1	Day 28-38 [2]	Approximately days 29-45 [3]	57-73 [3]
Duration	2 hours	28 days	[redacted] days	28 days (up to 4 weeks)	28 days (4 weeks)
[redacted]		[redacted]			
Inclusion/Exclusion criteria review. Includes bowel leakage questionnaire	X	X	X		
Demographics Data form	X				
Informed Consent	X				
Medical history review	X				
Physical examination, including Vital signs[4], height and weight	X				
Concomitant medication review (throughout study from consent to study exit)	X	X	X	X	X
Urine pregnancy test (as applicable)	X				
Teach subject how to complete diaries and	X				

	Screening visit	Baseline Period (weeks 1-4)	[redacted] Sub-Study, as applicable	Fitting Period (up to four weeks after baseline)	Treatment Period* (approximately weeks 9-12)
questionnaires					
Teach subject how to use device			X		
Subject's first exposure to study device			X		
Subject daily self-administration of study treatment				X	X
Assess adverse events and medication changes from consent through study exit.	X	X	X	X	X
Guidance is for site to consider calling subjects to remind them to maintain food records for 72 hours before visit to assess anorectal functions[5]		X			
Anoscopy			X		X* After the treatment period, all individuals who withdraw for reasons other than personal preference (i.e., for medical reasons) and a

	Screening visit	Baseline Period (weeks 1-4)	[redacted] Sub-Study, as applicable	Fitting Period (up to four weeks after baseline)	Treatment Period* (approximately weeks 9-12)
					minimum of 50% of all patients shall undergo an evaluation by anoscopy following the treatment period to assess for device related trauma
[redacted] data collection form			X [redacted]		
Optional [redacted] sub-study with [redacted] form			X		
Daily bowel diaries		X		X	X
Global assessment of FI (weekly, during baseline, fitting and treatment periods)		X		X	X

	Screening visit	Baseline Period (weeks 1-4)	[redacted] Sub-Study, as applicable	Fitting Period (up to four weeks after baseline)	Treatment Period* (approximately weeks 9-12)
Assessment of severity of fecal incontinence (FISS) and FI QOL questionnaires (to be completed once at end of Baseline Period and once at end of Treatment Period) [23 27]		X			X
PROMIS (Patient Reported Outcomes Measurement Information System) Short Form 8a: Anxiety and Depression only once at the end of the period		X		X	X
Therapy Evaluation (Credibility/Expectancy Questionnaire)	X				
Ease of Use, usability and comfort scale (completed once for each used size during fitting period and once at the end of the treatment period)				X	X
User satisfaction - Quebec User Evaluation of Satisfaction with Assistive Technology (QUEST 2.0)				X	X

Schedule of Assessments (continued)

[1] The screening visit may occur within 21 days before the first day of the baseline period; bowel diary. During the baseline period, subjects will maintain bowel diaries for 28 consecutive days.
[2] Depending on the logistics of scheduling, this visit will generally last 1-2 days. It can take place at any time between days 28-38.
[3] The treatment period will begin within 7 days after the assessment [redacted] is complete.
[4] Vital signs (VS) are to be obtained in the sitting position after at least 5 minutes of rest. Body temperature (°C) and respiration rate (breaths/minute) will also be recorded. Height (cm) and weight (kg) will be recorded in light clothing without shoes.
[5] [redacted] intake will be assessed at baseline using [redacted].

***** After the treatment period, all individuals who withdraw for reasons other than personal preference (i.e., for medical reasons) and a minimum of 50% of all patients shall undergo an evaluation by anoscopy following the treatment period to assess for device related trauma.

List of Patient Facing Documents (submitted under separate cover):

- [redacted]
- Quebec User Evaluation of Satisfaction with Assistive Technology
- Weekly Global Fecal Incontinence Questionnaire
- Bowel Habits Diary
- Emotional Distress - Anxiety Short Form 8a
- Severity of Fecal Incontinence - Baseline
- Severity of Fecal Incontinence - Post-Treatment
- Criteria for Fecal Incontinence
- Therapy Evaluation Form
- Impact of Fecal Incontinence and Quality of Life (FIQOL Scale)
- Ease of Use, Usability, and Comfort Scale
- Instructions for Use
- Product Ordering Instructions

2 INTRODUCTION

2.1 STUDY RATIONALE

Because existing approaches to manage FI are of limited efficacy,[4] there is an unmet need for additional approaches to manage this symptom, which can have a potentially devastating impact on quality of life. A systematic review observed that while anal plugs might be helpful in some subjects, they are poorly tolerated, with a dropout rate ranging from 12.5% to 68% across the four studies[32]. Another device, the Renew anal insert device (Renew Medical Inc., Foster City, CA), is approved for treating FI in the United States. In the intent-to-treat analysis, 62% of subjects achieved ≥ 50% reduction in the frequency of FI

with that device.[7] The Minnesota Medical Technologies Anal Insert Device is designed to engage with and conform to the anorectal junction and the anal canal to provide an anatomical fit in order to protect against bypass leakage. The device is very soft and pliable which is expected to provide superior performance relative to devices which are currently on the market, with relatively few adverse events and good patient acceptance.

2.2 BACKGROUND

Fecal incontinence (FI) is a common symptom that can significantly impair quality of life.[1] FI, the involuntary leakage of stool from the anus, is a common symptom not only in nursing home residents, but also in the community. Almost one of 15 adult women have moderate to severe FI.[2]

Therapeutic options for FI include dietary modification and education, medications to manage bowel disturbances, pelvic floor retraining by biofeedback therapy, anal plugs, minimally invasive procedures (i.e., perianal injection of a bulking agent and sacral nerve stimulation), and surgery (e.g., anal sphincteroplasty).[3] The approaches are of limited efficacy.[4] The use of medications is often limited by constipation.

At present, FI is attributed to bowel disturbances, particularly diarrhea, anorectal dysfunctions, and pelvic floor injury.[1] Pelvic floor injury, which may result from obstetric injury, iatrogenic factors, is often irreversible and may manifest as a patulous anal canal.[5] Anal plugs have been used to restore the anal seal. A Cochrane review identified 4 randomized cross-over or parallel studies of anal plugs, none of which are available in the United States.[6] This review observed that while anal plugs might be helpful in some patients but are poorly tolerated, with a dropout rate ranging from 12.5% to 68% across the four studies. More recently, based on open label studies, an anal and a vaginal device have been FDA-approved for treating FI in the United States. For the Renew anal insert device (Renew Medical Inc., Foster City, CA), the intent-to-treat analysis observed that 62% of patients achieved ≥ 50% reduction in the frequency of FI.[7] 78% of users were extremely satisfied with the device. There were no serious adverse events and only 3 moderate adverse events (i.e., fecal urgency, soreness, and bleeding hemorrhoids).

Another device incorporates a vaginal insert and pressure-regulated pump.[8] In the pivotal trial, 61 of 110 subjects completed successful fitting of the device. Of these, 78.7% achieved treatment success, defined as ≥50% reduction of incontinent episodes at 1 month.

Because many women with FI [redacted] to FI. For example, while several small studies observed [redacted] we recently observed [redacted] There are no data on the [redacted] associated with FI. Hence we propose to explore these questions in this study.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Only subjects who satisfy stringent inclusion and exclusion criteria and provide written informed consent will be included in the protocol. Additional details as follows:

The Minnesota Medical Technologies Anal Insert Device is manufactured of biocompatible materials which are soft and pliable. The user interface has been designed such that use errors are either eliminated or reduced to the extent possible.

All study procedures are standard of care, with the exception of the study-specific physical examination and [redacted] assessment, additional questionnaires, [redacted] with study device inserted, subject self-insertion and evacuation of the MMT Anal Insert Device.

Anticipated risks for this study include:

- Mild discomfort
- Unexpected expulsion of the device
- New onset, or, if pre-existing, increased anorectal pain or discomfort
- Diarrhea
- Abdominal pain
- Anorectal irritation, pain, soreness
- Rectal, anal, or perianal infection
- Device over-insertion or device migration into anal canal or rectum
- Injury to anus, anal canal, or rectum
- New onset, or, if pre-existing, increased anorectal urge
- New onset, or, if pre-existing, increased abdominal gas
- New onset, or, if pre-existing, increased hemorrhoids or rectal bleeding
- New onset, or, if pre-existing, increased colonic obstruction or fecal impaction
- Perforation of anal canal or rectum
- Device breakage
- Discomfort, bruising, redness, swelling, bleeding around the site of the blood draw
- Feeling of lightheadedness when blood is drawn
- Infection at the site of the blood draw
- Rectal bleeding due to rectal catheter use
- Allergic reaction to materials of the testing equipment or study device

- If a researcher finds that results obtained from the [redacted] performed on patient [redacted], the subject will be contacted and [redacted].

There may be additional risks to subjects or embryos or fetuses in women who are of childbearing potential that are not known at this time. Any new significant information learned during this study that could impact a subject's decision to participate in the study will be communicated to the subject.

2.3.2 KNOWN POTENTIAL BENEFITS

There are no known benefits to the use of this device. Data gathered in this study may be of use in future treatment of subjects with fecal incontinence.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The Minnesota Medical Technologies Anal Insert Device is a device which has similar technical and biological characteristics with other anal inserts currently available for the treatment of FI.

Conservative treatments for FI include lifestyle changes, dietary modifications, bowel management programs (medications and enemas), and pelvic floor muscle exercises, physical therapy with or without biofeedback therapy.[30] These treatments have minimal risk.

Surgical approaches to treat FI are high risk solutions.

Anal inserts provide a conservative middle step in treatment options between alternative treatments such as lifestyle changes, medications, pelvic exercises, physical therapy. and surgical treatments.

3 OBJECTIVES AND ENDPOINTS

1. **Primary: Primary Effectiveness Endpoint: A Relative Percentage Change in Episodes of Accidental Bowel Leakage (ABL) Determined by Comparing Treatment Results to Pre-treatment Results From the Baseline Period as Measured by Daily Diary Recordings . [Time Frame: Reduction in accidental bowel leakage from 4 week baseline period through 4 week treatment period (approximately Weeks 9-12).**

Measure Type	Primary
Measure Title	Primary Effectiveness Endpoint: A Relative Percentage Change in Episodes of Accidental Bowel Leakage (ABL) Determined by Comparing Treatment Results to Pre-treatment Results From the Baseline Period as Measured by Daily Diary Recordings.
Measure Description	This primary effectiveness endpoint will be calculated as a relative percentage

	of the baseline Accidental Bowel Leakage (ABL) using the following equation: % reduction in ABL = 100*(baseline period ABL - treatment period ABL) / (baseline period ABL)
Time Frame	Reduction in accidental bowel leakage from 4 week baseline period through 4 week treatment period (approximately Weeks 9-12).

