Medtronic **Clinical Investigation Plan**	
Clinical Investigation Plan/Study Title	Multicenter, prospective study comparing PillCam® Crohn's capsule endoscopy (CE) to ileocolonoscopy (IC) plus MRE for detection of active Crohn's Disease (CD) in the small bowel and colon in subjects with known CD and mucosal disease (the BLINK study)
Clinical Investigation Plan Identifier	COVSBCC0549
Study Product Name	PillCam® Crohn's capsule endoscopy system
NCT	NCT03241368
Document Version / Date	6.0 / 16November2018

Medtronic

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Clinical Investigation Plan Identifier	COVSBCC0549
Study Product Name	PillCam® Crohn's capsule endoscopy system
Sponsor/Local Sponsor	United States: Medtronic MITG Early Technologies GI Solutions A Medtronic company ("Medtronic") 555 Long Wharf Dr, New Haven, CT 06511 Phone: +(1)(203)562-1620 Europe: Medtronic MITG Early Technologies GI Solutions A Medtronic company ("Medtronic") Covidien Services Europe, Ltd., Block G, First Floor Cherrywood Business & Technology Park Loughlinstown, Dublin 18, Ireland Phone: +(353)-(1)-4393000 Israel: Medtronic MITG Early Technologies GI Solutions (Given Imaging Ltd.) A Medtronic company ("Medtronic") 2 Hacarmel St. New Industrial Park POB 258, 20692 Yoqneam, Israel Phone: +(972)-(4)-909-7700
Document Version	6.0 / 16November2018

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Confidentiality Statement

1. Investigator Statement

Study product Name	PillCam® Crohn's capsule endoscopy system
Sponsor	United States: Medtronic MITG Early Technologies GI Solutions A Medtronic company ("Medtronic") 555 Long Wharf Dr, New Haven, CT 06511 Phone: +(1)-(203)-562-1620 Europe: Medtronic MITG Early Technologies GI Solutions A Medtronic company ("Medtronic") Covidien Services Europe, Ltd., Block G, First Floor Cherrywood Business & Technology Park Loughlinstown, Dublin 18, Ireland Phone: +(353)-(1)-439300 Israel: Medtronic MITG Early Technologies GI Solutions (Given Imaging Ltd.) A Medtronic company ("Medtronic") 2 Hacarmel St. New Industrial Park POB 258, 20692 Yoqneam, Israel Phone: +(972)-(4)-909-7700
Clinical Investigation Plan Identifier	COVSBCC0549
Version Number/Date	Version 6.0 - 16November2018

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I agree to comply with United Stated Food and Drug Administration abbreviated requirements as defined in 21CFR812.2(b)(US) or local laws and regulations as required for post-market clinical trials (Outside of the US). I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Medtronic.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Medtronic. I will discuss this material with them to ensure that they are fully informed about the products and the study.

Investigator's Signature:	
Investigator's Name:	
Institution:	
Date:	

Table of Contents

2. Glossary

Term	Definition
ADL	Activities of Daily Living
AE	Adverse Event
BUN	Blood Urea Nitrogen
CBC	Complete Blood Cell Count
CD	Crohn's Disease
CE	Capsule Endoscopy
CFR	Code of Federal Regulations
CIP	Clinical Investigation Plan
CRP	C-reactive Protein
CTE	Computed Tomography Enterography
Device deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.
DMC	Data Monitoring Committee
DR	Data Recorder
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EC	Ethics Committee
ED	Emergency Department
EMA	European Medicines Agency
FDA	United States Food and Drug Administration

Term	Definition
FISP	Fast Imaging with Steady-state Free Precession
GCP	Good Clinical Practice
GRE	Gradient-Recalled Echo
GI	Gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
IBD	Inflammatory Bowel Disease
IC	Ileocolonoscopy
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exceptions
IFU	Instructions for Use; a manual or document accompanying a technical device that describes the directions by which the device should be used
Investigative site	An approved, participating study center/institution
Investigator	Individual member of the investigation site team designated and supervised by the principal investigator at an investigation site to perform critical clinical-investigation-related procedures or to make important clinical investigation-related decisions. NOTE An individual member of the investigation site team can also be called “sub-investigator” or “coinvestigator”.
IRB	Institutional Review Board
ISO	International Organization for Standardization
IV	Intravenous
MaRIA	Magnetic Resonance Index of Activity
MITG	Minimally Invasive Therapies Group
mITT	Modified Intent-To-Treat

Term	Definition
MRE	Magnetic Resonance Enterography
MRI	Magnetic Resonance Imaging
NPO	Nothing by mouth – no food or liquids
NPV	Negative Predictive Value
OC-RDC	Oracle Remote Data Capture
PEG	Polyethylene Glycol
PPV	Positive Predictive Value
RDC	Remote Data Capture
RCE	Relative Contrast Enhancement
SAE	Serious Adverse Event
SB	Small Bowel
SES-CD	Simple Endoscopic Score for Crohn's Disease
SF-ELS	Sulfate-Free Polyethylene Glycol Electrolyte Lavage Solution
SSFSE	Single-Shot Fast Spin Echo
WSI	Wall Signal Intensity
WT	Wall Thickness

3. Synopsis

Title	Multicenter, prospective study comparing PillCam® Crohn's capsule endoscopy (CE) to ileocolonoscopy (IC) plus MRE for detection of active Crohn's disease (CD) in the small bowel and colon in subjects with known CD and mucosal disease (the BLINK study)
Clinical Study Type	Multicenter, Prospective, Study
Product Name	PillCam® Crohn's Capsule Endoscopy System
Sponsor	United States: Medtronic MITG Early Technologies GI Solutions A Medtronic company ("Medtronic") 555 Long Wharf Dr, New Haven, CT 06511 Phone: +(1)-(203)-562-1620 Europe: Medtronic MITG Early Technologies GI Solutions A Medtronic company ("Medtronic") Covidien Services Europe, Ltd., Block G, First Floor Cherrywood Business & Technology Park Loughlinstown, Dublin 18, Ireland Phone: +(353)-(1)-439300 Israel: Medtronic MITG Early Technologies GI Solutions (Given Imaging Ltd.) A Medtronic company ("Medtronic") 2 Hacarmel St. New Industrial Park POB 258, 20692 Yoqneam, Israel Phone: +(972)-(4)-909-7700
Investigation Purpose	This study will evaluate the efficacy of PillCam Crohn's capsule endoscopy (CE) versus IC with MRE for detection of active Crohn's disease (CD) in the small bowel and colon in subjects with known CD and mucosal disease.
Product Status	Post-market
Primary Objective(s)	The primary objective of study is to assess the accuracy of CE versus IC plus MRE for detecting active CD, by visualizing the small bowel and colon in subjects with known CD and mucosal disease.

Secondary Objective(s)	• Specificity, negative predictive value (NPV), and positive predictive (PPV) value for active CD in the small bowel and colon by CE as compared to IC plus MRE. • Sensitivity, specificity, NPV, and PPV for active CD in designated bowel segments (proximal small bowel, terminal ileum, and colon) by CE as compared to IC plus MRE. • • Patient satisfaction • • Concomitant medication
Other Planned Analyses	[redacted]
Study Design	At baseline, subjects with known CD on routine clinical evaluation (e.g. history, physical exam, labs) and a history (within last 2 years) of mucosal disease (diagnosis based on radiologic, endoscopic, histologic, or other clinical evidence) will undergo MRE, CE, and IC, to assess presence or absence of CD in the small bowel and colon.
Study Location	United States, Israel, and Austria. Sites in the United States will include a minimum of 70% of total subjects; sites outside the US will be limited to 30% of subjects.
Sample Size	Up to 352 subjects.
Planned study duration	Based on the number of sites and enrollment rate, study duration is expected to be up to approximately 1.5 years. The expected duration of each subject's participation is approximately 3 months.
Planned # of Sites	Up to 40 investigational sites.
Video/Image Reading	Central readers will be used to read all videos/images and analyses will be based on these results. A consensus panel will be used if there are discrepancies in results between modalities at baseline. Capsule endoscopy and IC results will be read by gastroenterologists and MRE results will be read by radiologists.
Inclusion/Exclusion Criteria	*Inclusion Criteria:* 1. Subject has provided informed consent. 2. Subject is ≥ 18 years of age. 3. Subject is willing and able to comply with all aspects of the treatment and evaluation schedule. 4. Subject has known CD and a recent history (within last 2 years) of mucosal disease (based on radiologic, endoscopic, or histologic evidence) OR known CD and active disease, based on clinical judgment based on symptoms, laboratory data or other clinical information.

