Michigan ENdoluminal Distraction Device (MENDD) Tolerance Assessment Study

NCT06185088

IRB Approval Date: October 4, 2023

Protocol Number: HUM

Title: Michigan ENdoluminal Distraction Device (MENDD) Tolerance Assessment Study

National Clinical Trial (NCT) Identified Number: n/a

Principal Investigator: Meghan Arnold

Funded by: Internally Funded

Version Number: v.1.1

6-28-23

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
7/7/23	Initial approved version	
6/28/23	Change PI from Ralls to Arnold	Ralls leaving institution

1.0 Protocol Summary/Synopsis

Title:	Michigan ENdoluminal Distraction Device (MENDD) Tolerance Assessment Study
Study Description:	We hypothesize the radial and longitudinal forces necessary to produce enterogenesis will cause low levels of discomfort in healthy adult patients. Approved devices will be utilized in an off-label manner to reproduce forces similar to our novel medical device which is designed to treat short bowel syndrome.
Objectives:	The primary objective is to assess the discomfort level caused by balloon deployment (radial stretch) within the intestinal lumen in awake patients. Secondary objectives include assessment of the discomfort level caused by producing short term longitudinal stress on the intestinal lumen.
Endpoints:	Primary Endpoint: Completion of a pain rating scale during radial stretch. If tolerable pain thresholds are met, subjects will move on to the secondary objectives. Secondary Endpoints: Completion of a pain rating scale while enduring longitudinal stress on the small bowel.
Study Population:	Five otherwise healthy adult patients with small bowel stomas undergoing routine procedures at the University of Michigan will be recruited
Phase:	Early Feasibility
Description of Sites/Facilities Enrolling Participants:	All individuals will be enrolled at Michigan Medicine.
Description of Study Intervention:	The Michigan ENdoluminal Distraction Device (MENDD) centers around the well-known principle of mechano-transduction. This is defined as the conversion of mechanical stimuli to biochemical signals that elicit specific cellular response. In this case, intraluminal, longitudinal tensile forces result in intestinal growth and lengthening (enterogenesis). This study will utilize approved devices in an off-label manner to create forces required to induce intestinal lengthening.

	Radial and longitudinal forces are both required, and two devices will be used to create forces in order to test tolerability of a said forces. This is to provide evidence that humans could tolerate the forces produced by a proposed commercially built device.
Study Duration:	6-12 months
Participant Duration:	Subjects will be in the study for 15-60 minutes on the day of procedure and monitored per normal recovery under nursing care from their scheduled procedure. Phone interviews will take place at 30 days post procedure to monitor for adverse events.

2.0 Introduction

2.1 Study Rationale

Short-bowel syndrome (SBS) is found in children who undergo massive intestinal resection for several congenital or acquired conditions resulting in insufficient intestinal length to sustain life. These patients require IV nutrition and hydration (parenteral nutrition, PN) for adequate growth and development[1]. PN requires invasive surgery for placement of central catheters, and often a tethering for 24 hours a day to an IV pump. SBS patients and their families spend most of their time in a hospital. Further, these children are susceptible to complications of their underlying disease processes, as well as to PN use including electrolyte disturbances, dislodgment or infection of the central catheter and liver failure. Accurate estimates of incidence and prevalence of SBS are difficult for many reasons; however, a survey of Pediatric Intestinal Failure Consortium (PIFCON) centers resulted in an incidence of 1,650 pediatric SBS patients. Approximately 50-55% of these patients either do not survive beyond the first month of SBS diagnosis, or rapidly wean off of PN and therefore would not be included in our target patient population. Based on this line of rationale, it is estimated that the overall incidence of pediatric SBS is ≈700/year adding to the existing 10,000 to 20,000 patients who require home PN in the U.S.