Secondary Efficacy Endpoint(s):

- The mean % reduction in Fecal Incontinence Severity Index (FISS) score from the baseline period to the end of the treatment period, calculated according to the following equation: % reduction in FISS = 100% (baseline period FISS - end treatment period FISS) / (baseline period FISS).
- The proportion of subjects in whom the frequency of FI episodes during the treatment period is greater than or equal to 75% lower than the frequency observed during baseline period.
- The proportion of subjects in whom, during treatment period, the device will reduce the number of days with FI by 50% as compared to baseline.
- The proportion of subjects in whom the device will reduce the volume of FI during treatment period as compared to baseline.
- The proportion of subjects in whom the Minnesota Medical Technologies Anal Insert Device reduces the proportion of FI episodes which are associated with diarrhea.
- The proportion of subjects in whom the Minnesota Medical Technologies Anal Insert Device reduces the number of episodes of passive and of urge FI
- The proportion of subjects in whom the Minnesota Medical Technologies Anal Insert Device improves the Quality of Life (QOL) related to FI during treatment as compared to baseline.
- The proportion of subjects in whom the Minnesota Medical Technologies Anal Insert Device will affect the composition of stool leakage during treatment as compared to baseline.
- The proportion of subjects are satisfied with the Minnesota Medical Technologies Anal Insert Device.
- The time for which a bowel movement can be deferred after the occurrence of urgency will be affected by the Minnesota Medical Technologies Anal Insert Device.
- The proportion of complete bowel movements will be affected by the Minnesota Medical Technologies Anal Insert Device during treatment as compared to baseline.
- Treatment with the Minnesota Medical Technologies Anal Insert Device will affect anxiety and depression during treatment as compared to baseline.
- The Minnesota Medical Technologies Anal Insert Device reduces the use of medications for FI during treatment as compared to baseline.
- Exploratory Endpoints:
- - Evaluate in up to [redacted] subjects the effects of the Minnesota Medical Technologies Anal Insert Device [redacted], as measured [redacted].

- - Evaluate if the effects of the Minnesota Medical Technologies Anal Insert Device on symptoms of FI [redacted], and the acute effects of the Minnesota Medical Technologies Anal Insert device to prevent anal leakage.
- - Subjects [redacted] the Minnesota Medical Technologies Anal Insert Device [redacted].
- - Evaluate the [redacted] in subjects with FI
- - Investigate [redacted] associated with FI through [redacted] at baseline.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Investigate the effects of the Minnesota Medical Technologies Anal Insert Device on fecal continence in subjects with FI	1. Primary: Primary Effectiveness Endpoint: A Relative Percentage Change in Episodes of Accidental Bowel Leakage (ABL) Determined by Comparing Treatment Results to Pre-treatment Results From the Baseline Period as Measured by Daily Diary Recordings . [Time Frame: Reduction in accidental bowel leakage from 4 week baseline period through 4 week treatment period (approximately Weeks 9-12).	Determination of substantial equivalence to predicate device.
Secondary		
Evaluate subject acceptance and ease of use of the Minnesota Medical Technologies Anal Insert device	• The mean % reduction in Fecal Incontinence Severity Index (FISS) score from the baseline period to the end of the treatment period. • The proportion of subjects in whom the frequency of FI episodes during the treatment period is greater than or equal to 75% lower than to the frequency observed during baseline period. • The proportion of subjects in whom, during treatment period, the device will reduce the number of days with FI by 50% as compared to baseline. • The proportion of subjects in	

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	whom the device will reduce the volume of FI during treatment period as compared to baseline. • The proportion of subjects in whom the Minnesota Medical Technologies Anal Insert Device reduces the proportion of FI episodes which are associated with diarrhea. • The proportion of subjects in whom the Minnesota Medical Technologies Anal Insert Device reduces the number of episodes of passive and of urge FI • The proportion of subjects in whom the Minnesota Medical Technologies Anal Insert Device will improve the Quality of Life (QOL) related to FI during treatment period as compared to baseline. • The proportion of subjects in whom the Minnesota Medical Technologies Anal Insert Device will affect the composition of stool leakage during treatment period as compared to baseline. • The proportion of subjects are satisfied with the Minnesota Medical Technologies Anal Insert Device. • The time for which a bowel movement can be deferred after the occurrence of urgency will be affected by the Minnesota Medical Technologies Anal Insert Device. • The proportion of complete bowel movements will be affected by the Minnesota Medical Technologies Anal Insert Device during treatment period as compared to baseline. • Treatment with the Minnesota Medical Technologies Anal Insert Device will affect anxiety and depression during treatment period as compared to baseline.	

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	• The Minnesota Medical Technologies Anal Insert Device reduces the use of medications for FI during treatment period as compared to baseline.	
Evaluate the frequency of spontaneous expulsion of the Minnesota Medical Technologies Anal Insert Device during defecation, of involuntary expulsion, and of device migration into the rectum	Evaluation frequency rates	
Tertiary/Exploratory		
The Minnesota Medical Technologies Anal Insert Device will affect the amount of leakage [redacted]. Subjects [redacted] the Minnesota Medical Technologies Anal Insert Device [redacted].	- Evaluate the effects of the Minnesota Medical Technologies Anal Insert Device on [redacted] - Evaluate [redacted] the Minnesota Medical Technologies Anal Insert Device on [redacted] and the acute effects of the Minnesota Medical Technologies Anal Insert Device to prevent leakage - Evaluate [redacted] subjects with FI - Investigate [redacted] with FI through [redacted] at baseline - Observe subject [redacted] Minnesota Medical Technologies Anal Insert Device [redacted]	Evaluation for potential future study.
Evaluate if the effects of the Minnesota Medical Technologies		

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Anal Insert Device [redacted]		
Evaluate the [redacted] subjects with FI		
Investigate [redacted] with FI through [redacted] at baseline		

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a prospective, open-label, study during which 60 subjects with FI will be treated with the Minnesota Medical Technologies Anal Insert Device. Up to 150 subjects may be enrolled to ensure 60 subjects are eligible to participate in the Treatment Period. This study will consist of a baseline period and a treatment period. A fitting period, prior to the treatment period, will determine which of two devices sizes each study subject will use during the treatment period. Up to [redacted] of these 60 subjects will participate in a [redacted] sub-study to evaluate the effects of the Minnesota Medical Technologies Anal Insert Device on [redacted].

Subjects will sign the informed consent form at the screening visit. After signing the consent form, the subjects are considered enrolled in the study. At this visit, medical history and concomitant medications will be collected, as well as vital signs, and the ability of the subject to retain the device will be evaluated to determine eligibility for the study. Eligible subjects will proceed to baseline period (baseline bowel diary), during which subjects will record all bowel movements in a daily diary and complete questionnaires for 4 weeks. Subjects will be provided with a [redacted] and a [redacted] for use at home during the baseline period. Subjects will deliver, or send the [redacted] to the study site. Subjects who have 4 or more FI episodes during this 4-week baseline period will be eligible to continue to the fitting and treatment periods.

Subjects will return to the Mayo Clinic Rochester study site to have diaries assessed for compliance and eligibility for treatment and, if eligible, will complete quality of life questionnaire. Subjects eligible for treatment will be trained on the insertion and evacuation of the device and will be provided with instructions on how to contact [redacted] to have the devices shipped to them.

During this visit to the Mayo Clinic study site, subjects will receive the following assessments: baseline anoscopy (if not already performed within 6 months of informed consent), assessment of [redacted], a [redacted], and [redacted]. In up to [redacted] subjects who agree to participate in the [redacted] sub-study, [redacted] will be assessed [redacted].

Subjects who participate in the 2 to 4 week fitting period will insert the device after each bowel evacuation or expelling of the device, inserting only one device at a time and inserting a new device after each bowel evacuation or device expulsion. Subjects will be evaluated to determine which of two device sizes (10mm or 13mm) is preferred. Any changes in the use of device size will occur during the fitting period to ensure that the same size device is worn during the entire treatment period.

Subjects will proceed to a 4-week treatment period in which information on fecal incontinence, bowel habits, and global measures will be collected. Subjects will be asked to complete daily bowel diaries for 4 weeks during the Treatment period and to complete weekly questionnaires. After use, devices and applicators will be disposed of by subjects and not returned to the clinic, unless the subjects report concerns about the device function, in which case, subjects will be asked to return the expelled device to the clinic or directly to the sponsor, for device analysis.

While completing the treatment period of 4 weeks of daily diaries and weekly questionnaires, subjects will be asked to mail these diaries and questionnaires to the site on a weekly basis. At the end of the treatment period, subjects will be asked to complete additional fecal incontinence, quality of life and satisfaction questionnaires and mail them to the study site. Adverse events will be assessed between enrollment and study exit. Subjects will be asked to dispose of all unused devices and to confirm this with the study site.

After the treatment period, all individuals who withdraw for reasons other than personal preference (i.e., for medical reasons) and a minimum of 50% of all patients shall undergo an evaluation by anoscopy following the treatment period to assess for device related trauma.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Because existing approaches to manage FI are of limited efficacy,[4] there is an unmet need for additional approaches to manage this symptom, which can have a potentially devastating impact on QOL. A systematic review observed that while anal plugs might be helpful in some patients, they are poorly tolerated, with a dropout rate ranging from 12.5% to 68% across the four studies[32]. Another device, the Renew anal insert device (Renew Medical Inc., Foster City, CA), is approved for treating FI in the United States. In the intent-to-treat analysis, 62% of patients achieved ≥ 50% reduction in the frequency of FI with that device.[7] The Minnesota Medical Technologies Anal Insert Device is designed to engage with and conform to the anorectal junction and the anal canal to provide an anatomical fit in order to protect against bypass leakage. The device is very soft and pliable which is expected to provide superior performance relative to devices which are currently on the market, with relatively few adverse events and good patient acceptance.

4.3 JUSTIFICATION FOR TREATMENT

The treatment of anal leakage and bowel incontinence includes a range of treatments from lifestyle changes to surgical options. This study is designed to evaluate a low-risk, minimally invasive self-insertion anal device to help block anal leakage and bowel incontinence by assisting the body in forming a seal to reduce or block leakage.

The Minnesota Medical Technologies Anal Insert Device size was selected for design based on studies that characterized the anal canal in subjects with anorectal disorders. Among a cohort 119 patients with anorectal disorders, 49 patients (41%) had a patulous anal canal, which was more common in patients with FI (58%) than constipation (25%).[5] A patulous canal is associated with, and likely consequent to injury to the anal sphincters and pelvic floor muscles. It predisposes to fecal leakage. In that study, the anal canal diameter was ≤ 10 mm in 39 of 49 patients with a patulous canal; in the remainder, the diameter was between 10 and 20 mm. Hence, the Minnesota Medical Technologies Anal Insert Device will be available in two sizes (i.e., 10mm and 13mm).