	Exclusion Criteria: 1. Subject has indeterminate, ulcerative, or antibiotic-associated colitis. 2. Subject has stool positive for ova and parasite or for *Clostridium difficile* toxins within 3 months prior to enrollment. 3. Subject with other known infectious cause of abdominal symptoms. 4. Subject with clinical evidence of renal disease within the past 6 months, defined as estimated glomerular filtration rate (GFR) outside of the normal reference range. 5. Subject with known history of intestinal obstruction or current obstructive symptoms, such as severe abdominal pain with accompanying nausea or vomiting, based on investigator judgment. 6. Subject with a diagnosis of gastroparesis or small bowel or large bowel dysmotility. 7. Subject with suspected or known bowel obstruction, stricture (defined as unequivocal proximal upstream dilation ≥ 2.5 cm), or fistula. 8. Subject has used non-steroidal anti-inflammatory drugs including aspirin, two times or more per week, during the 4 weeks preceding enrollment. Low dose aspirin regimens (≤ 100 mg daily) are acceptable and not exclusionary. 9. Subject suffers from any condition, such as swallowing problems, that precludes compliance with study and/or device instructions. 10. Subject with cardiac pacemaker or other implanted electromedical device. 11. Subject has any allergy or other known contraindication to the medications used in the study. 12. Subject is pregnant (documented by a positive pregnancy test) or is actively breast-feeding. 13. Subject is considered to be part of a vulnerable population (e.g. prisoners or those without sufficient mental capacity). 14. Subject has known contraindication to MRE or IC. 15. Subject has participated in a drug or device research study within 30 days of enrollment that may interfere with the subject's safety or ability to participate in the study. 16. Subject has any medical condition that would make it unsafe for them to participate, per the Investigator's discretion 17. Subject with ileostomy or colostomy, history of total or subtotal colectomy (including those with ileosigmoidostomy, and ileorectostomy

4. Introduction

4.1. Background

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) that has been a focus of attention due to its increasing incidence and prevalence around the world (1, 2). It involves any site of the gastrointestinal (GI) tract, but is most frequently localized to the terminal ileum and the proximal colon (3). Inflammation of the GI tract may ultimately lead to stricturing or perforating complications (4). Symptoms of CD include abdominal pain, diarrhea, weight loss, nausea, and vomiting. Long-term management of CD can be achieved with immunosuppressive or anti-inflammatory therapy, however most patients undergo repeated relapses and remission (5).

Video capsule endoscopy was first approved for clinical use in 2001 for the evaluation of the small bowel and has served to be an effective, noninvasive technique for imaging of the entire small-bowel mucosa (6). Contraindications for use of capsule endoscopy include history of bowel obstruction and known bowel strictures or swallowing disorders; and recent abdominal surgery (7). The Capsule Endoscopy System, PillCam® SB, PillCam® Crohn's, PillCam® Patency System and PillCam® COLON 2, are all FDA cleared for the US market in patients aged ≥ 18 years and carry the CE mark for the European market in patients aged ≥ 8 years. The PillCam® Crohn's Platform includes 1) the ingestible Crohn's capsule, 2) Data Recorder (DR3), PillCam® Software, and 4) Given® Workstation. The Crohn's capsule is specifically designed to image the small and large bowels. The Crohn's capsule is a two-headed video capsule with a field of view of 172 degrees in each head and has a frame of rate up to 35 frames per second.

The PillCam® Crohn's capsules and the COLON 2 capsules share hardware design, components and assembly and differ only in programming and operation mode, since the COLON 2 is designed to visualize the colonic mucosa while the Crohn's capsule is intended for expanded visualization of the small bowel and the colon. The COLON 2 system has proven to be safe and effective in previous clinical studies (8-10) (ClinicalTrials.gov: NCT01087528, NCT01269372). Pre-clinical studies for the Crohn's capsule have not been conducted, however clinical studies have been performed. To-date, there have been three performance studies that have assessed the Crohn's capsule. One study included CD subjects (ClinicalTrial.gov: NCT01631435), another study included ulcerative colitis subjects (Clinical Trial.gov: NCT02025777), and a third which included suspected or established IBD patients (Clinical Trial.gov: NCT02742714). NCT01631435 study was a multi-center, prospective, controlled study, designed to establish the effectiveness of the PillCam® Crohn's endoscopy platform as demonstrated by visualizing the small bowel and colon in subjects with active symptoms associated with CD. The primary objective was to evaluate the diagnostic yield of the Crohn's capsule in the colon and terminal ileum compared to ileocolonoscopy (IC) (11). A total of 66 subjects with signs and symptoms of CD completed the study procedures and were included in the efficacy analysis. The per-subject diagnostic yield rate was 83.3% for capsule endoscopy (CE) and 69.7% for IC. The yield difference was 13.6% (95% CI 2.6%-24.7%), with CE having a higher diagnostic yield rate for detection of active CD. The Crohn's capsule was also able to evaluate and detect active CD in the more proximal small bowel, which cannot be reached by IC. There was only one device-related serious adverse event (bowel obstruction) reported, however the event resolved without sequelae. Since the comparison of the two modalities in this study was limited

only to the terminal ileum and the colon, there is a need to evaluate the performance of the Crohn's capsule in the entire small bowel and colon compared to a gold standard.

Clinical management of patients with known CD involves monitoring of disease activity for maintenance of clinical remission, early detection of relapse, and prevention of complications associated with the disease or treatment (12). Both the best measure of disease activity in CD and the measurement method are in question. Recent studies have shown that inflammation of the intestinal mucosa is not firmly correlated with laboratory inflammatory markers and patients' symptoms (12-16). Mucosal healing, which is defined as restoration of normal mucosal appearance and complete absence of ulceration and inflammation, is now considered an accepted measure of disease activity in CD (12, 17). Evidence show that mucosal healing and deep remission are associated with improved long-term outcomes including reduced need for corticosteroid treatment, improved quality of life, and reduction in complications requiring hospitalization or surgery (12, 18, 19).

Ileocolonoscopy is currently the gold standard for mucosal disease evaluation in CD patients (20). There are limitations to this technique due to its invasive nature and possible requirement of analgesia and sedation (17). Ileocolonoscopy reaches only to the terminal ileum, thus eliminating evaluation of the more proximal small bowel. Even though the terminal ileum is the most commonly affected area in the small bowel in CD, approximately half of the patients with CD have lesions detected in the jejunum (21). The prevalence of jejunal lesions is higher in patients with terminal ileum disease and associated with increased risk of relapse; therefore evaluation of the entire small bowel is necessary for monitoring patients with CD.

If proximal small bowel involvement is suspected, patients may receive examination with small bowel capsule endoscopy and/or balloon-assisted enteroscopy in addition to IC (20). Cross-sectional imaging techniques including magnetic resonance enterography (MRE) and computed tomography enterography (CTE) may also be used to evaluate the small bowel, however these techniques have some disadvantages. Magnetic resonance enterography is costly and CTE involves exposure to radiation; both techniques require intravenous (IV) contrast medium and bowel distension with oral and/or rectal contrast. Since the PillCam® Crohn's capsule is designed to evaluate both the small bowel and colon, the device would eliminate the need of using two different techniques for evaluation of both segments in patients with CD (11). Capsule endoscopy is safe, noninvasive, and does not involve radiation exposure, therefore making it a preferable alternative modality for assessment of CD activity and evaluation of mucosal healing in patients with CD.

4.2. Purpose

This purpose of this study is to evaluate performance of the PillCam Crohn's capsule [referred to as capsule endoscopy (CE)] as compared to IC with MRE.

5. Objectives and Endpoints

5.1. Objectives

5.1.1. Primary Objective(s)

The primary objective of this multicenter, prospective study is to assess the accuracy of CE versus IC plus MRE for detecting active CD, by visualizing the small bowel and colon in subjects with known CD and mucosal disease.