Caring for a SBS patients is costly. Best estimates put the cost of care for each SBS patient at over half a million U.S. dollars in the first year post-diagnosis, and $300,000 each year after[2]. Current treatments to alleviate SBS are high risk, expensive, and have varied results. The growth hormone Teduglutide®, a GLP-2 analogue, stimulates bowel growth and function[3]. Currently use is limited to adults and the adaptive process may reverse after drug termination[4]. Additional concerns with GLP-2 include a very high cost (≈$300,000/year) and a significant cause for concern for development of GI malignancies with prolonged use[5]. Surgical lengthening is another option[6]. These procedures require a laparotomy and long hospital stay. The operation carries a potential risk of injury to the bowel, intestinal vasculature, leakage of enteric contents, and can only be done if the intestine is overly dilated. Moreover, it is also associated with up to a -60% failure rate[7,8]. Finally, small bowel transplantation has

been used when other treatments fail. Although a viable option, transplantation is expensive (>$450,000/pt.)[9], requires long-term immunosuppression, and carries the risks of infection and graft failure. While early patient and graft survival are good, 3-year survival is ≈60%[10].

Short bowel syndrome is problematic not only for the patient, but also the family and the healthcare system with little hope of cure. **Thus, there remains a great need for an alternative procedure to treat SBS that will lower cost, have higher success rate and lead to greater quality of life**. Our 20 years of research and development have led to the point where we have a nonoperative strategy to increase intestinal length in an animal model. We need to ensure the forces created by the device are tolerable to humans. While there is no evidence of pain in the numerous animal models, human data is essential. Healthy adults afford us the opportunity to discuss the sensations created by bowel distension (albeit minimal) and longitudinal stress on the small bowel. The MENDD team consider these data critical to pursue the costly endeavor of building a device fit for human testing based on our animal prototype created at the university of Michigan mechanical engineering labs of Drs. Diann Brei and Jon Luntz.

2.2 Background

MENDD therapy comprises the progressive application of distractive forces to the small intestine to induce cellular proliferation, also known as mechanotransduction-induced growth. This is a concept that has been used in numerous clinical applications for over 100 years, including limb-length discrepancy, tissue expanders, and dental braces. Confirmation of these mechanisms of growth for bowel tissue has been recently demonstrated in rodent[11], rabbit[12], and porcine models[13,14,15], all using pre-clinical methods of applying distractive forces. In our own key study, a pre-clinical hydraulic device induced significant bowel growth in pigs and re-implantation of the lengthened intestine into the normal continuity of enteric flow preserved bowel length as well as absorptive and peristaltic function. This demonstrates the viability of the mechanotransduction approach for growth in bowel[16]. In another study, a non-clinical iteration device was placed in a Roux-en-Y jejunal segment. In a 6-pig trial, distracted segment lengths increased 67±15% corresponding to 12.9±5.6cm gain (1.0-1.2cm/day), vs. minimal growth in fed, non-distracted bowel. Moreover, the distracted segment showed an increased epithelial cell proliferation (by PCNA staining) vs. control as further evidence of true growth. MENDD therapy results of 67% growth is a significant increase over current surgical lengthening procedures, where a mean gain of 37 and 47% has been reported[17,18]. Distracted segments show thicker smooth muscle, increased villus height, increased crypt depth and restored segments after distraction demonstrated equal water absorption and greater glucose absorption[19]. Though these study and others demonstrate the great potential for MENDD therapy, none of the devices utilized in these studies are directly clinically applicable for humans.

Our current MENDD prototype is dual catheter-based device with a

proprietary attachment on both an inner and outer catheter (Figure 1). Once the intraluminal attachments are engaged, the inner catheter is advanced increasing the inter-attachment distance thus providing longitudinal tension on the intervening segment of intestine. This most recent prototype can produce the necessary forces to induce growth, but the tolerability of the device is unknown. This study will answer the question if forces required to induce growth are tolerable to awake humans and will be accomplished by using approved devices to reproduce the forces generated by MENDD. This will provide confidence in the investigators, the university, regulatory bodies, as well as in funding sources of the potential MENDD device. With completion of this study, we will proceed with commercial manufacturing of the device under design controls and specifications with the eventual goal of applying for an IDE in order to place the MENDD device into humans.

2.3 Risk Benefit Assessment

2.3.1 Known Potential Risk

Immediate risks include intraoperative complication. These are similar to any endoscopic procedure and are rare. The deployment of a ballooned catheter in the intestinal lumen is common practice. However, in this study, a balloon designed for intravascular deployment will be used. This is because the balloon characteristics are most like that of our future device. With intraluminal balloon deployment, risks include damage to the bowel wall and perforation. This is very rare, and risk will be mitigated by the known dimensions of the balloon and other balloon characteristics. Further, this will be done in healthy bowel. Balloon dilation is typically done for diseased bowel that is at higher risk of damage.