4.4 END OF STUDY DEFINITION

Subject participation is voluntary, and subjects may leave the study at any time. Subjects will be instructed to contact their doctor if they choose to leave the study, to make arrangements for standard of care treatment of their fecal incontinence moving forward and to assess if the subjects experienced any adverse events. The study sponsor or the U.S. Food and Drug Administration may decide to stop the study at any time. The study investigators may decide that participation in the study is not in the subject's best interest for health reasons.

A subject is considered to have withdrawn or been withdrawn from the study, or if the subject has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3. The end of the study is defined as completion of the last subject's last visit or procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

A sufficient number (up to 150) of subjects with a diagnosis of fecal incontinence in the general population of Mayo Clinic will be screened and consented for eligibility to participate in the study and to facilitate the enrollment of 60 subjects into the treatment period of the study. Of these, up to [redacted] of the subjects will be recruited for the [redacted] sub-study.

The specific inclusion and exclusion criteria for enrolling subjects in this study are presented below. Exceptions to these inclusion and exclusion criteria must be discussed in advance and approved by the Principal investigator and sponsor. Any exemptions to the study entry criteria will be documented in the source documents and on the appropriate page of the case report form.

5.1 INCLUSION CRITERIA

Male and female subjects aged 18 years and older at screening who meet the following inclusion criteria and none of the exclusion criteria will be eligible for enrollment:

- Able to provide signed (written) informed consent

- Diagnosis of fecal incontinence, with duration of symptoms six months or longer with a history of at least one fecal incontinence (FI) episode per week or at least four episodes per month
- Subject comprehends study meaning and is capable of carrying out study duties
- Patient is fluent in English as study questionnaires have been validated using English
- If female and of childbearing potential, patient has had a negative urine pregnancy test within 21 days of the first day of the baseline visit
- If applicable, Patient agrees to use acceptable birth control (surgical sterilization, abstinence, approved hormonal contraceptives such as birth control pills, barrier methods such as condom or diaphragm used with a spermicide, or an intrauterine device (IUD)). If not applicable, the reason why shall be documented on the screening log.
- Subject is at least 18 years of age at time of consent
- Patients has failed conservative medical therapy (i.e., the use of bulking agents, anti-diarrheal agents (e.g., loperamide) and biofeedback therapy as appropriate) for Fecal Incontinence

5.2 EXCLUSION CRITERIA

Subjects who meet the following criteria will be excluded from enrollment:

- Unable or unwilling to provide informed consent or to comply with study procedures
- History of anorectal pathology in the past 6 months (perianal abscess or fistula, fecal impaction, or clinically significant rectocele).
- History of inflammatory bowel disease with active proctosigmoiditis
- History of rectal surgery in past 6 months where the Investigator determines that the use of the study device may be associated with an increased risk of complications.
- History of acute or chronic illness or history of illness or any other reason which in the opinion of the Investigator, could pose a threat or harm to the subject or obscure interpretation of laboratory test results or interpretation of study data such as frequent angina, Class III or IV congestive heart failure, etc. The reason for exclusion of any enrolled subject shall be documented on the screening log.
- Patient has known clinically-significant immune deficiency state (e.g., HIV infection).
- Patient is taking drugs with a low therapeutic index, such as warfarin, digoxin, and anti-seizure medications
- If patient has clinically suspected upper or lower gastrointestinal (GI) obstruction, they must be excluded or have been evaluated per standard of care and obstruction ruled out before screening. Determination of obstruction shall be documented on the screening log.
- History of fecal impaction with overflow diarrhea in the past 6 months
- History of Ileo-anal pouch
- History of allergy to silicone or one of its components
- Patient is pregnant and/or nursing
- Any other reason, which in the opinion of the Investigator, would confound proper interpretation of the study
- Patient whom, after training from a healthcare provider, cannot insert or expel the device themself or with assistance from a caregiver
- History of anal or rectal pain and/or rectal bleeding in the past month
- Subject cannot retain either device (10 or 13 mm) while ambulating at the screening visit

- Post baseline anoscopy examination, presence of an anal fissure, Grade III-IV internal hemorrhoids, or thrombosed external hemorrhoids.

In addition, subjects will not be eligible to participate in the Treatment Period if during the baseline period or at the [redacted] visit:

- Used rescue medications beyond those allowed by the protocol
- demonstrated lack of compliance (for e.g., did not complete bowel diaries for 3 days in any week during the baseline diary period)

Subjects will not be considered for the optional [redacted] sub-study if:

- they are not eligible to proceed to the treatment period
- they have contraindications for [redacted] e.g., subjects have [redacted], such as, [redacted]
- American Society of Anesthesiologist (ASA) score of 4 or higher

5.3 LIFESTYLE CONSIDERATIONS

Not-applicable.

5.4 SCREEN FAILURES

Subjects who are candidates for enrollment into the study will be evaluated for eligibility by the Investigator to ensure that the inclusion and exclusion criteria have been satisfied and that the subject is eligible for participation in this clinical study. Subjects who consent to participate in the study but (i) withdraw before participating in the baseline bowel diary because they can retain neither device size at the screening visit or no longer satisfy eligibility criteria (e.g., because they developed an inter-current illness) or (ii) do not have 4 or more episodes of FI during the 4-week baseline diary period will be considered screen failures.

Subjects will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care, penalty, or loss of benefits. The Investigator also has the right to withdraw subjects from the study for any of the following reasons:

- Adverse events which, in the judgment of the Investigator, justify treatment study withdrawal
- Non-adherence to study device use regimen or protocol requirements
- Non-compliance with instructions
- General or specific changes in the subject's condition unacceptable for further treatment in the judgment of the Investigator
- Subject requires use of an unacceptable concomitant medication
- Subject no longer meets the study inclusion or meets exclusion criteria
- Subject request

- Sponsor or FDA terminates study
- Administrative reasons

If a subject is withdrawn or discontinued from the study, the primary reason for withdrawal from the study is to be recorded in the source documents. If the subjects withdraws or is withdrawn prior to consent, the reason should be documented on the screening log. If the subject withdraws or is withdrawn after consent, the reason should be documented on the Case Report Forms (CRFs). All subjects withdrawn prior to completing the study should be encouraged to complete study safety assessments. All adverse events should be followed to resolution as described in Section 7.

Subjects who withdraw from the study prior to completion of [redacted] will be included in study intent to treat analysis and additional subjects will be enrolled into the [redacted] sub-study to achieve the goal of [redacted] subjects completing all study activities per protocol. In the event that an enrolled subject does not wish to participate in the [redacted] sub-study and this subject continues to meet all study inclusion/exclusion criteria, that subject may proceed to the Fitting and Treatment phases of this study.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

All men and women aged 18 years and older will be eligible to participate regardless of ethnicity. The study may enroll up to 150 subjects until 60 subjects have been treated with the study device. Up to [redacted] subjects will be enrolled in the [redacted] sub-study. It is anticipated that that subjects will be recruited over 10-12 months from the outpatient clinic and patient databases at Mayo Clinic, Rochester and by public advertisement. Potential subjects may be approached by advertising, letter, phone, in person, or by e mail. All patient-facing materials will have sponsor and IRB approval prior to use. It is anticipated that the distribution of sex, race, and ethnicity will be consistent with the 2016 American Community Survey (ie, White (86.1%), African American (6.4%), Asian (7.1%), American Indian (0.8%), and other (1.6%).

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Figure 3: Minnesota Medical Technologies Anal Insert Device.

This Minnesota Medical Technologies Anal Insert Device is a non-sterile soft, flexible, liquid-filled anal insert meant for single use only (Figure 3). The device is self-inserted into the anal canal where the liquid-filled bulb of the device is designed to rest against, conform to, and provide a seal at the anorectal junction to prevent fecal discharge from the rectum. The liquid-filled shaft of the device is designed to conform to and fill the anal canal allowing the pressure from the internal and external anal sphincters to seal the canal. The device's external retainer flare is designed to rest against the outside of the anus and prevent migration of

the insert into the anal canal and rectum. These mechanisms are designed to work together to prevent the involuntary leakage of fecal matter through the anal canal.

Subjects will be instructed to grasp the applicator and device retainer in their hand (**Figure 3**). After relaxing their anorectal muscles, subjects will gently insert the device until the retainer rests on the anus. The applicator is to be withdrawn and discarded. The bulbous tip is designed to facilitate retention of the device in the rectum.

6.1.2 DEVICE ADMINISTRATION

The sizes to be evaluated in this study are:

- Minnesota Medical Technologies Anal Insert Device 10 mm size – to be inserted in the anorectum during the day. Subjects who have nocturnal FI should also use the device at night.
- Minnesota Medical Technologies Anal Insert Device 13 mm size – to be inserted in the anorectum during the day. Subjects who have nocturnal FI should also use the device at night.

At the screening visit, the 10 mm, and, if necessary thereafter, the 13 mm device will be inserted into the rectum to determine if the device stays in situ while subjects are ambulating. Subjects who can retain neither device size will be withdrawn from the study.

Study subjects eligible for the study at the end of the baseline period will be given instructions as to ordering the study devices to be shipped to them by Minnesota Medical Technologies. The clinical site will train study subjects in the proper use of devices.

Eligible study subjects will proceed to a up to 4-week fitting period where subjects will evaluate which of two device sizes (10mm or 13mm) is preferred. Subjects who can retain the 10mm device at the screening visit will begin the fitting period with the 10mm device. Subjects who cannot retain the 10 mm but can retain the 13 mm device will begin the fitting period with the 13 mm device. The sequence of events for the fitting period will be as follows:

1) Subjects who begin with the 10 mm device will use the device for a minimum of 2 weeks during the fitting period. , Subjects will be asked to complete daily bowel diaries to determine the percent reduction in FI episodes, and subject comfort will be assessed using question #7 on the QUEST questionnaire. If greater than or equal to 75% reduction in FI episodes is observed during this fitting period, the subject will proceed immediately to the treatment period and will continue using the 10mm device for the entire treatment period. If the reduction in FI episodes is less than 75%, and the QUEST score is 1-2 (indicating dissatisfaction with comfort), the subject will proceed immediately to the treatment period and will continue using the 10mm device for the entire treatment period. If the reduction in FI episodes is less than 75%, and the QUEST score is 3-5 (indicating satisfaction with comfort), the participant will use 13 mm devices

for a minimum of 2 weeks as their fitting period and complete daily bowel diaries. At the end of this fitting period, the subject comfort will be reassessed with question #7 of the QUEST questionnaire. Subjects who report QUEST scores of 1-2 (indicating dissatisfaction with comfort) with the 13mm device will use the 10mm device for the entire treatment period. However, subjects who report QUEST scores of 3-5 (indicating satisfaction with comfort) at the end of the fitting period will proceed immediately to the treatment period and will continue using the size 13mm device for the entire treatment period.

2) Subjects who begin with the 13mm device will use the device for a minimum of two weeks during the fitting period. Thereafter, the subject will proceed to the treatment period and will continue using the 13mm device for the entire treatment period.