5.1.2. Secondary Objective(s)

Secondary objectives include:

1. Specificity, negative predictive value (NPV), and positive predictive (PPV) value for active CD in the small bowel and colon by CE as compared to IC plus MRE.
2. Sensitivity, specificity, NPV, and PPV for active CD in designated bowel segments (proximal small bowel, terminal ileum, and colon) by CE as compared to IC plus MRE.
3. Patient satisfaction

5.2 Endpoints

5.2.1 Primary Endpoint

The primary endpoint is the sensitivity for detecting active CD in the small bowel and colon by CE as compared to IC plus MRE.

5.2.2 Secondary Endpoints

The following secondary endpoints will be assessed:

1. Specificity, negative predictive value (NPV), and positive predictive (PPV) value for active CD in the small bowel and colon by CE as compared to IC plus MRE (see Section 11.12.1).
2. Sensitivity, specificity, NPV, and PPV for active CD in designated bowel segments (proximal small bowel, terminal ileum, and colon) by CE as compared to IC plus MRE (see Section 11.12.1).
3. Patient satisfaction (see Appendix I).

5.2.3 Safety Endpoints

Adverse events (AEs) will be reported by number, severity, and relationship to the study procedures (imaging modality, colonoscopy), as described in Section 11. The recording of AEs for all enrolled subjects will begin with the start of baseline imaging procedures (MRE) and end 14 days following completion of the final baseline imaging procedure (IC). Subjects with AEs at 14 days following the IC procedure will be followed for 30 days or until event resolves, whichever comes first.

6. Study Design

This is a multicenter, prospective study, evaluating the efficacy of CE versus IC with MRE for detecting active CD in the small bowel and colon in subjects with known CD and a recent history (within last 2 years) of mucosal disease (based on radiologic, endoscopic, or histologic evidence) OR subjects with known CD and active disease based on clinical judgment based on symptoms, laboratory data or other clinical information. Subject population will include adult subjects (age ≥18 years).

At baseline, subjects with known CD on routine clinical evaluation (e.g. history, physical exam, labs) and a recent history of mucosal disease (within last 2 years and diagnosis based on radiologic, endoscopic, or histologic findings) OR subjects with known CD and active disease based on clinical judgment based on symptoms, laboratory data or other clinical information will undergo MRE, CE, and IC, to assess presence or absence of CD across the small and large bowel.

All CE and IC videos and MRE images will be evaluated by central readers. CE and IC videos and MRE images will be randomly distributed among the central readers.

The planned number of subjects is up to 352. A total of approximately 352 Crohn's capsules will be utilized in this study.

There are no procedures for the replacement of subjects.

Other than known contraindications and precautions of the PillCam® Crohn's system, described in the PillCam User Manual, there are no foreseeable factors that may compromise the outcome of the clinical investigation or the interpretation of results (e.g. baseline characteristics, concomitant medication, the use of other study products, or subject-related factors such as age, gender or lifestyle). If any adverse occurrences are identified, they will be assessed, reported and documented.

6.1. Duration

Subjects will be enrolled at up to 40 clinical sites in the United States, Israel, and Austria. United States sites will include a minimum of 70% of total subjects; sites outside the United States will be limited to 30% of subjects. The minimum number of subjects enrolled at each site participating in the study will be 0 as enrollment is expected to be challenging and there is a possibility that an individual site will be unable to enroll any subjects. The maximum number of subjects at each site will be 70 so that no more than 20% of the total study population will be enrolled at any individual site. Expected enrollment is 1 subject per site per month.

The planned number of subjects is up to 352. Based on the number of sites and enrollment rate, study duration is expected to be up to approximately 1.5 year. The expected duration of each subject's participation is approximately 3 months.

6.2. Rationale

This clinical study design was formulated in order to capture performance of the Crohn's capsule as compared to IC with MRE.

The combination of the two procedures (IC plus MRE) will allow evaluation of the entire colon and small bowel and can be compared to the single procedure with CE.

To-date, there have been few performance studies that have assessed the Crohn's capsule. One study included CD subjects (ClinicalTrial.gov: NCT01631435),another study included ulcerative colitis subjects (Clinical Trial.gov: NCT02025777) and a third included suspected or established IBD patients (Clinical Trial.gov: NCT02742714). Results from NCT01631435 study demonstrated that the diagnostic yield rate for active CD in the terminal ileum and colon was higher with CE compared to ileocolonoscopy. However, due to the small sample size (66 subjects in efficacy analysis), further studies are warranted to confirm these findings (11). Additionally, since the comparison of the two modalities in this study was limited only to the terminal ileum and the colon, there is a need to evaluate the performance of the Crohn's capsule in the entire small bowel and colon compared to a gold standard.

7. Product Description

7.1. General

The PillCam® Crohn's capsule endoscopy platform is comprised of four main subsystems: (1) an ingestible PillCam® Crohn's capsule; (2) PillCam® Recorder (DR); (3) PillCam® Software (Version 9.0); and (4) Given® Workstation. The PillCam® Crohn's capsule endoscopy platform includes the PillCam® Software, which is designed to focus on targeted pathologies detected with the capsule, and an audio-visual guidance platform integrated into the PillCam® Recorder that is intended to help guide the subject through the procedure. The PillCam® Crohn's capsule platform is fully compliant with all safety and radio standards and regulations similar to the currently marketed capsule Endoscopy Systems. PillCam® Crohn's has been approved for use in the US, Europe and Israel.

The device does not incorporate any medicinal product, human blood derivative or tissues of animal origin.

The PillCam® Crohn's capsule, specifically the capsule outer envelope, will be in contact with human tissues or body fluids after ingestion.

7.2. Dosage Form and Route of Administration

The PillCam® Crohn's capsule is intended to be swallowed by the patient (after appropriate bowel preparation and fasting) with a sip of water. Only one capsule will be ingested per endoscopy procedure. The device is intended to travel through the patient's gastrointestinal tract and be excreted naturally.

7.3. Manufacturer

PillCam® Crohn's capsule endoscopy system is manufactured by Medtronic Minimally Invasive Therapies Group (MITG) Early Technologies GI Solutions (formerly GIVEN Imaging).

7.4. Packaging

All equipment associated with the clinical study will be identified with visible markings stating, "For clinical trial use only." Labeling of devices will be provided in accordance with local language requirements.

7.5. Intended Population

The PillCam® Crohn's capsule indications for use in US are:

The PillCam® Crohn's capsule is intended for visualization of the small bowel and colonic mucosa.

- It may be used in the visualization and monitoring of lesions in the small bowel that may indicate Crohn's disease not detected by upper and lower endoscopy, and for visualization of inflammation of the colon in patients with colonoscopy-diagnosed Crohn's disease.
- It may be used in the visualization and monitoring in the small bowel of lesions that may be a source of obscure bleeding (either overt or occult) or that may be potential causes of iron deficiency anemia (IDA) not detected by initial upper and lower endoscopy.
- The PillCam® Crohn's capsule may be used as a tool in the detection of abnormalities of the small bowel and colon. It is intended for use in adults

The PillCam® Crohn's capsule indications for use in Europe and Israel are:

The PillCam® Crohn's capsule is intended for visualization of the small bowel and colonic mucosa.

- It may be used in the visualization and monitoring of lesions that may indicate Crohn's disease.
- It may be used in the visualization and monitoring of lesions that may be a source of obscure bleeding (either overt or occult).
- It may be used in the visualization and monitoring of lesions that may be potential causes of iron deficiency anemia (IDA).

• The PillCam® Crohn's capsule may be used as a tool in the detection of abnormalities of the small bowel and colon. It is intended for use in adults and children from 8 years of age

The PillCam® Crohn's capsule is contraindicated for use under the following conditions:

- In patients with known or suspected gastrointestinal obstruction, strictures, or fistulas based on the clinical picture or pre-procedure pre-ingestion testing and profile.
- In patients with cardiac pacemakers or other implanted electromedical devices.

In patients with dysphagia or other swallowing disorders.

7.6. Equipment

7.6.1 PillCam® Crohn's Capsule

PillCam® Crohn's capsule has been designed to achieve more complete coverage of the small bowel and colonic mucosa, so its adaptive frame rate is set to ensure that images of both anatomical regions are captured for analysis. Features include:

- Optics with super wide field of view (172 degrees for each imaging head).
- Higher and adaptive frame rate (up to 35 frames per second). High frame rate is activated when the capsule enters the small bowel.