Long term risks could result from in intraoperative complication including the need to repair any damage to the intestinal tract. This could result in unplanned hospitalization which in turn could have psychological, social, legal, and economic consequences.

The MENDD design is unique, and no other procedure can be performed to gather the necessary data. Numerous animal models have been completed and have not demonstrated pain, but human data is required.

2.3.2 Known Potential Benefits

The benefits of this study are purely societal. Individuals would be helping make a case for continuation of device development with the aims of helping short bowel patients in the future.

2.3.3 Assessment of potential risk to benefit

Participants enrolled in this study will gain no benefit other than providing information that may lead to lessen the hardship of others through device development. Children with short bowel syndrome live an exceedingly difficult life that stresses not only the patient, but also the family and the healthcare system. Any innovation to treat short bowel syndrome could save thousands of hospitalizations and millions of dollars. The risk to individuals is possible damage to intestine ranging from minor mucosal damage to frank perforation. Our understanding of intestine as well as balloon mechanics has led us to choose devices that we feel carry a low

risk profile yet will reproduce the forces created by MENDD.

In the first step, The Coda® balloon is specially constructed to radially expand with a known diameter dependent on the fill volume (figure 2). This device is approved for intravascular use within the aorta and other major vessels where precision and accuracy are of the utmost accuracy and are of the utmost importance. Further, the FDA has approved balloon devices made of similar material for use in the bowel with a diameter of 40mm or larger. Not only are these sizes FDA approved, but intended for use in narrowed, diseased bowel. The difference in these GI specific balloons is that they are quite long and do not match the MENDD specifications. Moreover, these balloons will only be inflated on the order of minutes. The purpose of this study is to evaluate the sensation of discomfort generated by intraluminal inflation of the balloons and respond to the survey. The risk of damage to the participants' intestine is very low. The study is designed to have an awake patient so any pain will alert the staff to deflate the balloon if the subject expresses severpain.

The second step of the study comprises the placement of a double balloon enteroscope (DBE) retrograde into a stoma (Figure 3). This device is approved for use by advanced endoscopists and carries a low risk profile. A Gastroenterologist with expertise with this device has been involved in planning of this study as well as will be performing the portion of the study requiring the DBE. The device has numerous risk mitigation features listed in the appendix of this protocol. In short, the balloons are pressure regulated to not cause damage to the bowel. These sensors also alarm if undue tension is placed on the intestine. We will be able to monitor those alarms as well as the response from study subjects for discomfort. The risk of intestinal damage is low. The DBE itself is 9.4mm at its largest point which should pass through the stoma without complication. However, should an individual have a minor narrowing of the fascial defect through which the stoma is matured, there may be some discomfort and minor trauma to the intestinal mucosa. This may cause the termination of the subject's participation in the study but would not be considered a failure to meet the endpoints.

3.0 Objectives and Endpoints

The primary objective is to assess the discomfort level in awake patients with radial distension of the intestine to a known diameter. This will be accomplished with deployment of a balloon with similar characteristics to a proposed medical device. The secondary objective is to place longitudinal forces on intestine using a DBE and asses the discomfort level. Longitudinal tension is necessary to create the mechanotransductive forces necessary to induce intestinal growth. However, in this current study, the forces will not be of the duration to induce growth. These studies serve as precursor studies to obtain data on the tolerability of forces placed on bowel during proposed MENDD therapy. Future studies would include placement of a MENDD prototype device in healthy adult volunteers with ileostomies with the objectives to include 1) to demonstrate feasibility of endoscopic placement of MENDD via an existing stoma and 2) to demonstrate no serious adverse events with actuation of the device while in human intestine.

Discomfort levels will be assessed through an interview process

performed by the study team members during the procedures described. Simple validated pain scales and surveys will be used (Figure). The observation period of the study will end either with conclusion of the questionnaire of discomfort described as too great to continue.