Subjects will be contacted at least twice per month during the fitting period. Attempts will be made to space these calls at an interval of 7 days. The devices which they are assigned to receive will be dispensed to study subjects by Minnesota Medical Technologies for use during the treatment period.

The devices will be packaged individually. Each subject will self-administer the devices. Subjects will be provided instructions for how to order the device and also an Instructions For Use, both of which will have Institutional Review Board (IRB) approval prior to use.

After the treatment period, all individuals who withdraw for reasons other than personal preference (i.e., for medical reasons) and a minimum of 50% of all patients shall undergo an evaluation by anoscopy following the treatment period to assess for device related trauma

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

[redacted] will ship study devices to the study site using a trackable courier for use in the [redacted]. Accountability for the study devices at the study site is the responsibility of the Investigator and their designated staff as well as the subjects. The study site personnel will instruct subjects to use study devices are used only in accordance with this protocol. The Investigator may choose to assign Mayo clinic device accountability responsibilities to an appropriate Mayo study team member. Accountability records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and subject numbers. The Sponsor or its designee will review devices accountability at the site on an ongoing basis during monitoring visits and at the end of the study when all unused devices are returned or disposed of, per sponsor instructions.

Device accountability records will be maintained by Minnesota Medical Technologies to document the batch/serial number, quantity, size, and date shipped to or from subjects. Devices will be provided to subjects using a trackable courier. Subjects will be responsible for keeping their study devices secure and for confirming with the study site that they (the subjects) have disposed of all unused and used

devices. The exception to this process will be if a subject experiences a device deficiency or malfunction. In this case, the subject will be asked to return the device to the study site or to Minnesota Medical Technologies for analysis, using trackable courier as the shipping method.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Study subjects eligible for the study at the end of the baseline period will be dispensed the devices. Clinical sites will train study subjects (or a caregiver) in the proper use of devices.

The sizes to be evaluated in this study are:

- Minnesota Medical Technologies Anal Insert Device 10 mm size.
- Minnesota Medical Technologies Anal Insert Device 13 mm size.
    - The devices will be packaged individually for patient use. Each subject will self-administer the devices

Study devices are packaged in kits for subjects enrolled in the study.

Study packages will contain the following information:

- Caution: Investigational device - Limited by United States Law to Investigational Use.

Study packages will not bear any statement that is false or misleading in any manner or represents that the study device is safe or effective for the purposes for which it is being investigated.

A copy of package labeling is provided under separate cover. Any changes to package labeling during the study, if applicable, will be provided under separate cover to the IRB and study site.

6.2.3 PRODUCT STORAGE AND STABILITY

All study devices are for investigational use only and are to be used only within the context of this study. All study devices will be supplied by Minnesota Medical Technologies.

The device is provided non-sterile in individual single-use packages which are shelf-stable at ambient temperature. Device size is indirectly indicated on the package label with a device code [redacted]. Multiple individually packaged devices and a single IFU sheet are placed in a box for distribution to subjects. Study site must store devices in a secure location accessible only to authorized personnel.

6.2.4 PREPARATION

No special preparation is required for this device. The device will be removed from the package and inserted by the subject according to the instructions for use.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This is a within-subject control study with a 4-week baseline period followed by a 2 to 4-week fitting period and a 4-week treatment period. Up to [redacted] subjects who meet all inclusion and meet no exclusion criteria at the end of the baseline phase of the study may be included in the optional [redacted] sub-study

Subjects who are candidates for screening into the study will be evaluated for eligibility by the Investigator to ensure that the inclusion and exclusion criteria have been satisfied. Once the subject signs the informed consent, they are considered enrolled in the study. At that time, the study site personnel will register the subject and assign a sequential and unique subject number. Once a subject number has been assigned, it cannot be reused.

6.4 STUDY INTERVENTION COMPLIANCE

In order to evaluate the efficacy, safety and tolerability of the study device, it is critical that subjects use the study device as directed. All unused devices will be disposed of. Only one device is to be used at a time. All study devices are to be self-administered by the study subject or a trained caregiver. Subjects will be required to answer a question using the daily stool diary regarding administration of their study devices each day during the treatment period.

If a subject does not receive or use all assigned study devices, the reason is to be recorded in source documents and the CRF.

Subject will be contacted via telephone by the study site personnel during the study to encourage the subject to be compliant in completion of daily bowel diaries and questionnaires and to ensure reporting of adverse events.

6.5 CONCOMITANT THERAPY

Concomitant procedures: conducted during the study, including those used to treat adverse events, are to be reported in the source documents and on the CRF. Exceptions to inclusion and exclusion criteria must be discussed in advance and approved by the Principal investigator and sponsor. Any exemptions to the study entry criteria will be documented in the source documents and on the appropriate pages of the case report form, including protocol deviations.

Permitted Medication: Subjects must be on a stable dose of any chronic concomitant medications while participating in the study. This is defined as no changes in regimen for at least 2 weeks prior to

Day 1. [Daily adjustments of insulin doses or other medications used for non-gastrointestinal diseases (e.g., diuretics) are permitted.]

If it becomes necessary for a subject to take any other medication during the study, the specific medication(s) and indication(s) must be discussed with the Investigator prior to beginning this medication. All concomitant medications taken during the course of the study must be recorded in the source documents and the CRF.

Prohibited Medication and Substances: Medications that could impact the efficacy assessments during the study are prohibited. Subjects must withdraw from opioids at least 48 hours prior to the baseline period and throughout the study participation (except as protocol defined rescue medications). Other medications that alter gastrointestinal GI transit including [redacted] will be permitted as long as these medications are prescribed for regular (i.e., not as needed) use and the dose is stable for 2 weeks before the study. Drugs with a low therapeutic index, such as [redacted] medications are prohibited. All medications shall be reviewed and dis/approved by the investigator or sub-investigator on a case by case basis). Medications that may impact fecal incontinence will be tracked on a concomitant medication log.

6.5.1 RESCUE MEDICINE

Use of drugs after Day 1 which may impact efficacy evaluations is strongly discouraged. Subjects who need rescue medication, i.e., if they have 3 watery bowel movements in 24 hours, can use loperamide as needed at a dose of 2 mg every 6 hours, with no more than four doses over the course of 24 hours and no more than seven doses over the course of 48 hours. Subjects who need rescue medication for constipation, after three full days without a bowel movement, can receive 1-2 bisacodyl 5 mg tabs or a bisacodyl suppository (10 mg). In addition, subjects who need relief of mild pain can use analgesic drugs such as NSAIDs and COX-2 inhibitors for up to two doses per week. Intake of acetaminophen up to 1.5g per day in divided doses is permissible. Subjects who need rescue medication for constipation, after three full days without a bowel movement, can receive 1-2 bisacodyl 5 mg tabs or a bisacodyl suppository (10 mg).

6.6 DISCONTINUATION OF STUDY INTERVENTION

This study may be prematurely terminated if, in the opinion of the Investigator or Minnesota Medical Technologies or the Institutional Review Board, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the Investigator or Minnesota Medical Technologies by the terminating party and all required regulatory notifications will be made.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects.

- Insufficient complete and/or evaluable data.
- Plans to modify, suspend or discontinue the development of the study device.

Should the study be closed prematurely, all study materials must be returned to Minnesota Medical Technologies or designee.

6.7 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

If signs of a major side effect (e.g., rectal perforation) should occur, the subject will be treated as clinically indicated and Principal Investigator and Sponsor will be notified immediately. Such events will be reported on the case report form.

Patients with AEs will be evaluated by the investigator. An anoscopy will be performed to determine the etiology of anal pain or bleeding and if a significant anal-rectal abnormality is identified the patient will exit the study. Any data collected from a patient who is withdrawn because of an AE will be included in the ITT safety but not effectiveness summary. Any patient with a mucosal abnormality should be followed to resolution. After the treatment period, all individuals who withdraw for reasons other than personal preference (i.e., for medical reasons) and a minimum of 50% of all patients shall undergo an evaluation by anoscopy following the treatment period to assess for device related trauma.

Subjects will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care, penalty or loss of benefits. If the subject withdraws, they should be treated with standard of care. The Investigator also has the right to withdraw subjects from the study for any of the following reasons:

- Adverse events which, in the judgment of the Investigator, justify treatment study withdrawal
- Non-adherence to study device use regimen or protocol requirements
- Non-compliance with instructions
- General or specific changes in the subject's condition unacceptable for further treatment in the judgment of the Investigator
- Subject requires use of an unacceptable concomitant medication
- Subject no longer meets the protocol criteria (Section 4.2)
- Subject request
- Administrative reasons

If a subject is withdrawn or discontinued from the study, the primary reason for withdrawal from the study is to be recorded in the source documents and the Case Report Form. All subjects withdrawn prior to completing the study should be encouraged to complete study safety assessments.

6.8 LOST TO FOLLOW-UP

A subject will be considered lost to follow-up if he or she is unable to be contacted by the study site staff.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site will attempt to contact the subject and reschedule the missed visit and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls, electronic emails or texts and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or study file.
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.]

7 STUDY ASSESSMENTS AND PROCEDURES

7.1 SAFETY AND EFFICACY ASSESSMENTS

Inclusion Criteria Assessment

An assessment of accidental bowel leakage and the ability to retain the device is performed as part of subject screening. This assessment includes a questionnaire which asks subjects about bowel leakage frequency and intensity.

Daily Bowel Diary Assessment

Subjects will complete a daily bowel diary card on which each subject will be asked to record every bowel event. The card includes a questionnaire onto which subjects will record details relating to bowel event cause, stool type, leakage, pain, urgency, medications used, and study device usage.

Weekly Global Fecal Incontinence Assessment

Subjects will complete a weekly questionnaire to assess global fecal incontinence. The questionnaire records subject overall relief of incontinence symptoms each week.

Fecal Incontinence Severity (FISS) Assessment

Subjects will complete a questionnaire to assess fecal incontinence severity (FISS) at the end of the baseline period and at the end of the treatment period. The questionnaire records the severity of subject fecal incontinence.

Fecal Incontinence Quality of Life (FI QOL) Assessment

Subjects will complete a questionnaire to assess fecal incontinence quality of life (FI QOL) at the end of the baseline period and at the end of the treatment period. The questionnaire records the subject quality of life in relation to fecal incontinence.

Patient Reported Outcomes Measurement Information System (PROMIS) Anxiety Assessment

Subjects will complete a questionnaire to assess their level of anxiety using the PROMIS short form instrument Emotional Distress – Anxiety 8a.

Patient Reported Outcomes Measurement Information System (PROMIS) Depression Assessment

Subjects will complete a questionnaire to assess their level of depression using the PROMIS short form instrument Emotional Distress – Depression 8a.