The PillCam® Crohn's capsule is provided as a single use disposable product. PillCam® Crohn's capsule is ingested by the subject after bowel preparation, with a sip of water. The capsule will be ingested a maximum of three times for the entire duration of the study (ingestion at baseline and 6- and 12-month follow-ups for subjects randomized to CE arm; ingestion at baseline only for subjects randomized to IC with or without MRE arm. The capsule will be ingested at baseline to evaluate presence/absence of active CD in the small bowel and colon. At 6- and 12-month follow-ups, the capsule will be ingested to evaluate mucosal healing.

7.6.2 PillCam Recorder (DR3)

The new generation of PillCam® Recorder used in this study has enhanced communication features, computing power, and incorporates a Real-Time Viewing screen. These modifications are detailed in the PillCam User Manual.

7.6.3 PillCam Workstation

The Workstation is a modified standard personal computer that is intended for reviewing the Pillcam® Software (Version 9.0) videos generated from the images acquired by the capsule, interpretation and analysis of the acquired data, and for generating reports.

The software program used for video creation and interpretation has several useful features incorporated that aid the physician during the video review.

7.7. Product Use

A member of the Medtronic Technical Support team will install the PillCam Workstation at each participating research site and ensure all equipment is fully functional. Information regarding Instructions for Installation and Use can be found in the provided PillCam Endoscopy User Manual (US PillCam User Manual for sites in the US and International PillCam User Manual for sites outside of the US). Specific instructions for Site Investigators for transferring video images to the Core Imaging Lab will be provided separately.

7.8. Product Training Requirements

Gastroenterologists selected as Principal Investigators participating in the clinical study and the associated clinical study staff will receive training on the device and system (including procedural use, device characteristics, shelf life and storage requirements, warnings, precautions, and contraindications). It is the responsibility of the Principal Investigator at each participating site to assure any staff performing tasks related to the clinical trial (Study Coordinators, Study Nurses, Radiologists, Gastroenterologist Sub-Investigators, etc) have been properly trained, training documented, and included on the Delegation of Authority Log.

For CE videos, central readers will be experienced gastroenterologists trained to read PillCam® Software videos. Experience and training are required in order to accurately interpret capsule endoscopy videos. The central readers will be trained by the Sponsor on reading PillCam® Software videos. The training will include PillCam® version 9.0 software and PillCam® Software videos evaluation training.

Central readers will be experienced gastroenterologists for IC videos and radiologists for MRE images.

7.9. Product Receipt and Tracking

The Sponsor will initiate shipment of equipment to the site upon receipt of all required documents (e.g., Site Qualification Report, fully executed Clinical Trial Agreement). The site may not use the equipment/product or begin subject enrollment until IRB/EC approval is received and the Sponsor provides notification of Site Activation. The Sponsor will maintain tracking for all shipment documentation. Prior to any shipment, the site will be informed by the Sponsor on the upcoming shipment, expected arrival date, and content of the shipment. The site should confirm receipt of the shipment and maintain shipping receipts.

For each capsule, the appropriate Device Tracking and Device Identification electronic Case Report Forms (eCRFs) should be completed upon receipt and upon dispensing, respectively, by the site.

7.10. Product Storage

PillCam® Crohn's capsule should be stored in an area where the temperature is controlled between 0-25°C. As storage is at ambient temperature and PillCam Crohn's capsule is a readily marketed product, temperature logs are not required for BLINK; however storage area should be locked/secure with access limited only to approved study staff to avoid use of the study device on non-trial patients.

To avoid accidental activation (blinking) of the capsule while in its box:

- Keep the PillCam capsules in their box until use.
- Store the PillCam capsules only in the packaging supplied with the product.
- Do not use a PillCam capsule if the packaging is damaged.
- Keep the capsule package away from strong magnetic fields (such as magnetic resonance imaging [MRI] devices).
- Stack PillCam capsule boxes with the clear lid facing up only; never stack capsule boxes lid to lid.
- Keep metal objects away from the lid of the capsule box.
- After ingesting the PillCam capsule, instruct the patient not to sit on bare metal surfaces, such as chairs with a metal sitting area, during the procedure.

7.11. Product Return

At the termination of the study, all unused study material must be returned with the corresponding documentation as directed by Medtronic. Any capsule that reaches its expiration date before it has been dispensed should be returned to the Sponsor or destroyed on site; with proper documentation in either scenario. The Device Tracking eCRF should be completed once a capsule is dispensed, returned or destroyed.

7.12. Product Accountability

Good clinical research practice requires that investigators and research teams ensure accurate accountability for any device used in a research study. It is expected that all devices will be used in the manner intended during the study, that they will be stored under appropriately controlled conditions and that they will be used only by (on) subjects who have consented to participate in the research study. Access should be limited to designated study staff only. Device accountability should be managed through the site's completion of the Device Tracking and Device Identification eCRFs.

Any device being used in clinical research must be strictly accounted for and will not be shipped to any site unless all of the necessary approvals (e.g. Regulatory, IRB/EC) have been received.

This includes keeping records of:

1. Site receipt and inventory management
2. Storage
3. Subject Disbursement
4. Return (by Subjects and Center) and/or disposal

It is the site's responsibility to return the PillCam Workstation and Recorder to Medtronic within 30 days of the End of Study.

8. Selection of Subjects

8.1. Study Population

Subjects aged ≥18 years with known CD and mucosal disease.

8.2. Subject Enrollment

After being informed of the nature of the study, the subject will sign a written informed consent form (ICF) that has been approved by the Sponsor and the appropriate IRB/ EC of the respective clinical site or the central IRB/EC during the screening visit. A subject is considered enrolled in the study when the ICF is signed and it is determined that all inclusion/exclusion criteria are met. Inclusion/Exclusion may only be determined once screening lab results (C. Dificile, Stool O&P) and pregnancy test (as required) are reviewed. Documented ICF will be collected prior to any data collection. See Section 11.4 for details on subject informed consent procedure.

8.3. Inclusion Criteria

1. Subject has provided informed consent.
2. Subject is ≥ 18 years of age.
3. Subject is willing and able to comply with all aspects of the treatment and evaluation schedule.
4. Subject has known CD and a recent history (within last 2 years) of mucosal disease (based on radiologic, endoscopic, or histologic evidence) OR known CD and active disease, based on clinical judgment based on symptoms, laboratory data or other clinical information.

8.4. Exclusion Criteria

1. Subject has indeterminate, ulcerative, or antibiotic-associated colitis.
2. Subject has stool positive for ova and parasite or for *Clostridium difficile* toxins within 3 months prior to enrollment.
3. Subject with other known infectious cause of abdominal symptoms.
4. Subject with clinical evidence of renal disease within the past 6 months, defined as estimated glomerular filtration rate (GFR) outside of the normal reference range.
5. Subject with known history of intestinal obstruction or current obstructive symptoms, such as severe abdominal pain with accompanying nausea or vomiting, based on investigator judgment.
6. Subject with a diagnosis of gastroparesis or small bowel or large bowel dysmotility.
7. Subject with suspected or known bowel obstruction, stricture (defined as unequivocal proximal upstream dilation ≥ 2.5 cm), or fistula.