4.0 Study Design

4.1 Overall Design

Our team posits intraluminal forces placed on the intestine required to produce distraction eneterogenesis are tolerable in awake individuals. This early feasibility study serves as a bridge from preclinical animal studies that have demonstrated pain free intestinal lengthening. The purpose is to demonstrate that our proposed clinical device will not cause discomfort so great in humans that the procedure will require sedation. FDA approved devices will be used in an off-label manner to reproduce the forces required to induce intestinal growth in an acute setting. Because this is simply a study to test the tolerance of the forces required, the goal is not to produce any bowel lengthening during this procedure.

The trial to be conducted is adaptive - completion of all endpoints will be dependent upon completion of previous endpoint. Adult subjects will be approached based on a medical condition of having an ileostomy. Age, gender, race, or any other identifying factor will not be considered in recruitment at this single site study.

4.2 Scientific Rationale for Study Design

This early feasibility study will answer a simple question of whether the forces required to induce intestinal growth cause pain in humans. Two distinct forces will be tested. First, radial stretch of the intestine to a known diameter will be tested. Should the individual tolerate the radial stretch, the subject will move to the second step of the study. A second device will be used to create longitudinal stress on the intestine, the second force required. Two approved devices are necessary due to the unique characteristics of each device. Radial stretch will be tested with a balloon with a known diameter maximum used in intra vascular procedures. This is a similar diameter to our future device. Larger balloons are approved for intestinal use, suggesting this balloon deployment will have little effect on the physiology and sensation of the intestine. However, we aim to understand the interaction of the intestine with balloons that are comparable to our device.

If the subject tolerates the radial stretch, a DBE will be used to generate acute longitudinal tension. The proposed MENDD will be able to create longitudinal stress over periods of minutes to hours while the DBE can create this tension over seconds to minutes. The balloon characteristics on the DBE are far different from the MENDD balloons and thus cannot be used for the first step in the study.

4.3 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including a 30 day follow up phone interview or the last scheduled procedure.

5.0 Selection of Patients

5.1 Inclusion Criteria (list):

- Adults 18 - 80
- Existing Ileostomy older than 6 weeks
- Undergoing any existing procedure in endoscopy suite or operating room.

5.2 Exclusion Criteria (list):

- Inflammatory bowel disease of small bowel
- Pregnant
- Short bowel syndrome
- Bleeding disorder
- Chronic pain disorder
- Individuals taking chronic pain medications including prescriptions, cannabinoids or over the counter.
- Individuals taking pain medications at the time of the procedure
- Cognitive Impairment to the extent that the questionnaire cannot be completed

5.3 Strategies for Recruitment

The study team will work directly with the PI and the departmental scheduler to identify subjects scheduled for any case meeting the criteria. We are aiming to recruit subjects already undergoing a minor procedure for routine health screening or other health matters, thus, avoiding any unnecessary procedures for subjects. Rather, we intend to approach participants undergoing the procedure as standard of care and will add on the study intervention(s).

Compensation will be offered to participants who complete study activities. Participants who complete the initial screening and procedure will receive a $100 gift card and an additional $100 gift card once the follow up phone call is completed to assess for adverse events.

6.0 Study Intervention

6.1 Study Intervention Administration

In this study, we will use two FDA approved devices in an off-label manner to replicate forces generated by the MENDD device. To test radial stretch of the small bowel, Coda® Balloon Catheters (K032869) will be introduced into the volunteers' intestine over a guide wire. The guide wire (TERUMO Radifocus Glidewire Angled Stiff Shaft .035" x 180cm (X) GS3508, K152740) is used routinely in the gastrointestinal tract as well as endovascularly and will be advanced under endoscopy and fluoroscopy. Coda® Balloons are intended for temporary occlusion of large blood vessels, or to expand vascular prostheses. Because of the primary indications, the balloon diameter must be extremely precise and accurate. A Coda® balloon with a similar diameter and length, compared to our MENDD design, will be used in the first portion of the study. Pain questionnaires will be administered to the subjects in real time. Due to the subjectivity of pain, the pain scales must be completed at the time and cannot be completed after the procedure is over. The balloon will be inflated for 1-2 minutes. If pain is severe, the balloon will be deflated immediately. The balloon will be repositioned and attempted once more

for the duration of 1-2 minutes.