Credibility/Expectancy Assessment

Subjects will complete a questionnaire to assess their level of belief that the therapy received will reduce their anxiety relating to fecal incontinence. The questionnaire gathers information relating to what each subject thinks will happen during treatment, and what each subject feels will happen during treatment.

User Satisfaction Assessment

Subjects will complete a Quebec User Evaluation of Satisfaction with assistive Technology (QUEST) questionnaire to assess their level of satisfaction with the study device. The questionnaire gathers information relating to user satisfaction with various aspects of the device and service provided during treatment.

Exploratory Study Assessments: [redacted] Procedures (for [redacted] sub-study subjects only)

A schema and rationale for the [redacted] is as follows.

Table 1. Schedule of Events – [redacted].

Steps	Purpose
i) [redacted] will be performed if this not been performed previously* - ii) [redacted] and randomize subjects, equally [redacted] to one	i) Evaluate for [redacted] ii) Evaluate device [redacted]

of groups: Minnesota Medical Technologies Anal Insert Device (10 mm), and Minnesota Medical Technologies Anal Insert Device (13 mm). . Measure . Remove subjects . Ask subjects . Then and measure . Compare . iii) Add (until) to . iv) subject randomize subjects to 10 mm or 13 mm device. Obtain	iii) Determine iv) Assess a) relationship between b) rectoanal and c) ability to .

*With one exception, ie, the use of the Minnesota Medical Technologies Anal Insert Device, is comparable to that performed in clinical practice.

**: The consists of the he Minnesota Medical Technologies Anal Insert Device . The prepared by the device. A , approximately , is passed through . The is placed and with the .

Randomization to 10 or 13 mm device

This include these assessments arranged in chronological order. We anticipate that these studies will be performed in . Established techniques used in our clinical practice and research will be used

(i)

After [redacted], the anal [redacted] in conjunction with a [redacted] will be categorized [redacted]).

(ii) [redacted] test

[redacted] randomize subjects, equally (i.e., [redacted] each) to one of [redacted] groups: [redacted] Minnesota Medical Technologies Anal Insert device (10 mm), and Minnesota Medical Technologies Anal Insert device (13 mm). In the [redacted] group, [redacted], in [redacted] device. Then, apply [redacted]. Measure [redacted]. Then, [redacted]. Ask subjects [redacted] as follows: [redacted], [redacted], and [redacted]. Now [redacted] and measure [redacted]. Remove subject [redacted], [redacted], and [redacted]. [redacted] after reporting [redacted].

(iii) Anal [redacted] rectum

[redacted] rectum and [redacted]. The [redacted]. Thereafter, subjects should be [redacted]. [redacted] the device in situ]. A [redacted] will be documented by measuring [redacted]

(iv) Evaluate [redacted] the device

Subjects should [redacted]. Add the anal insert device, randomizing subjects to 10mm or 13mm device. Then [redacted]. [redacted] will be measured with a [redacted]

(v) Subjects will be asked to [redacted]

If the insert device was [redacted], document if the device is [redacted]. If it was [redacted], ask subjects to [redacted].

Assessment: [redacted]

This will be performed in all subjects at baseline unless this had been performed within 6 months prior to consent. [redacted]) will be performed using established validated approaches that our used in our clinical practice and research studies. After [redacted]

with [redacted] will be assessed using standard and established techniques in [redacted] will be measured [redacted] by [redacted]. Since clinical observations suggest that [redacted], [redacted] will also be assessed.

Anoscopy will also be performed for subjects who complain of new anorectal bleeding or moderate or severe pain on the bowel diary. After the treatment period, all individuals who withdraw for reasons other than personal preference (i.e., for medical reasons) and a minimum of 50% of all patients shall undergo an evaluation by anoscopy following the treatment period to assess for device related trauma

Assessment: [redacted]

This test will be done in all subjects either just prior to [redacted] or during the initial visit in subjects who [redacted]. Similar to ongoing studies in [redacted], we propose to use [redacted]), which is a [redacted] comprised of [redacted] is used to [redacted]. It is FDA cleared (FDA K[redacted]) for [redacted] with an [redacted] The [redacted] and the [redacted]. The [redacted] of the [redacted] when [redacted] and the [redacted]. We propose to [redacted] under [redacted] during the rectal examination. Once the [redacted], the [redacted] will be [redacted] into the rectum and the [redacted]. This will [redacted]. The [redacted] will be [redacted] in the [redacted] with the [redacted]. The [redacted] then be [redacted].

Assessment: [redacted]

1. [redacted]: [redacted] will be used to [redacted]. This will be [redacted] as described in literature [redacted]. The [redacted] will be calculated by [redacted]. [redacted] will be with subject [redacted] and a [redacted] to assess [redacted].
2. [redacted] analysis: [redacted] will be [redacted] using standardized methods [redacted]. [redacted] of the [redacted] will be [redacted] which has been validated for use [redacted] and is one of the methods of choice for [redacted]. With the [redacted] will include both the [redacted] analysis [redacted]. [redacted] of the [redacted] will be [redacted] using [redacted], which has been validated for standard use by [redacted]. The [redacted] will

ensure . will yield , ensuring) and). Identifying data. In order to accomplish this task we will follow protocols that we have quantitatively shown to be optimal. using our) that has been . will be . be used to that will be used in . Second, will be following published protocols [ ]. Similarly, will be . The will be . Subsequent may also be performed.

3. Assessment: will be assessed at baseline using a) ( ). This questionnaire is based on the and has been adapted by in an electronic computer-administered format to evaluate over a three month period. It employs the database for . The been validated and compares well with . (ii) Subjects will prior to analysis. The will be analyzed for staff using the developed by .

4. analysis. Mayo Clinical is currently exploring Towards our long-term objective of , we propose to study subjects. The will be . The will be . . will be conducted or comparable approaches. All subjects who qualify for the study based on physician assessment in Period 1 . will be examined using these subjects and .

5. Analysis of . In order to investigate , we will at Mayo Clinic Rochester. We will at the time of the initial visit. . Further will be at Mayo Clinic, Rochester.

Summary of [redacted]. The [redacted] for this study [redacted].

Item	Test ID	Lab	[redacted])
[redacted]	[redacted]	[redacted]	Use [redacted])
[redacted] and [redacted]	[redacted]	[redacted]	[redacted])

7.2 SAFETY AND OTHER ASSESSMENTS

The following procedures/evaluations will be performed for safety assessments:

- **Screening visit –** Review of medical history, physical examination (including rectal examination) following consent, vital signs [ie, temperature, pulse, and blood pressure), height and weight
- **Assess adherence** to **intervention. Inquire about adverse events with phone calls during the fitting and treatment periods.**
- **Review medical records** prior to and during study participation for adverse events. This process will adhere to Health Insurance Portability and Accountability Act (HIPAA) rules, other relevant federal or state laws, and local institutional requirements should be followed, as applicable.
- **Administer questionnaires and a daily diary to record subject-reported outcomes**
- **Assessment of adverse events.** Adverse events will be evaluated promptly. Subjects will be referred for additional tests and/or provided treatment.

7.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

7.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Utilizing ISO 14155:2011, an adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. An adverse event (also referred to as an adverse experience) can be associated with the use of a device, without any judgment about causality.

NOTE 1 This definition includes events related to the investigational medical device or the comparator, if applicable.

NOTE 2 This definition includes events related to the procedures involved.

NOTE 3 For users or other persons, this definition is restricted to events related to investigational medical devices.

7.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Adverse event that:

a) Led to death,

b) Led to serious deterioration in the health of the subject, that either resulted in
   1) a life-threatening illness or injury, or
   2) a permanent impairment of a body structure or a body function, or
   3) in-patient or prolonged hospitalization, or
   4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c) Led to fetal distress, fetal death or a congenital abnormality or birth defect

NOTE Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

7.3.3 CLASSIFICATION OF AN ADVERSE EVENT

7.3.3.1 SEVERITY OF EVENT

AEs will be graded according to the severity of the AE and ranges from Grade 1 (mild AE), Grade 2 (moderate AE), Grade 3 (severe AE) and Grade 4 (life-threatening or disabling AE) to Grade 5 (death related to AE).

Adverse events will be graded as follows:

- Mild: discomfort noticed but no disruption of normal daily activity.
- Moderate: discomfort sufficient to reduce or affect daily activity.
- Severe: inability to work or perform normal daily activity.
- Life threatening: represents an immediate threat to life.

Relationship to study device and/or procedure will be determined by the Investigator according to the following criteria.

- None: No relationship between the event and the administration of study device. The event is related to other etiologies, such as concomitant medications or subject's clinical state.
- Unlikely: The current state of knowledge indicates that a relationship to study device is unlikely or the temporal relationship is such that study device would not have had any reasonable association with the observed event.
- Possible: A reaction that follows a plausible temporal sequence from administration of the study device and follows a known response pattern to the suspected study device. The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject.

- Probable: A reaction that follows a plausible temporal sequence from administration of the study device and follows a known response pattern to the suspected study device. The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

7.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

For the purpose of safety analyses, all AEs that are classified as unlikely, possible, or probable will be considered treatment-related events.

7.3.3.3 ANTICIPATED ADVERSE EVENTS

Anticipated risks for this study include:

- Mild discomfort
- Unexpected expulsion of the device
- New onset, or, if pre-existing, increased anorectal pain or discomfort
- Diarrhea
- Abdominal pain
- Anorectal irritation, pain, soreness
- Rectal, anal, or perianal infection
- Device over-insertion or device migration into anal canal or rectum
- Injury to anus, anal canal, or rectum
- New onset, or, if pre-existing, increased anorectal urge
- New onset, or, if pre-existing, increased abdominal gas
- New onset, or, if pre-existing, increased hemorrhoids or rectal bleeding
- New onset, or, if pre-existing, increased colonic obstruction or fecal impaction
- Perforation of anal canal or rectum
- Device breakage
- Discomfort, bruising, redness, swelling, bleeding around the site of the blood draw
- Feeling of lightheadedness when blood is drawn
- Infection at the site of the blood draw
- Rectal bleeding due to rectal catheter use

There may be additional risks to subjects or embryos or fetuses in women who are of childbearing potential that are not known at this time.

7.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Adverse events will be recorded from Screening through study exit. Adverse events should be assessed and reported to the sponsor from enrolment through resolution or study exit, whichever comes first. Subjects should continue to be followed per standard of care after study exit.

7.3.5 ADVERSE EVENT REPORTING

Each subject must be carefully monitored for the development of any adverse events. This information should be obtained in the form of non-leading questions (e.g., "How are you feeling?") and from signs and symptoms detected during each examination, observations of study personnel, and spontaneous reports from subjects.

All adverse events (serious and non-serious) spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded in the source documentation and on the appropriate page of the CRF. Any clinically relevant deterioration in laboratory assessments or other clinical findings is considered an adverse event and must be recorded on the appropriate pages of the CRF. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. Participants who have a T score ≥ 70 on the PROMIS depression instrument will be managed according to the flow diagram immediately after Section 11, References.