8. Subject has used non-steroidal anti-inflammatory drugs including aspirin, two times or more per week, during the 4 weeks preceding enrollment. Low dose aspirin regimens (≤100 mg daily) are acceptable and not exclusionary.
9. Subject suffers from any condition, such as swallowing problems, that precludes compliance with study and/or device instructions.
10. Subject with cardiac pacemaker or other implanted electromedical device.
11. Subject has any allergy or other known contraindication to the medications used in the study.
12. Subject is pregnant (documented by a positive pregnancy test) or is actively breast-feeding.
13. Subject is considered to be part of a vulnerable population (e.g. prisoners or those without sufficient mental capacity).
14. Subject has known contraindication to MRE or IC.
15. Subject has participated in a drug or device research study within 30 days of enrollment that may interfere with the subject's safety or ability to participate in the study.
16. Subject has any medical condition that would make it unsafe for them to participate, per the Investigator's discretion
17. Subject with ileostomy or colostomy, history of total or subtotal colectomy (including those with ileosigmoidostomy, and ileorectostomy

9. Study Procedures

9.1. Schedule of Events

Table 1: Study schedule and Site Collection Data

	Screening (No more than 30 days prior to first Baseline Procedure - MRE)	Baseline Procedures [1, 2]
Informed consent[1]	X	
Eligibility criteria	X	
Demographics	X	
Montreal classification[3]	X	
Medical history	X	
Previous GI procedures	X	
Surgical history	X	

Laboratory tests[4, 5]	X	X
Pregnancy test[4, 5]	X	
Concomitant medications		X
PillCam® patency test		X
IC, MRE AND PillCam® Crohn's[1]		X
Patient satisfaction[6]		X
Adverse events		X
Study deviations	X	X
Study exit		X

1. Informed consent may be collected more than 30 days prior to first baseline imaging procedure – MRE.

2. All baseline imaging procedures (MRE, patency capsule [if needed], CE, and IC) need to be performed within 4 weeks. If MRE demonstrates a stricture with unequivocal upstream dilatation of at least 2.5cm, then the subject must be exited from further study participation. If any other stricture is identified on MRE, or there is clinical suspicion that the PillCam Crohn's capsule will not be excreted naturally, then a patency capsule procedure needs to be performed. IC will take place on the same or following day after CE.

3. See Appendix A for more details.
4. See Appendix B for a complete listing of tests to be performed.

5. Please note that Screening Laboratory results for Stool O&P, C.Difficile and pregnancy test are required to determine subject inclusion/exclusion. Screening Laboratory results MUST be evaluated prior to enrolling a subject in the trial. Baseline labs must be collected and results reviewed within 14 days prior to MRE.

6. The patient satisfaction questionnaire will be completed by subjects after the last baseline procedure (IC) in person or via phone on the same or next business day of IC procedure completion.

9.2. Subject Consent

Informed consent will be obtained before any study-specific procedures are initiated or data collected. Principal Investigator or his/her authorized designee will conduct the informed consent process.

At the screening visit, subjects will be approached to obtain written informed consent prior to any data collection. Once the ICF is collected, screening of subject will follow. The purpose of the study and the benefits and risks of the procedures will be explained to the subject and the consent process must be documented accordingly in the medical record. Subjects who agree to study participation must sign a Sponsor and IRB/EC-approved ICF. Consent to participate in this study must be given in writing. Subjects that are unable to give consent will not be included in study.

Informed Consent will be obtained in accordance with the CFR Title 21, Part 50 (US) or ISO14155:2011 (Austria and Israel) as well as the Declaration of Helsinki. The Investigator or designee must obtain written informed consent before any clinical study related activity takes place. Prior to entry into the study, the IRB/EC and Medtronic-approved ICF form, and the Health Insurance Portability and

Accountability Act (HIPAA) Authorization Form (US only) will be given to each subject. The Investigator or designee will fully inform the subject of all aspects of the clinical study that are relevant to the subject's decision to participate in the clinical study (e.g. purpose and duration of the study, requirements of the subject during the study, potential risks and possible benefits associated with participation in this study). All items addressed in the Informed Consent Form must be explained. The language used shall be as non-technical as possible and must be understandable to the subjects.

The subject must have ample time and opportunity to read and understand the Informed Consent Form, to inquire about details of the clinical study, and to decide whether or not to participate in the clinical study. All questions about the clinical study should be answered to the satisfaction of the subject. In the case that a subject is unable to read, an impartial witness must also be present and sign the informed consent to confirm that the research has been clearly explained and all of the subject's questions have been answered.

Neither the Investigator, nor the investigation site staff shall coerce or unduly influence a subject to participate or to continue to participate in the clinical study. The informed consent process shall not waive or appear to waive the subject's rights.

When the subject decides to participate in the clinical study, the HIPAA Form (US only) and the Informed Consent Form must be personally signed and dated by the subject

After all persons have signed and dated the Informed Consent Form, the Investigator must provide the subject with a copy.

Medtronic will inform the Investigators whenever information becomes available that may be relevant to the subject's confirmed participation in the clinical study. The Investigator or his/her authorized designee should inform the subject in a timely manner.

Medtronic will revise the written Informed Consent Form whenever new information becomes available that may be relevant to the subject's confirmed participation in the clinical study. The revised information will be sent to the Investigator for approval by the IRB/EC. After approval by the IRB/EC, a copy of this information must be provided to the participating subjects, and the informed consent process as described above needs to be repeated.

If the ICF is amended during the course of the study, the IRB/EC will determine:

- Whether or not active subjects should be re-consented at their next visit and
- Whether or not subjects who have completed the study at the time of the amendment should repeat the informed consent process.

Subjects will be informed that qualified personnel from the investigational center, the Sponsor (Medtronic), agencies such as the FDA/local regulatory authority in Europe (Austria) and Israel and/or the IRB/EC may have access to clinic records that reveal their identity.

The investigational center must report the following violations to their IRB/EC:

- Failure to obtain informed consent from subject.
- Failure to obtain informed consent prior to performing one or more study procedures.
- Failure to maintain ICFs on file for all subjects who have provided informed consent.

- Use of an ICF that has not received approval from the IRB/EC.
- Use of an incorrect version of the ICF.

9.3. Subject Screening

All subjects must be properly consented prior to any screening and/or baseline procedures. Once consented, a screening visit will be performed within 30 days prior to baseline procedures to assess pre-procedure eligibility. In the event that the screening and eligibility assessment takes place more than 30 days prior to the planned procedure date, the Investigator should contact the subject prior to the procedure date to assure there is no change in the subject's medical condition.

Screening visit (No more than 30 days prior to first Baseline Procedure - MRE) - the following assessment will be performed at screening and the results will be recorded on the appropriate subject eCRFs:

- Informed consent (may be completed >30 days prior to MRE)
- Inclusion/Exclusion criteria
    - Please note evaluation of results of several Screening Laboratory tests (Stool O&P, C. Difficile, pregnancy) is required to assess Inclusion/Exclusion criteria.
- Demographics – including gender, year of birth, height, and weight.
- Montreal classification – see Appendix A.
- Medical history – relevant (related to inclusion/exclusion criteria) medical historywithin the last 2 years will be assessed including recent history of mucosal disease, history of swallowing problems, history of intestinal stricture, presence of implanted electromedical device, any known allergies, current GI symptoms (e.g. obstructive symptoms, history of gastroparesis) or other GI motility disorder, contraindication to MRE or IC, and enrollment in any other drug/device study within 30 days.
- Previous GI procedures – all previous IBD–related procedures within the last 5 years (including but not limited to IC, MRE, CTE, capsule endoscopy, esophagogastroduodenoscopy), including date and results from the last procedure will be documented.
- Surgical history – other GI-related surgical procedures not captured under 'previous GI procedures.'
- Prior and concomitant medications – All current medications, including type and dose, need to be reported. Subject will be excluded from the study if he/she has used non-steroidal anti-inflammatory drugs including aspirin, two times or more per week, during the 4 weeks preceding enrollment. Low dose aspirin regimens (≤100 mg daily) are acceptable and not exclusionary. Additionally, subjects must not use NSAIDs including aspirin, two times or more per week, from the time of enrollment until completion of the IC procedure.
- Laboratory tests – See Appendix B.
- Pregnancy test – see Appendix B.
- Study deviations

A subject is considered enrolled in the study when the ICF is signed (See Section 11.4 for details) and it is determined that all inclusion/exclusion criteria are met. Documented ICF will be collected prior to any data collection. Subjects who provide study consent, but then are determined to be ineligible prior to the MRE procedure at baseline will be considered a screen failure and will not require additional study follow-up visits. The reason for the screen failure will be clearly captured on the applicable eCRFs.

9.4. Baseline

All baseline procedures must be completed within 4 weeks (completion of MRE to completion of IC). All baseline labs must be completed prior to, but no more than 14 days before, MRE. Subjects will first undergo MRE evaluation as outlined in Appendix C. If MRE shows evidence of a stricture with unequivocal proximal upstream dilation ≥ 2.5 cm, based on local reading results, then the subject will be exitedfrom the study. If any other stricture is identified on MRE, based on local reading, or if there is clinical suspicion that the PillCam Crohn's capsule will not be excreted naturally, then
the subject must undergo a Patency procedure before proceeding with the CE procedure and then the IC procedure, all within 4 weeks after the MRE..