Volunteers who tolerate the radial stretch will move on to the second portion of the study. The Coda will be removed, and a Double Balloon Endoscope (DBE) (©FUJIFILM Healthcare, K183032) will be introduced retrograde into the stoma. An advanced endoscopist with specific training and credentialling will perform the endoscopic procedure. Typically, this procedure is done antegrade through the oropharynx in an anesthetized individual. In short, the DBE is an endoscope that has a balloon on the scope itself and on an overtube. The scope is advanced through the small bowel by alternately inflating and deflating balloons and bringing the small bowel to the endoscopist by pleating the bowel over the overtube, similar to pulling a curtain over a rod. Our procedure will deviate from the described use. In this study, the DBE will be introduced retrograde through the ileostomy and the inter-balloon distance will be increased causing stretch on the intestine instead of decreased causing the intestinal pleats. As this is a common unintentional consequence of the DBE procedure, safety precautions and alarms have been implemented to prevent damage to the intestine. The device will be left with balloons inflated on tension for 30-60 seconds or until the device turns off due to safety measures built into the device.

Visual Analog Scale Pain Scoring will be used to assess the participants sensation during both parts of the study. Because pain tolerance differs for all people, we will not set pre-determined score in which the procedure will be stopped, but rather rely on the participant and their willingness to continue. The trial will be discontinued if three participants do not tolerate the first stage of this study i.e., the Coda balloons. Pain during the second portion of the protocol (DBE) will not result the termination of the study. The dissimilar characteristics of the DBE balloons with the MENDD prototype balloons are the reason the Coda balloons are used in the first portion of the study and discomfort from the DBE will be noted, but in itself will not be considered a failure of the study.

The VAS will be used at several timepoints beginning with immediately after insertion of the catheter and prior to balloon expansion. Next the score will be assessed after the balloon is inflated to a known diameter. Should the subject move to the second phase of the study, the VAS will be given after insertion of the DBE prior to deployment of balloons, after deployment of each balloon and during the extension procedure.

7.0 Study Intervention Discontinuation

7.1 Discontinuation of Study Intervention

Participants may withdraw voluntarily from the study, or the PI may discontinue a participant from the study. Discontinuation from study intervention will disqualify participant from further continuation. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE). Participants will have access to reach the study team should any concerns arise, and a phone call interview will be

scheduled for post procedure day 30 to assess for AEs.

7.2 Participant Discontinuation/Withdrawal

Participants may withdraw voluntarily from the study or discontinue the study intervention at any time.

7.3 Loss to Follow up

A participant will be considered lost to follow-up if he or she fails to return for scheduled visits or is unable to be contacted by the study site staff.

8.0 Adverse Events

8.1 Adverse Events and other reportable events

Any adverse event reported or observed by the participant will be reported per standard IRB reporting. Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention related. Adverse events will be recorded from the time the consent is obtained until the final procedure is complete including completion of VAS and the 30 day follow up phone call. Other reportable information will be reported to the IRB according to standard reporting procedures.

Expected possible adverse events include:

- Damage to the intestinal wall ranging from mild mucosal irritation to full thickness injury or perforation.
- Damage to the stoma
- Bleeding from the intestinal lumen is usually self-limited and will resolve with observation. However, severe damage may require endoscopic or surgical evaluation and/or intervention to obtain hemostasis or repair perforation.
- Discomfort or pain
- Radiation-related risks associated with fluoroscopy include: radiation-induced injuries to the skin and underlying tissues (“burns”), which occur shortly after the exposure, and. radiation-induced cancers

9.0 Statistical Considerations:

9.1 Proposed sample size (number of records to be reviewed):

5 subjects will be enrolled. If 3 fail to complete the radial stretch test with Coda balloon, the study will be terminated.

9.2 Proposed time period to be evaluated

We aim to achieve our enrollment goal within 6 months of approval

9.3 Specify how data will be analyzed and by whom:

Data will be reviewed and analyzed by the study team and departmental statistician

10.0 Supporting Documentation and Operational Considerations:

10.1 Informed Consent Process

Once the study team has been notified of a potential participant, the study team will contact the patient via phone using a phone script (see appendix) or approach the participant in the pre-procedure area at which time the consent will be reviewed, allowing time for any follow up

questions and consideration. Once the participant has agreed to participate, and eligibility has been confirmed and documented including medical history by a study member, the consent process will be completed.