7.3.6 REPORTING UNANTICIPATED PROBLEMS INVOLVING RISKS TO SUBJECTS OR OTHERS (UPIRTSOS)

Adverse Event reporting will follow the Mayo Clinic IRB policy for submitting reportable events. Consistent with this policy, "an UPIRTSO is defined as any problem or event which, in the opinion of the local Investigator, meets all reporting criteria for events that are serious, unanticipated and related (at least "possibly" related) to research procedures or the study device, as noted in protocol section 7.4.1.

The Principal Investigator must report internal UPIRTSOs to the IRB, using the IRB electronic Reportable Event form, **within five working days** of the PI or study team becoming aware of the problem or event. Reportable events having the potential to meet the UPIRTSO criteria will be forwarded to the IRB. An IRB Chairperson has the authority to determine that the criteria were not met. If the IRB Chairperson considers the event to be a UPIRTSO it must be reviewed by a convened IRB. The investigator is notified in writing. The review, determination, and relevant communication is documented in the IRB electronic system. A UPIRTSO, as determined by the convened IRB, is reported to the Mayo Clinic Institutional Official and relevant federal agencies, when required, within 30 days from the date of IRB determination. The investigator is notified in writing of this action.

The timing of investigator reporting of protocol violation/deviations to the IRB, using the IRB electronic Reportable Event form, is dependent on the severity of the protocol violation/deviation. Major protocol violations/deviations that affect the rights and welfare of subjects and others, increase risks to subjects and others, decrease potential benefits, compromise the integrity or validity of the

research; or represent willful or intentional misconduct must be reported by the investigator **within five working days** of the PI or study team becoming aware of the violation/deviation. Minor protocol violations and/or deviations should be summarized and submitted to the IRB at the time of continuing review.

Information that indicates a significant new serious risk or increased severity of known risk, or a safety issue which requires immediate action must be reported to the IRB using the IRB electronic Modification form, within **five working days** of the PI or study team becoming aware of the information. The modification must be titled **Urgent Action Required** and include the Subject Notification Form attachment. The investigator is responsible to review new information to determine if it meets the above criteria for immediate action.

If IRB reporting requirements change during the study, the most current IRB reporting policies will be followed.

All SAEs must be reported whether or not considered causally related to the study device. SAE forms will be completed and the information collected will include subject number, a narrative description of the event and an assessment by the Investigator as to the severity of the event and relatedness the to study device. Follow-up information on the SAE may be requested by Minnesota Medical Technologies or designee.

Contact Information:

[redacted]

Minnesota Medical Technologies

2446 Henry Road NW

Stewartville, MN 55976 USA

Fax:

[redacted]

Preferred method of contact is by email:

[redacted]

Follow-Up SAE Reports:

The Investigator must continue to follow the subject until the SAE has resolved or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment) or the subject dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form for the study and submit any supporting documentation (e.g., subject discharge summary or autopsy reports) via fax or e-mail.

For both serious and non-serious adverse events, the Investigator must determine the severity, anticipatedness, and the relationship of the event to study device and/or study procedure.

7.3.7 REPORTING EVENTS TO PARTICIPANTS

Any information which could impact a subject's decision to participate in the study will be communicated to them in writing.

7.3.8 EVENTS OF SPECIAL INTEREST

Anoscopy will be performed for subjects who complain of new anorectal bleeding or moderate or severe pain on the bowel diary. After the treatment period, all individuals who withdraw for reasons other than personal preference (i.e., for medical reasons) and a minimum of 50% of all patients shall undergo an evaluation by anoscopy following the treatment period to assess for device related trauma

If signs of a major side effect (e.g., rectal perforation) should occur, the subject will be treated as clinically indicated and Principal Investigator and Sponsor will be notified immediately. Such events should be reported on the case report form. Unanticipated serious adverse events will be immediately reported to the sponsor.

A device deficiency is defined as inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequate labelling.

A malfunction is defined as a failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or clinical protocol.

If a device deficiency or device malfunction is noted, this will be immediately reported by the site to the sponsor.

7.3.9 REPORTING OF PREGNANCY

Reports of pregnancy should be communicated by the site to the study sponsor immediately.

7.4 UNANTICIPATED PROBLEMS

7.4.1 DEFINITION OF ANTICIPATED AND UNANTICIPATED ADVERSE EVENTS, UNANTICIPATED PROBLEM (UP)

Per ISO 14155:2011, an anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

Per ISO 14155:2011, unanticipated serious adverse device effect (USADE) IS A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. Per 21 CFR 812, If there are serious, unexpected adverse reactions associated with the use of the study device, Minnesota Medical Technologies or designee will notify the appropriate regulatory agency(ies) and all participating investigators on an expedited basis. An unanticipated serious adverse device effect (USADE) is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. It is the responsibility of the Investigator and sponsor to promptly notify the Institutional Review Board (IRB) of all unexpected serious adverse device reactions involving risk to human subjects. A sponsor who determines that an unanticipated adverse device effect presents an unreasonable risk to subjects shall terminate all investigations or parts of investigations presenting that risk as soon as possible. Termination shall occur not later than 5 working days after the sponsor makes this determination and not later than 15 working days after the sponsor first received notice of the effect. The sponsor shall report the results of such USADE evaluation to FDA and to all reviewing IRBs and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.

In accordance with the Institutional Review Board (IRB) at Mayo Clinic, an unanticipated problem involving risk to subjects or others (UPIRTSO) will be defined any problem or event which, in the opinion of the Investigator meets all three of the following criteria:

• Serious: Problem or event that resulted in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or place the subjects or others at a greater risk of harm than was previously known or recognized. Note that actual harm need not have occurred.

• Unanticipated: A problem or event that was unforeseeable at the time of its occurrence and meets one or more of the following criteria:

- Not already described as a potential risk in the approved informed consent
- Not already described as a potential risk in the approved protocol
- Not listed in the Investigator's Brochure
- Not part of an underlying disease
- Occurred at an increased frequency or at an increased severity than expected.

• Related: A problem or event is "related" if it is possibly related to the research procedures.

7.4.2 UNANTICIPATED PROBLEM REPORTING

All UPIRTSOs will be reported to the study Sponsor and the Mayo Clinic IRB who will decide whether the event(s) should be reported to regulatory agencies (e.g., OHRP, FDA, etc).

7.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Subjects will be notified about any significant or new information which could impact their decision to participate in the study. This may include unanticipated problems.

8 STATISTICAL CONSIDERATIONS

8.1 STATISTICAL HYPOTHESES

The hypotheses for the primary endpoints, which all apply to subjects with FI, are indicated below. For the primary study, these endpoints will be assessed for all 60 participants and separately for the 10 mm and 13 mm devices (versus baseline).

1. Primary Effectiveness Endpoint: A Relative Percentage Change in Episodes of Accidental Bowel Leakage (ABL) Determined by Comparing Treatment Results to Pre-treatment Results From the Baseline Period as Measured by Daily Diary Recordings . [Time Frame: Reduction in accidental bowel leakage from Baseline (Weeks 1-4) through Treatment period (approximately Weeks 9-12).

Measure Type	Primary
Measure Title	Primary Effectiveness Endpoint: A Relative Percentage Change in Episodes of Accidental Bowel Leakage (ABL) Determined by Comparing Treatment Results to Pre-treatment Results From the Baseline Period as Measured by Daily Diary Recordings.
Measure Description	This primary effectiveness endpoint will be calculated as a relative percentage of the baseline Accidental Bowel Leakage (ABL) using the following equation: % reduction in ABL = 100*(baseline period ABL - treatment period ABL) / (baseline period ABL)
Time Frame	Reduction in accidental bowel leakage from Baseline (Weeks 1-4) through Treatment period (approximately Weeks 9-12).

Secondary Efficacy Endpoint(s):

- The mean % reduction in Fecal Incontinence Severity Index (FISS) score from the baseline period to the end of the treatment period, calculated according to the following equation: % reduction in FISS = 100% (baseline period FISS - end treatment period FISS) / (baseline period FISS).
- The proportion of subjects in whom the frequency of FI episodes during the treatment period is greater than or equal to 75% lower than the frequency observed during baseline period.
- The proportion of subjects in whom, during treatment period, the device will reduce the number of days with FI by 50% as compared to baseline.
- The proportion of subjects in whom the device will reduce the volume of FI during the treatment period as compared to baseline.
- The proportion of subjects in whom the Minnesota Medical Technologies Anal Insert Device reduces the proportion of FI episodes which are associated with diarrhea.
- The proportion of subjects in whom the Minnesota Medical Technologies Anal Insert Device reduces the number of episodes of passive and of urge FI
- The proportion of subjects in whom the Minnesota Medical Technologies Anal Insert Device l improves the Quality of Life (QOL) related to FI during the treatment period as compared to baseline.

- The proportion of subjects in whom the Minnesota Medical Technologies Anal Insert Device will affect the composition of stool leakage during the treatment period as compared to baseline.
- The proportion of subjects are satisfied with the Minnesota Medical Technologies Anal Insert Device.
- The time for which a bowel movement can be deferred after the occurrence of urgency will be affected by the Minnesota Medical Technologies Anal Insert Device.
- The proportion of complete bowel movements will be affected by the Minnesota Medical Technologies Anal Insert Device during the treatment period as compared to baseline.
- Treatment with the Minnesota Medical Technologies Anal Insert Device will affect anxiety and depression during the treatment period as compared to baseline.
- The Minnesota Medical Technologies Anal Insert Device reduces the use of medications for FI during the treatment period as compared to baseline.
- [redacted].
- [redacted].

8.2 SAMPLE SIZE DETERMINATION

The sample size determination was based on literature review. In a controlled clinical trial with clonidine, the mean and standard deviation (SD) for weekly FI episodes over a 4 week baseline period was 2.642 and 1.066 respectively in the placebo group.[29]

Assuming a mean frequency of 2.6 and a very conservative estimated SD of differences (post-pre treatment) of 1.3, a sample size of 13 subjects provides 90% power with a two sided paired t test and an alpha level of 0.05 to detect a 50% reduction (i.e., from 2.6 to 1.3 episodes/week) in the number of episodes of FI. Hence, a sample size of 30 FI subjects per group (i.e., 10mm and separately 13 mm inserts) is more than sufficient.

In order to test whether the treatment provides an improvement up to 60% response rate (50% response) from an assumed historical rate of 30%, the exact one-sample binomial test (2-sided) will be used at the 0.05 level. A sample size of n=30 provides 90% power to detect this effect.

No previous studies have evaluated [redacted]. We estimated that FI subjects [redacted] will [redacted]) of the [redacted]). If [redacted] with a sample size of [redacted] in the [redacted] and [redacted] in the [redacted] (i.e., [redacted] devices), provides [redacted].