Subjects whose patency cannot be confirmed through either the baseline MRE procedure or capsule patency study will be discontinued from the study.

Prior to the CE procedure, subjects will be instructed to perform the bowel preparation procedure and follow a detailed dietary regimen. All sites and subjects will follow the same preparation procedure as outlined in Appendix E1 for the CE procedure.

Following completion of the CE procedure (either the same or following day), the subjects will undergo an IC procedure with intubation of the terminal ileum, if possible. In case the IC procedure follows the CE procedure on the same day, it is recommended to start the CE procedure early in the morning. If the IC procedure is done the following morning, the subject will stay on clear liquid diet (or NPO, if required per physician's discretion for sedation) and receive additional preparation per physician discretion. Day 0 will be in reference to the last day of baseline procedures, which will be the day of completion of IC.

Baseline visit - the following assessment will be performed at baseline and the results will be recorded on the appropriate subject eCRFs:

- Laboratory tests– see Appendix B
- Concomitant medications:

  At baseline subjects must not use NSAIDs including aspirin, two times or more per week, during the 4 weeks preceding CE, IC and MRE procedures. Low dose aspirin (<100 mg daily) regimens are acceptable and not exclusionary.
  All current medications, including type and dose, need to be reported
  Need to specify related/non-related medication for CD
- Patient satisfaction – see Appendix I. At baseline, questionnaires will be completed by subjects after IC. If subjects are unable to complete the questionnaires immediately following IC due to sedation, appropriately delegated research staff may interview the subject by phone the following day in order to obtain the subject's responses.

- Adverse events
- Study deviations

9.5. Medication Compliance

Subjects will take a preparation for CE, IC, and MRE. The CE system has a regimen alert system to remind subjects to take the prescribed preparation materials. There will also be medications taken by subjects as prescribed by their respective physicians to treat Crohn's disease. The medication usage will be tracked in appropriate eCRFs.

9.6. Magnetic Resonance Enterography

Sites may be asked to submit sample imaging studies to the Imaging Core Lab. The sample cases demonstrate that local site can follow the study protocol for the MRE procedure before subject recruitment begins. If there are errors in the sample imaging studies, corrections need to be made before enrollment begins.

MRE will be performed by local radiologists with experience in conventional and GI MRI who have been properly trained to the study protocol and included on the Delegation of Authority Log. MRE procedure must be performed in alignment with Appendix C and the BLINK Imaging Manual. A 1.5T or 3T whole-body MRI unit will be used. All sites and all subjects will follow the same procedure as outlined in Appendix C for MRE.

The MRE images must be uploaded and transferred to the Imaging Core Lab (ICON) within 48 hours of completion of the procedure, based on instructions provided.

9.7. PillCam Patency Study

If a stricture with unequivocal upstream dilation of at least 2.5cm is evident on baseline MRE (based on local read), then the subject must be exited from further participation in the study. If any other stricture is evident on baseline MRE, or there is clinical suspicion that the PillCam Crohn's capsule will not be excreted naturally, then a PillCam Patency procedure (Appendix D) should be performed prior to the baseline CE procedure.

9.8. Capsule Endoscopy Procedure

Subjects will be instructed to perform a preparation procedure and follow a detailed dietary regimen prior to and during the CE procedure. All preparation products will be standard GI cleansing products approved by FDA and European Medicines Agency (EMA). All sites and all subjects will follow the same preparation procedure as outlined in Appendix E1 for the CE procedure.

CE procedure must be performed per instruction provided in Appendix E1 and the BLINK Imaging Manual. During the CE procedure, subjects will be asked to use a Subject Instructions Form (Appendix E2) to document their activities. This form will be used to document the subject's adherence to the procedure steps. The Subject Instructions Form will also serve as source data for eCRF entries. Trained

Medtronic personnel may be present at the capsule ingestion and at study follow-up visits. The role of the Medtronic person is to give technical support only.

All CE videos and raw data files will be downloaded to the PillCam work station and then saved in a digital format on the provided external hard drive. The CE video files must be uploaded and transferred to the Imaging Core Lab (ICON) within 48 hours of the completion of the procedure, based on instructions provided in the BLINK Imaging Manual. The raw data files should be maintained on the external hard drive and will be collected by Medtronic personnel.

9.9. Ileocolonoscopy

The IC will be performed on the same or following day after the CE procedure. To avoid repetitive bowel preparation for subsequent colonoscopy, the CE bowel preparation (Appendix E1) is to be followed at baseline. If IC is done the following day, the subject will stay on clear liquid diet (or NPO, based on physician's discretion for sedation) and receive additional preparation per physician discretion.

Prior to discharge, the subject will be instructed to notify study staff in case of any abdominal pain, vomiting or other GI problems.

The IC examination will be recorded in digital format. The site number and subject number (NOT name) should appear in the recorded video either by inserting the information to the recording or by taking a video recording at the beginning of the procedure video with the endoscope of the site and subject number written on a piece of paper.

All IC videos will be saved in a digital format (an external hard drive will be provided, if necessary). The IC videos must be sent to the Imaging Core Lab (ICON) within 48 hours, based on instructions provided.

9.10. Central Reader Image/Video Reading

All CE and IC videos and MRE images will be randomly distributed to and evaluated by central readers at an Imaging Core Lab. Central readers will be blinded to the site and subject from which the videos/images they are assigned originate.

All study analyses will be based on the results of the central readers. A consensus panel will be used if there are discrepancies in results between modalities at baseline.

In cases when an imaging modality is not available for a given segment (small bowel, TI, and/or colon), that modality will be considered "null" for the segment and will not be used to assess modality agreement or disease activity for the segment. The available modality or modalities will be reviewed by central readers and (if necessary) the Consensus Panel and used to assess disease activity in these cases.

Detailed instructions will be provided to sites for transferring videos/images to the Imaging Core Lab via the BLINK Imaging Manual. Detailed reader instructions will be provided to the central readers via the Imaging Core Lab. All central readers must read each video or image independently without input from

other readers, investigators, or other site staff. Each reader will produce an independent report (CE Readers) and complete appropriate eCRFs for each video or image assigned to them.

9.10.1 Imaging Scores for Central Reading

Active CD, and subtle (defined as ulcers ≤ 5mm) lesions will be assessed with central reader results across the three modalities.

Presence of active CD in the proximal small bowel, terminal ileum, and colon will be assessed at baseline (see Appendix G for more details). The scores detailed below will be used to compare the accuracy (sensitivity, specificity, NPV, PPV) of CE and IC plus MRE in the identification of active CD in the small bowel and colon. The combination of all three procedures (MRE, CE, and IC) will serve as the gold standard.

Additionally, subgroup analyses will be performed to compare the accuracy of CE and IC plus MRE in the following designated bowel segments: proximal small bowel, terminal ileum, and colon. The following procedures will serve as the gold standard in the designated bowel segments: MRE+CE in the proximal small bowel, MRE+CE+IC in the terminal ileum, and CE+IC in the colon.

Capsule Endoscopy Scores:

The scores used for identification of active CD will be the Lewis score (Appendix H1) and Simple Endoscopic Score for Crohn's Disease Index (SES-CD) (Appendix H2) for CE. The Lewis score will be used to evaluate active CD in the proximal small bowel and the SES-CD will be used for the terminal ileum and colon.

Ileocolonoscopy Score:

The score used for identification of active CD will be the SES-CD (Appendix H2) score for IC. SES-CD score will be used to evaluate active CD in the terminal ileum and colon.

MRE Score:

The score used for identification of active CD will be the Magnetic Resonance Index of Activity (MaRIA) score for MRE (Appendix H3). The MaRIA score will be used to evaluate active CD in the small bowel (proximal and terminal ileum).