10.2 Study Discontinuation and Closure

At which time the study is complete and all data collection, analysis, and publication, if applicable is complete, the study will be terminated.

10.3 Future Use of Data

We plan to keep this data for future use as this data will contribute to a future project. The data obtained will help to inform future projects and may be included as we further investigate this cohort/disease. Future use of data will be permitted and will be included in the consent.

10.4 Data Handing and Record Keeping

All electronic data will be kept on password protected, encrypted devices within the University of Michigan system which meet current security standards. Any paper records utilized during this review will be kept in a locked cabinet within the Pediatric Surgery research space and/or PI's office. Only study personnel approved by the IRB will have access to study data and records.

Once data collection and analysis is complete, any PHI will be removed from the dataset and data will be maintained for 3 years after the study completion.

11.0 References:

12.0 Appendix

A. **Data Collection Forms with data elements to be collected from the medical record**
B. **Patient reported pain scales**
    a. **See Figure 3**
C. **Specification and safety information for Double Balloon enteroscope**
    a. **https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=876.1500**
    b. **https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=876**
    c. **https://healthcaresolutions-us.fujifilm.com/endoscopy/fujifilm-580-series-interventional-endoscopes/fujifilm-en-580t-double-balloon-endoscope**

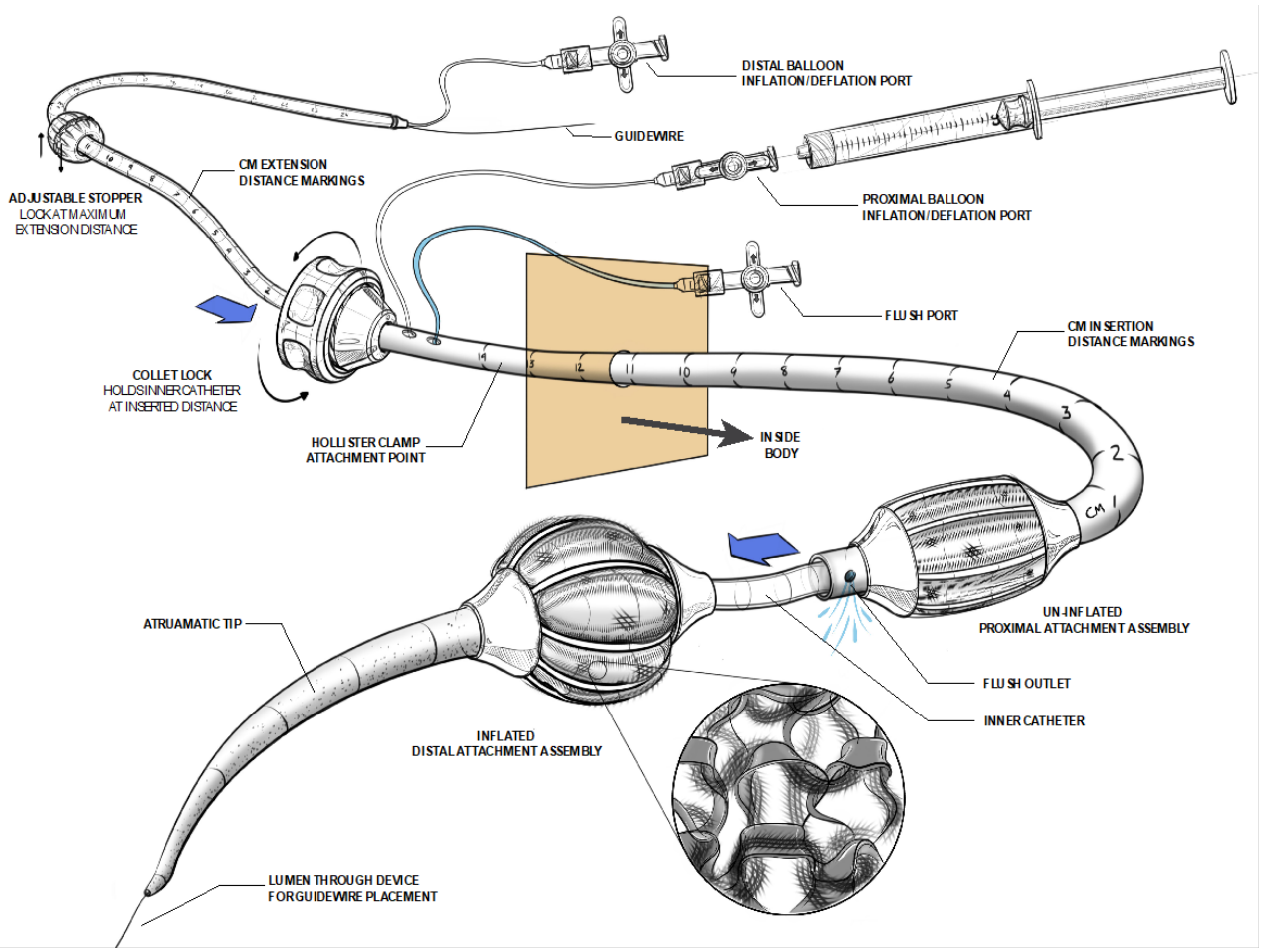

Figure 1. Artist rendition of MENDD showing all features of the device.

Maximum Inflation Volumes

Catheter Size	Max. Volume
CODA-2-10.0-35-120-40	40 cc
CODA-2-9.0-35-100-32	30 cc
CODA-2-9.0-35-120-32	30 cc