For anoscopy, the sample size of 31 patients (i.e., 52%), provides 80% power to detect an event rate of 5% and 96% power to detect an event rate of 10%. In this context, an event refers to a side effect such as an anal fissure.

8.3 POPULATIONS FOR ANALYSES

Male and female, aged 18 and above, with a diagnosis of fecal incontinence. For the main and the sub-study, the analyses will follow the intent to treat (ITT) paradigm with all subjects randomized included in the analyses. Subjects with missing values for a particular endpoint will have their missing values imputed using the corresponding overall mean value from all subjects with non-missing data for that endpoint. An adjustment in the ANCOVA error degrees of freedom (subtracting one for each imputed value) will be made to account for the imputation. A similar adjustment for the Wilcoxon rank sum test (adjusting the degrees of freedom for the t-approximation) will also be examined. Similar analyses will be performed for the completer cohorts, i.e., all subjects who completed the 4 week treatment bowel diary and the [redacted] sub-study. For the bowel diary study, the modified ITT (mITT) cohort, which comprises those subjects who entered treatment and completed at least 1 week of device use will also be considered.

8.4 STATISTICAL ANALYSES

8.4.1 GENERAL APPROACH

Male and female subjects aged 18 and above, with a diagnosis of fecal incontinence will be consented and screened for inclusion/exclusion criteria. It is anticipated that up to 250 subjects may be screened to result in 60 subjects that qualify via baseline diary data and can retain the device for inclusion in the Treatment Period of the study. Of these, [redacted] of the subjects will be recruited for the [redacted] sub-study at Mayo Rochester where [redacted] performed.

Outcome variables are summarized below.

Primary and secondary outcomes and other variables

Primary Outcomes	Secondary Outcomes	Mechanism or Moderator Variables
1. Primary Effectiveness Endpoint: A Relative Percentage Change in Episodes of Accidental Bowel Leakage (ABL) Determined by Comparing Treatment Results to Pre-treatment Results From the Baseline Period as Measured by Daily Diary Recordings. [Time Frame: Reduction in accidental bowel leakage	• A relative percentage change derived by comparing post-treatment Mayo Fecal Incontinence Severity Index (FISS) Scores to pre-treatment (End of Baseline Period) FISS Scores. [Time Frame: FISS score will be calculated at the end of the 4-week baseline period (Weeks 1-4) and the end of the 4-Week Treatment Period (approximately weeks 9-12).] In 50% of subjects, the FISS score will decline by ≥ 3 units. • The proportion of subjects in whom, during the treatment period, the frequency of FI episodes is greater than or equal to 75% lower than the frequency observed during the baseline period.	[redacted]

from 4 week baseline period through 4 week treatment period (approximately 9-12 weeks).] 70% of subjects would have greater than or equal to 50% reduction in incontinence frequency. 2. ▪ Safety (AEs and SAEs)	• The proportion of subjects in whom, during the treatment period, the device will reduce the number of days with FI by 50% as compared to baseline. • The proportion of subjects in whom the device will reduce the volume of FI during the treatment period as compared to baseline. • The proportion of subjects in whom the Minnesota Medical Technologies Anal Insert Device reduces the proportion of FI episodes which are associated with diarrhea. • The proportion of subjects in whom the Minnesota Medical Technologies Anal Insert Device reduces the number of episodes of passive and of urge FI • The proportion of subjects in whom the Minnesota Medical Technologies Anal Insert Device improves the Quality of Life (QOL) related to FI during the treatment period as compared to baseline. • The proportion of subjects in whom the Minnesota Medical Technologies Anal Insert Device will affect the composition of stool leakage during the treatment period as compared to baseline. • The proportion of subjects are satisfied with the Minnesota Medical Technologies Anal Insert Device. • The time for which a bowel movement can be deferred after the occurrence of urgency will be affected by the Minnesota Medical Technologies Anal Insert Device. • The proportion of complete bowel movements will be affected by the Minnesota Medical Technologies Anal Insert Device during the treatment period as compared to baseline. • Treatment with the Minnesota Medical Technologies Anal Insert Device will affect anxiety and depression during the treatment period as compared to baseline. • The Minnesota Medical Technologies Anal Insert Device reduces the use of medications for FI during the treatment period as compared to baseline.	
Exploratory study	• Evaluate the effects of the Minnesota Medical Technologies Anal Insert Device [redacted]. • Evaluate if the effects of the Minnesota Medical Technologies Anal Insert Device [redacted], and the [redacted] the Minnesota Medical Technologies Anal Insert Device [redacted]. • Evaluate [redacted] subjects with FI. • Investigate [redacted] obtained at baseline. • The Minnesota Medical Technologies Anal Insert Device [redacted]. • Evaluate [redacted] Minnesota Medical Technologies Anal Insert Device [redacted].	• [redacted] • [redacted] • [redacted]

8.4.2 ANALYSIS OF THE PRIMARY AND SECONDARY EFFICACY ENDPOINT(S)

[redacted]

detailed methods for the analyses outlined below,

All bowel diary parameters (e.g., stool frequency, form, urgency, use of rescue medications, and FI) will be averaged first for each day and then over 4 weeks (baseline period and the last 4 of 12 weeks (approximately Weeks 9-12, treatment period) in each subject. These responses will also be assessed using ANCOVA models, with the corresponding baseline value as the primary covariate. [During the fitting period (approximately weeks 5-8), bowel diaries and questionnaires will be maintained to determine the right size of device. However, these data will not be used to evaluate the efficacy of the device.]

The analyses of the primary and secondary quantitative endpoints will utilize analysis of covariance (ANCOVA) models using corresponding baseline measurements, if available, as covariates. The adequate relief endpoint will first be summed over 4 treatment weeks, and then assessed using the Wilcoxon rank sum test. Treatment effects between groups (i.e., 10 mm vs 13 mm) will be evaluated, as appropriate with ANCOVA adjusted for the baseline variable. Individual adverse events (AEs) will be summarized and, where appropriate, (i.e., for parameters that are recorded during baseline and treatment bowel diaries such as pain during defecation), the overall frequency of AEs be compared using the Wilcoxon rank sum test. For the volume of FI episodes, a weighted score will be computed as follows (proportion of minor episodes*2 + proportion of major episodes*3).[25] An FI episode is defined as any episode of stool leakage that is more than a stain. A “minor FI episode” is more than a stain but not an entire bowel movement. A “major FI episode” is an entire bowel movement.

8.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

See section 9.4.2

8.4.4 SAFETY ANALYSES

Safety endpoints (e.g., adverse events, serious adverse events, unanticipated serious adverse events, device deficiencies, and device malfunctions) will be analyzed and reported with summary statistics. The start date, stop date, severity, relationship, expectedness, outcome, and duration of each AE will be reported. Adverse events leading to premature discontinuation from the study intervention and serious treatment-emergent AEs will be presented either in a table or a listing.

8.4.5 BASELINE DESCRIPTIVE STATISTICS

The intervention groups will be compared on baseline characteristics, including demographics and clinical features using descriptive statistics.

8.4.6 PLANNED INTERIM ANALYSES

There are no planned interim analysis for this study.

8.4.7 SUB-GROUP ANALYSES

Data for the primary endpoint will be evaluated separately in men and women, and also separately in younger and older subjects. The precise age cut off will depend on the distribution of subjects. Data for the secondary endpoints will be analyzed likewise.

8.4.8 TABULATION OF INDIVIDUAL SUBJECT DATA

If appropriate, individual subject data will be listed by measure and time point in the figures.

8.4.9 EXPLORATORY STUDY AND ANALYSES

STUDY

For the EXPLORATORY study, the [redacted], will be compared between both device groups (i.e, 10 and 13 mm) [redacted] Similarly, [redacted] 10 and 13 mm devices will be compared [redacted]. The relationship between [redacted] will be compared [redacted]. Linear regression models will evaluate [redacted]. The [redacted] will be one or more of the following variables: [redacted]. The anal [redacted], proportion of subjects [redacted]) and anorectal [redacted]) will be summarized.

ANALYSIS

[redacted] will be anonymized before being [redacted]. These results [redacted]. [redacted] will [redacted] Mayo Clinic [redacted] Mayo Clinic or at other institutions. [redacted].

The exploratory objectives are to:

- Evaluate the effects of the Minnesota Medical Technologies Anal Insert Device [redacted], as measured with [redacted]
- Evaluate if the effects of the Minnesota Medical Technologies Anal Insert Device [redacted] the Minnesota Medical Technologies Anal Insert device [redacted]
- Evaluate the [redacted] subjects with FI

- Investigate [redacted] associated with FI [redacted] obtained at baseline

9 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

9.1.1 INFORMED CONSENT PROCESS

9.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO SUBJECTS

This study will be conducted in compliance with 21 CFR Parts 11, 50, 54, 56 and 812. The consent form is provided under separate cover.

9.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's voluntary documented agreement to participate in the study. Informed consent forms will be developed by the study sponsor together with the study site in a language and reading level understandable by the subject, reviewed by an accredited Institutional Review Board (IRB) and approved by the IRB prior to use. Each potential study subject will be asked to read and review the document. The investigator or designee will explain the research study to the subject and ensure enough time to answer any questions that may arise. The subjects should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The subject will sign and date the informed consent document prior to any procedures being done specifically for the study. Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice, penalty, or loss of benefits. A copy of the informed consent document will be given to the subjects for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed and dated, before the subject undergoes any study-specific procedures. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

9.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be prematurely terminated, if in the opinion of the IRB, Investigator, or Minnesota Medical Technologies, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the Investigator or Minnesota Medical Technologies by the terminating party. Appropriate notification to the IRB will be ensured by the study site and sponsor.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects.

- Insufficient complete and/or evaluable data.
- Plans to modify, suspend or discontinue the development of the study device.

Should the study be closed prematurely, all study materials must be returned to Minnesota Medical Technologies or designee.

9.1.3 CONFIDENTIALITY AND PRIVACY

Subject confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover [redacted] in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or company supplying study product may inspect and copy all documents and records required to be maintained by the investigator, including but not limited to, consent forms, study regulatory documents, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements, for at least two years after the data is no longer needed to support the marketing application.

9.1.4 FUTURE USE OF [redacted] DATA

Data collected for this study will be analyzed and stored at Mayo Clinic for future research. The study team will use [redacted] study analysis at present time and with further consent from subjects for future research. If subjects agree to give future permission of [redacted], they will then become the property of Mayo Clinic. Other researchers at Mayo Clinic who are not involved with this study and researchers at other institutions may ask [redacted] for future research. The [redacted] will be sent to researchers in a coded format, which protects their identity. Some future studies may examine [redacted] and subjects may be contacted by the Principal Investigator if there are findings deemed useful to the subject, with consideration of the potential risks, benefits, and costs of choosing to learn about the findings. Finally, subjects will be asked for individual consent on the use [redacted] for future research (i) on fecal incontinence and defecatory disorders, (ii) on other health problems, and iii) permission to [redacted] to researchers at other institutions.
During the conduct of the study, an individual subject can choose to withdraw consent to have [redacted] for future research. However, withdrawal of consent with regard to [redacted]

[redacted] may not be possible after the study is completed. This information will be included in the consent form.