Table 2: Central Reader Collection Data

	Screening	Baseline Procedures
Presence of Active CD[1]		X
Subtle lesion		X
Bowel cleansing level scale[2]		X

1. Presence of active CD will be used to calculate accuracy measures comparing CE to IC plus MRE. Active CD will be assessed based on the following scores: the Lewis score (see Appendix H1) will be used to evaluate the proximal small bowel with CE; the SES-CD scores (see Appendix H2) will be used to evaluate both the terminal ileum and colon with CE and IC; and the MaRIA (see Appendix H3) score will be used to evaluate the small bowel (proximal and terminal ileum) with MRE.
2. Following bowel preparation, the bowel cleansing level scale as detected with CE (see Appendix E4)/IC (see Appendix F3) will be collected.

9.11. Assessment of Efficacy

Data for accuracy of CE versus IC plus MRE for detecting active CD will be collected and evaluated by central readers after all baseline procedures (MRE, CE, and IC) have been completed. All CE and IC videos and MRE images will be randomly distributed to and evaluated by central readers. Presence of active CD will be used to calculate accuracy measures comparing CE to IC plus MRE. Active CD will be assessed based on the following scores: the Lewis score (see Appendix H1) will be used to evaluate the proximal small bowel with CE; the SES-CD scores (see Appendix H2) will be used to evaluate both the terminal ileum and colon with CE and IC; and the MaRIA (see Appendix H3) score will be used to evaluate the small bowel (proximal and terminal ileum) with MRE. See Section 9.13.1 for details on imaging scores for central reading.

Each reader will produce an independent report (CE readers only) and complete appropriate eCRFs for each video or image assigned to them.

9.12. Assessment of Safety

Type, incidence, severity, duration, and procedure/device relationship of adverse events (AEs) will be collected. AEs for all enrolled subjects will be collected from the start of baseline imaging procedures (MRE) and end 14 days after completion of the last imaging procedure (IC). Subjects with AEs at 14

days after the IC procedure will be followed for 30 days or until event resolves, whichever comes first. Adverse event data will be collected and reported on eCRFs.

For safety analyses, adverse events will be summarized using frequency counts and percentages. Descriptive statistics will be provided by study arm and by severity and relationship, according to the definitions in Section 11. Between groups comparison will be performed by Chi-square test or Fisher's exact test as appropriate**.** Individual listings of adverse events, (including modifications and deleted events), including event type, start date, duration, severity, and device-relatedness will be provided as appropriate.

9.13. Recording Data

This study will utilize an electronic database and eCRF. All data requested on the eCRF are considered required. Data points not collected and/or recorded will be considered deviations unless otherwise specified. Procedures used for data review, database cleaning, and issuing/resolving data queries will be included in the Data Management Plan.

The Principal Investigator must ensure the accuracy and completeness of the recorded data and then provide his/her signature on the appropriate eCRFs. The Investigator's electronic signature for specific eCRFs will be documented in compliance with local regulations. Changes to data previously submitted to the Sponsor will be reviewed for potential AE and complaint data and will require a new signature by the Investigator to acknowledge/approve the changes.

Visual and/or computer data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the Oracle Remote Data Capture (OC-RDC) system and will be issued to the site for appropriate response. The site staff will be responsible for resolving all queries in the database.

This study will be using a 21 CFR Part 11 compliant electronic data capture system. All system level validation documentation is retained within the Information Systems group.

9.14. Deviation Handling

No changes to the protocol will be permitted without the written approval from Medtronic, the IRB/EC, and Competent Authority. The investigator is not allowed to deviate from the Clinical Investigation Plan (CIP), except under emergency circumstances to protect the rights, safety and well-being of human subjects. The investigator must notify Medtronic and the reviewing IRB/EC of any deviation, which will be recorded in the eCRF, from the CIP when specific to the protection of the life or physical well-being of a subject in an emergency. Such notice must be given as soon as possible, but in no event later than 5 working days after the emergency has occurred. Except in such an emergency, prior written approval by Medtronic is required for changes in or deviations from the CIP. If these changes or deviations affect the scientific soundness of the CIP or the rights, safety, or welfare of human subjects the IRB/EC will also be notified. All other deviations will be reported per the site's IRB/EC deviation policy. Should any deviations from the CIP occur, these will be reviewed by Medtronic for their clinical significance. If the event is performed without written approval from all parties, the investigator may be terminated from the study. Corrective and preventive actions and principal investigator disqualification will be included in the Clinical Study Management Plan and/or Monitoring Plan. If further escalation is needed, it may result in

Corrective and Preventive Action (CAPA), suspension, or termination. If it is determined that there is investigator fraud, or strong evidence of fraud, the course of action may include, but is not limited to: potential exclusion from analyses, site closure, notification of the responsible IRB/EC of the actions to be taken, notification of key stakeholders and/or study team of the actions to be taken, notification of appropriate regulatory authority(ies) and/or restrictions on future participation in clinical studies.

9.15. Subject Withdrawal or Discontinuation

The reason for study exit, including screen failure, will be documented on the applicable eCRF and in the subject file. The Sponsor must be informed of each withdrawal case.

In the event the subject withdraws consent during the study, the date of withdrawal will be documented. Individual subjects will not be replaced.

If the Investigator voluntarily removes a subject from further study participation, supporting documentation must be in place for the rationale and date of removal. The Investigator may withdraw a subject from the study at any time for the following reasons:

- Severe side effects clearly related to the study procedures
- Presence or appearance of exclusion criteria
- Appearance of accompanying diseases rendering further participation in the study impossible
- A significant protocol violation, as determined either by the Sponsor or the Investigator
- Subject noncompliant with procedures
- Subject noncompliant with visits
- At the specific reasonable request of the study Sponsor

For Austria and Israel only: If patient withdrawal is due to problems related to the device safety or performance, the Investigator shall ask for the subject's permission to follow his/her status/condition outside the clinical investigation.

Every attempt will be made to contact subjects that are noncompliant with study visits Subjects will be considered lost to follow-up once the following steps have been taken:

- Two phone calls should be made to the subject. Each attempt should be clearly documented in the source documents and the response or lack thereof should be captured.
- If there is no response to the phone calls, then an official, certified letter should be written to the subject. A copy of the letter and return or delivery receipts should be retained in the subject's source document.

When all due diligence attempts to contact have been made, after a period of two (2) weeks, the subject will be considered Lost to Follow-up. The Sponsor should be notified and the End of Study (EOS) form should be completed.

10. Risks and Benefits

10.1. Potential Risks

For female subjects that are pregnant or have childbearing potential, there may be risks to the subject or unborn child that are not yet known.

There may be additional risks related to this study (other than those listed here) that are not yet known.

Risks must be continuously monitored, assessed and documented by the Investigator.

10.1.1 PillCam® Crohn's Capsule

Possible Risks associated with use of the PillCam® Crohn's capsule, include but are not limited to the following:

- Nausea
- Vomiting
- Diarrhea
- Abdominal pain
- Headache
- Vertigo
- Difficulty or inability to swallow the capsule
- Asymptomatic capsule retention
- Fatigue
- Capsule aspiration
- Capsule retention or delayed excretion
- Physical intervention, which could include surgery, to remove the capsule
- Obstruction
- Perforation
- Mucosal injury or bleeding
- Small bowel obstruction

Implanted electronic devices such as, but not limited to, pacemakers, neurostimulators, implantable cardioverter defibrillators, ventricular assist devices, spinal cord stimulators, cochlear implants, infusion pumps, and bone growth stimulators may be influenced by interference produced by PillCam® Crohn's.

10.1.2 MRE

Although the MRE examination poses almost no risk to the average patient when appropriate safety guidelines are followed; there are still risks which include, but are not limited to the following:

- Possibility of excessive sedation, if used.
- Nephrogenic systemic fibrosis (thickening and scarring of connective tissue in the skin, joints, eyes, and internal organs)
- Allergic reaction if contrast material is injected. If subject experience allergic symptoms, a radiologist or other doctor will be available for immediate assistance.
- Nausea

- Vomiting
- Abdominal pain
- Blurry vision
- Dry mouth
- Tachycardia
- Electrolyte disturbance
- Dehydration
- Kidney injury
- Fluid retention
- Hypotension, hypertension or vasovagal reaction

10.1.3 Ileocolonoscopy

Possible risks associated with Ileocolonoscopy, include but are not limited to the following:

- Cramping
- Pain
- Bloating
- Diarrhea
- Nausea
- Vomiting
- Abdominal swelling
- Perforation, infection, or bleeding to the intestinal wall
- Postpolypectomy syndrome
- Undetected abnormalities
- Allergic reaction to sedation
- Respiratory depression, hypoxia, chest pain, cardiac arrhythmias
- Hypotension or hypertension, and vasovagal reactions
- Fluid retention
- Kidney injury

10.2. Potential Benefits

Professional guidelines for the management of Crohn's disease have recommended ongoing monitoring of disease activity with tools such as those used in this study (22). A "treat to target" strategy is increasingly recommended to tailor therapy based on mucosal evidence of disease (23). Thus, subjects may benefit from results of diagnostic tests performed during the study as treating physicians may be able to make more informed decisions in the care of subjects based on results of study procedures.