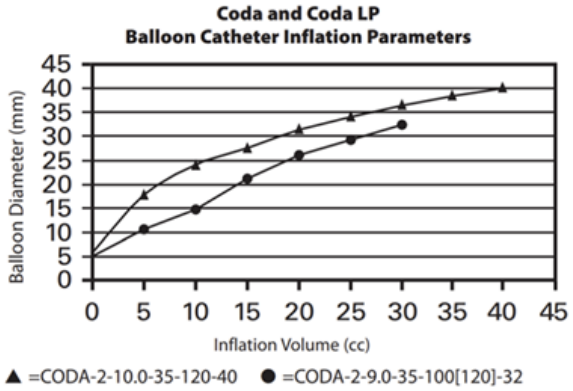

Figure 2. Coda Balloon Fill volume curves

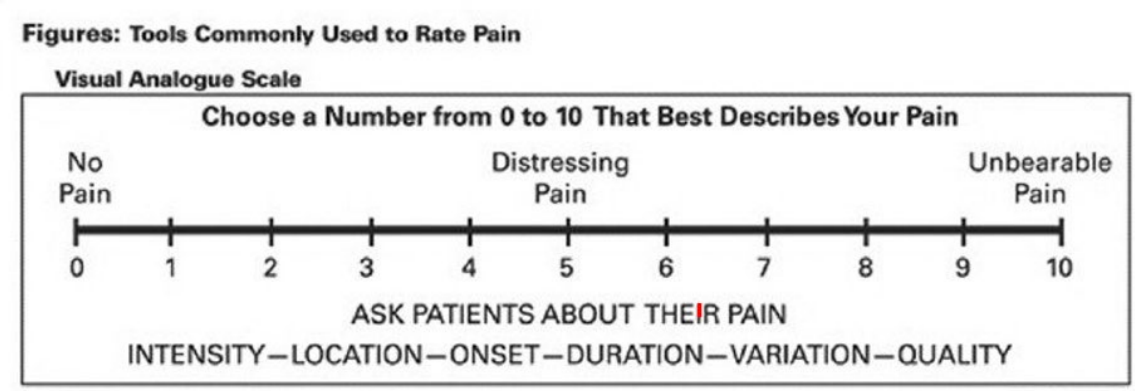

Figure 3. Visual analog scale for pain assessment