9.1.5 KEY ROLES AND STUDY GOVERNANCE

Name and contact information of the Principal Investigator and the Medical Monitor. Any changes to these roles or personnel will be documented, and the sponsor will be notified.

Co-Principal Investigator	Co-Principal Investigator	Physician Medical Monitor
Dr. Adil E. Bharucha, MBBS, MD Consultant, Division of Gastroenterology and Hepatology, Professor of Medicine	Dr. Lawrence Szarka, MD. Consultant, Division of Gastroenterology and Hepatology, Professor of Medicine	Drs. David Prichard, M.B., B.Ch., Ph.D. and Dr. Lawrence Szarka, MD. Consultant, Division of Gastroenterology and Hepatology, Professor of Medicine
Mayo Clinic	Mayo Clinic	Mayo Clinic
200 First Street SW, Rochester, MN 55905	200 First Street SW, Rochester, MN 55905	200 First Street SW, Rochester, MN 55905
(507) [redacted]	(507) [redacted]	(507) [redacted]
[redacted]@mayo.edu	[redacted]@mayo.edu	[redacted]@mayo.edu [redacted]@mayo.edu

9.1.6 SAFETY OVERSIGHT

Safety oversight will be provided by a Data Safety and Monitoring Plan (DSMP). A Data and Safety Monitoring Board (DSMB) is not necessary because the site and sponsor will (i) carefully screen subjects and, not initiate, or terminate participation of subjects that are at an increased risk of developing side effects, (ii) the design of the Minnesota Medical Technologies Anal Insert Device is very similar to a predicate device (Renew) that is associated with a very low risk of side effects, (iii) the anorectal procedures (i.e, [redacted]) will be conducted by experienced personnel using established techniques, and , (iv) the FDA has determined that this study is a nonsignificant risk (NSR) device study because it does not meet the definition of a significant risk (SR) device under § 812.3(m) of the investigational device exemptions (IDE) regulation (21 CFR 812). As detailed previously, the study coordinator(s) will inquire about side effects when they contact subjects. The coordinators will review these side effects with the study Investigator and Medical Monitor. If none of these individuals is available, the side effects will be reviewed with Dr. Adil E. Bharucha. All side effects will be reviewed by either of the medical monitors listed above. All these individuals will be available to address unexpected events including after-hour subject safety concerns. Study discussions and minutes will be documented. Deviations to study protocol and AE reports will be communicated to IRB and sponsor, and the relevant review meetings minutes or results will be documented and included in the study protocol file.

9.1.7 CLINICAL MONITORING

Before study initiation, the applicable Good Clinical Practice (GCP), FDA regulations, investigator responsibilities, the study protocol, safety reporting requirements, monitoring and auditing procedures, data collection procedures, case report form completion, possibility of FDA inspection, and other study requirements will be reviewed with the investigators and their staff. The investigator is responsible for ensuring protocol and GCP compliance for the integrity of the site's data and study conduct. An independent site monitor will visit the site to assess compliance to the regulations, IRB conditions of approval, the study protocol, and other study requirements. The monitor will assess the accuracy and completeness of entries on the Case Report Forms (CRFs), the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that the study device is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits. The investigator must maintain source documents for each subject in the study, consisting of case history and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is to be given to the subject). The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. The Minnesota Medical Technologies designated study site monitor will follow the study monitoring plan requirements.
Additional checks of the consistency of the source data with the CRFs are to be performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

9.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control (QC) procedures will be implemented, including within the data entry system. Data edit checks will be run on the validated database, and any missing data or data anomalies will be communicated to the site(s) for clarification/resolution via queries which will include an audit trail and be maintained on file.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, FDA regulations in 21 CFR Parts 11, 50, 54, 56, and 812.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

9.1.9 DATA HANDLING AND RECORD KEEPING

Database management and quality control

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification. The clinical study monitor will review the data entered into the eCRFs by

investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries will be sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be provided to the site. Site personnel will complete, sign, and date the paper query, then scan and return to the sponsor via email or provide to the sponsor in person. If a paper query must be used, the study monitor who will make the correction to the database and will reference the paper query as the source of the data entry. The paper query form(s) will be maintained at the site and also in the sponsor trial master file.

9.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets may be provided for use as source document worksheets for recording data for each subject enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source document worksheets and medical records.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a 21 CFR Part 11-compliant data capture system provided by the study sponsor or designee. The data system is to include unique user IDs, unique password protection, audit trails, 21 CFR Part 11 compliance analysis, and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered as documented in the source documents.

9.1.9.2 STUDY RECORDS RETENTION

The investigator agrees to keep the records and documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), paper or electronic copy of CRFs, including the audit trail, and detailed records of device disposition and accountability to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, the investigator is required to retain essential documents until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not

approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. Study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the study site agreement between the investigator and sponsor. Refer to the study site agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

9.1.10 PROTOCOL DEVIATIONS

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria. The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. A Protocol Deviation Form should be completed by the site and signed by the investigator and sponsor for any significant deviation from the protocol. A protocol deviation is any noncompliance with the clinical trial protocol, IRB requirements, and/or FDA regulations. The noncompliance may be either on the part of the subject, the investigator, or the study site staff.

9.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

This trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

9.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial and in accordance with guidance from the Conflict of Interest Review Board at Mayo Clinic.

9.2 ADDITIONAL CONSIDERATIONS

Not applicable.

9.3 ABBREVIATIONS

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list).

AE	Adverse Event
ANCOVA	Analysis of Covariance
ANSI	American National Standards Institute
CDRH	Center for Devices and Radiological Health
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
COX-2	Cyclooxygenase
CRF	Case Report Form
CRF	Code of Federal Regulations
CRTU	Clinical Research and Trial Unit
CTCAE	Common Terminology Criteria for Adverse Events
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DNA	Deoxyribonucleic Acid
DRE	Disease-Related Event
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
eCRF	Electronic Case Report Forms
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
EN	English
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFQ	Food Frequency Questionnaire
FFR	Federal Financial Report
FI	Fecal Incontinence
FIQOL	Fecal Incontinence Quality of Life
FISS	Fecal Incontinence Symptom Severity
FMEA	Failure Mode and Effect Analysis
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IBS	Irritable Bowel Syndrome
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
ISMP	Institute of Safe Medical Practices

ISO	International Organization for Standardization
ITT	Intent to Treat
MAUDE	Manufacturer and User Facility Device Experience
mITT	modified Intent to Treat
MMT	Minnesota Medical Technologies
MRI	Magnetic Resonance Imaging
NCT	National Clinical Trial
NSAID	Non-Steroidal Anti-Inflammatory Drugs
OHRP	Office for Human Research Protections
PD	Protocol Deviation
PI	Principal Investigator
PROMIS	Patient Reported Outcomes Measurement Information System
QA	Quality Assurance
QC	Quality Control
QOL	Quality of Life
QUEST 2.0	Quebec User Evaluation of Satisfaction with Assistive Technology
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAP	Statistical Analysis Plan
SD	Standard Deviation
SMC	Safety Monitoring Committee
SNP	Single nucleotide polymorphisms
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Effect
UP	Unanticipated Problem
US	United States
VS	Vital Signs

9.4 PROTOCOL AMENDMENT HISTORY

The protocol amendment history will be included on page 1 of this protocol.

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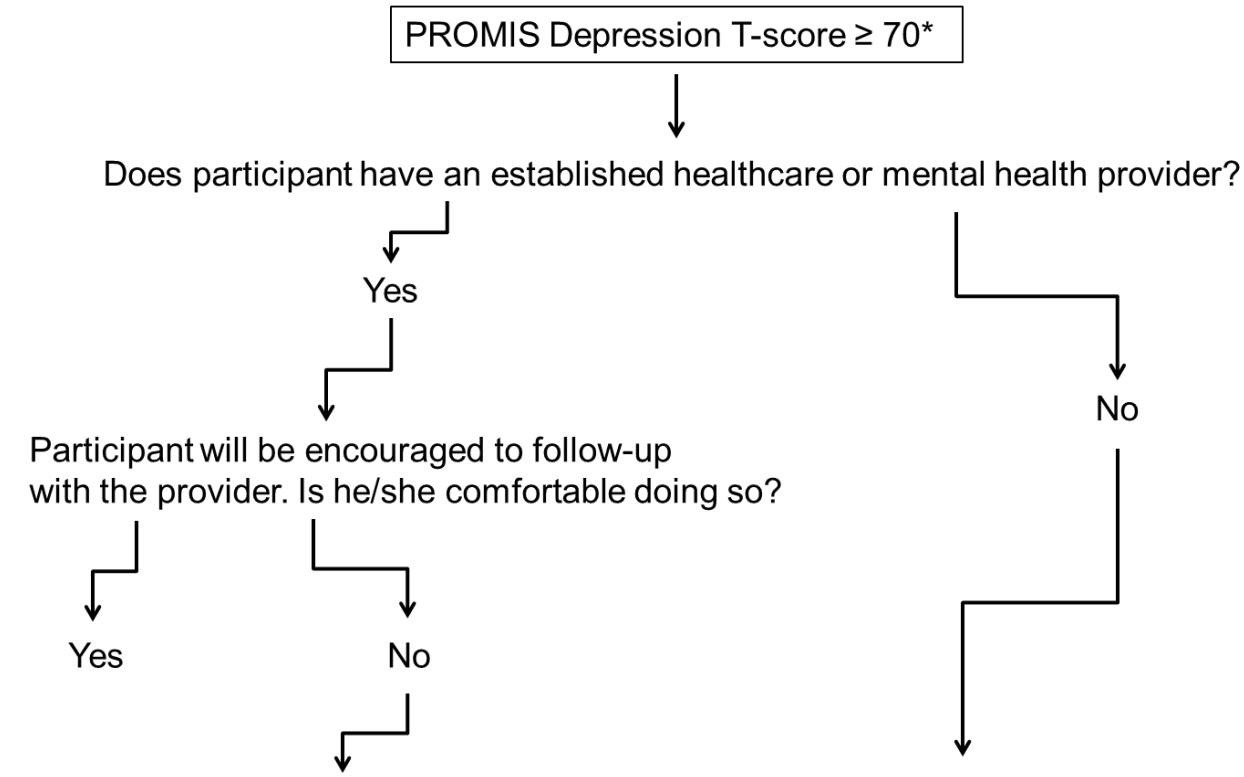
Management of Depression:



The PROMIS scale the average T-score for the United States population is 50. The Profile Report also provides a standard error for this scale.

Study Informed Consent
(provided under separate cover)

Device Labeling
(provided under separate cover)