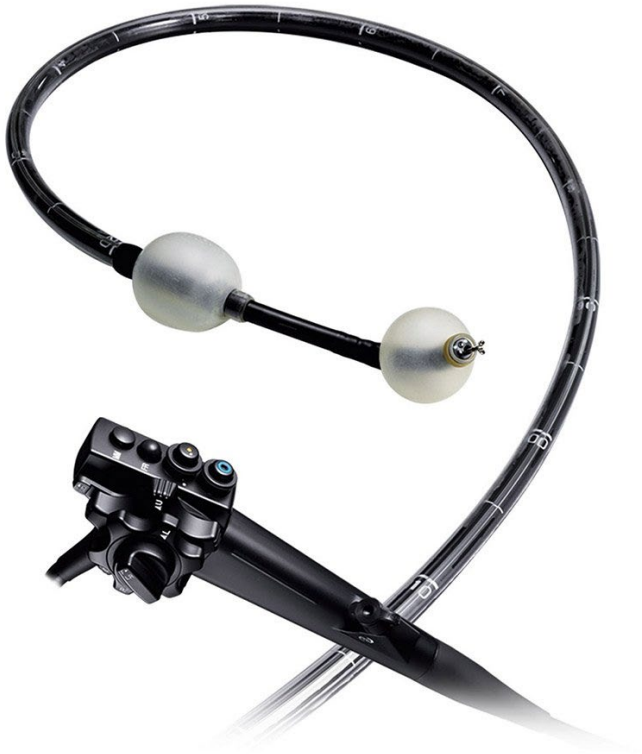

Figure 4. Double balloon enteroscope (©FUJIFILM)

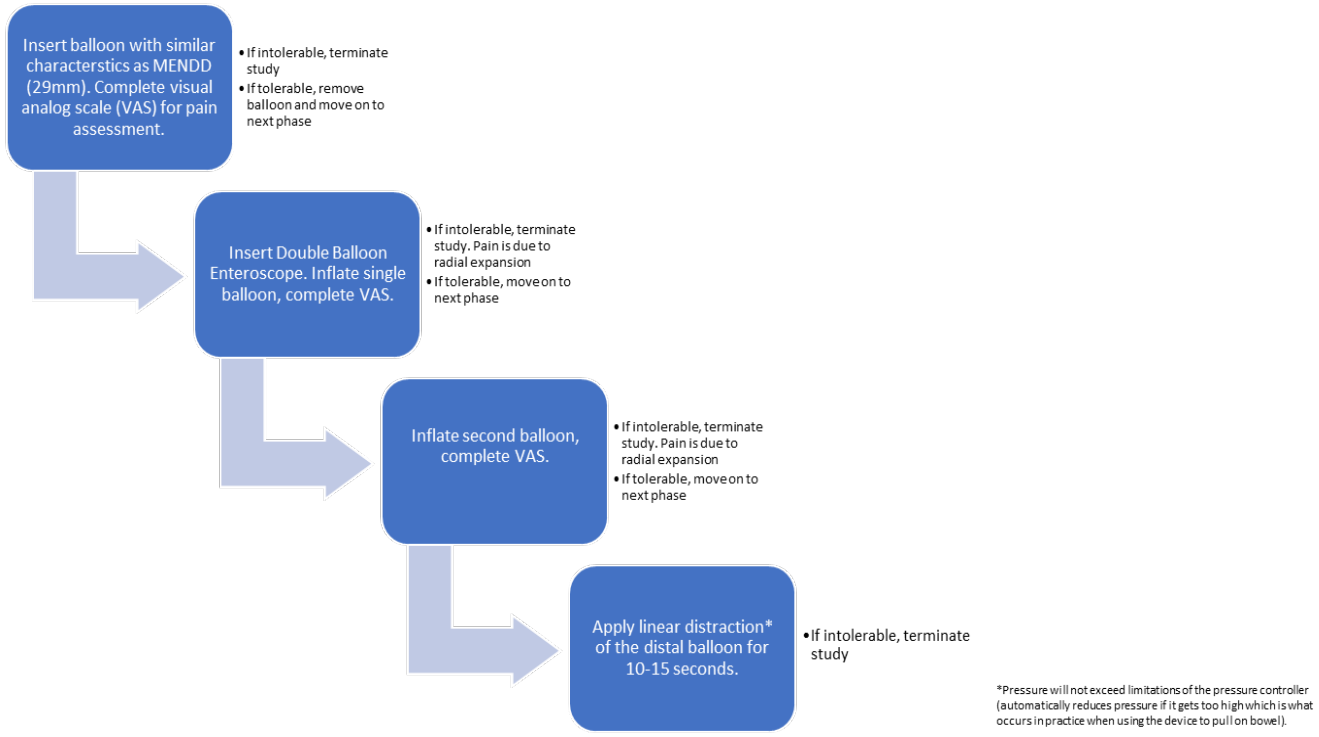

Figure 5. Adaptive study design

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