The information from this study may benefit other subjects with CD in the future.

10.3. Risk-Benefit Rationale

This study will include up to 352 subjects, aged 18 years and older, that have known CD and mucosal disease. Subject may be female or male. All study procedures are part of the standard medical management of patients with Crohn's disease. The risks to subjects would be similar to the expected risks to Crohn's disease patients in standard medical practice. MR enterography has been advocated to be very useful in the assessment of mucosal disease without endoscopy but its utility is limited to the small bowel. The PillCam® Crohn's capsule has the advantage of being able to assess both the small bowel and colonic mucosa in a single examination, which has the potential to reduce time, expense and inconvenience to the subject. This study is designed to evaluate the ability of the Crohn's capsule to assess mucosal disease with MRE and ileocolonoscopy.

The risks for MRE, as noted, will be minimized by excluding subjects who have evidence of renal insufficiency. This should service to greatly reduce the potential for nephrogenic systemic fibrosis. In addition, subjects with sensitivity to substances used in the course of the MRE, or during the preparation for the CE and IC procedures will be excluded. Sedation will be performed only in accredited facilities by qualified personnel and the ileocolonoscopy will be performed by board certified gastroenterologists to decrease the risk to study subjects.

Retention of the Crohn's capsule will be minimized since capsule will be administered only to those subjects who have demonstrated patency of the gastrointestinal tract by MRE. MRE has shown to be an effective predictor of safe passage of the video capsule (24). Also, investigators have the option of using the Patency capsule to determine whether the video capsule will be excreted. Patency capsule is useful in identifying patients that can undergo capsule enteroscopy without risks of capsule retention (25).

Subjects with swallowing disorders are excluded to avoid the risk of capsule aspiration or inability to swallow the capsule. Known side effects of the purgatives used for the preparation for capsule endoscopy and colonoscopy will be minimized by allowing both procedures to be performed with a single preparation.

11. Adverse Events and Device Deficiencies

11.1. Definitions/Classifications

Adverse event definitions used in this study are based on ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects -- Good Clinical Practice), which is aligned with MEDDEV 2.7/3 Revision 3, May 2015 (Guidelines on Medical Devices, Clinical Investigations: Serious Adverse Event Reporting).

Events will be collected for all enrolled subjects with the start of baseline imaging procedures (MRE) and end 14 days following completion of the IC procedure. Subjects with AEs 14 days following the IC procedure will be followed for 30 days or until event resolves, whichever comes first. During the course of the study, the following AEs will be collected and reported on the eCRF:

- All AEs related to PillCam® Crohn's
- All AEs related to IC

- All AEs related to MRE
- All AEs related to bowel preparation
- All device deficiencies
- All SAEs

The following should not be considered an AE:

- A condition requiring a preplanned procedure unless the condition worsened since screening.
- A preexisting condition found as a result of screening, unless the condition has worsened since enrollment.

For purposes of this protocol, the following occurrences are considered to be expected observations and will not be considered AEs, as long as the event is not associated with significant sequelae, does not prolong hospitalization, and responds to standard medical therapy:

- Transient nausea, diarrhea, vomiting, headache or abdominal pain that is determined to be related to one of the study procedures (including the preparation) and that resolves within 48 hours without extended hospitalization (>24 hours).

All responses to the above events that require treatment beyond the institution's standard procedures will be reported as AEs.

11.1.1 Adverse Event (AE)

An 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 medical device.

Note 1: This definition includes events related to the medical device or the comparator.

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 medical devices.

Documented pre-existing conditions are not considered to be reportable AEs unless there is a change in the nature or severity of the condition

OR

A condition requiring a preplanned procedure unless the condition worsened since screening

11.1.2 Serious Adverse Event (SAE)

A serious adverse event (SAE) is any untoward medical occurrence in a subject that meets the criteria of "serious." A SAE is one that:

- led to death,

- led to serious deterioration in the health of the subject that either resulted in
- a life-threatening illness or injury, or
- a permanent impairment of a body structure or a body function, or
- an in-patient or prolonged hospitalization, or
- medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function, or
- 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 clinical investigation plan, without serious deterioration in health, is not considered an SAE.

11.1.3 Customer Complaint

Any written, electronic, or verbal communication indicating a deficiency in the identity, quality, durability, reliability, safety, effectiveness, or performance of any product after it is released for distribution.

11.1.4 Device Deficiency

A device deficiency is an inadequacy of a medical device related to its identity, quality, durability, reliability, safety, or performance. This may include malfunctions, misuse or use error and inadequate labeling.

11.1.5 Adverse Event Severity Classification

Severity will be defined according to the following criteria:

Mild	Awareness of event, but easily tolerated
Moderate	Discomfort enough to cause some interference with activities of daily living (ADL)
Severe	Incapacitating, with an inability to perform ADL

An AE can be classified as severe and not deemed an SAE. Similarly, an SAE is not automatically severe in nature.

11.1.6 Adverse Event Relationship Classification

Causality assessments define the relationship between the use of the medical device (including the medical-surgical procedure) and the occurrence of each adverse event. During causality assessment activity, clinical judgment shall be used and the relevant documents, such as the Clinical Evaluation Report and the Risk Management Report shall be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

Each AE will be classified according to five different levels of causality. The Sponsor and the Investigators will use the following definitions to assess the relationship of the serious adverse event to the medical device or procedures:

Relationship to study product administration will be determined as follows:

- *Not related*: relationship to the device or procedures can be excluded when:
    - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;
    - the event has no temporal relationship with the use of the device or the procedures;
    - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
    - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
    - the event involves a body-site or an organ not expected to be affected by the device or procedure;
    - the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
    - the event does not depend on a false result given by the device used for diagnosis, when applicable;
    - harms to the subject are not clearly due to use error;
    - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

- *Unlikely*: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

- *Possible*: the relationship with the use of the device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

- *Probable*: the relationship with the use of the device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.

- *Causal relationship*: the serious event is associated with the device or with procedures beyond reasonable doubt when:
    - the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
    - the event has a temporal relationship with device use/application or procedures;
    - the event involves a body-site or organ that
        - the device or procedures are applied to;
        - the device or procedures have an effect on;

- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the device used for diagnosis, when applicable;
- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

The Sponsor and the Investigators will distinguish between the AEs related to the device and those related to the procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedures and the device. Complications of procedures are considered not related if the said procedures would have been applied to the subjects also in the absence of device use/application.

In some particular cases the event may be not adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The Sponsor and the Investigators will make the maximum effort to define and categorize the event and avoid these situations. Where the Sponsor remains uncertain about classifying the serious event, it should not exclude the relatedness and classify the event as "possible".

11.1.7 Adverse Event Outcome Classification

Outcome of the event will be defined according to the following:

- *Fatal:* This event is determined to be the cause of death.
- *Not Recovered/Not Resolved:* The event has not fully resolved at the end of the study.
- *Recovered/Resolved:* The event has fully resolved at the end of the study.
- *Recovered/Resolved with sequelae*: The event has resolved, but retained pathological conditions resulting from the prior disease or injury.
- *Recovering/Resolving:* The event is ongoing at the end of the study.
- *Unknown*

11.2. Recording of Adverse Events

Assessment of the occurrence of an AE will be based on changes in the subject's physical examination, laboratory results and/or signs and symptoms. The recording of AEs for all enrolled subjects will begin at the start of baseline imaging procedures (MRE) and end 14 days after completion of the IC procedure. Subjects with AEs at 14 days after the IC procedure will be followed for 30 days or until event resolves, whichever comes first. Medical care will be provided, as defined in the informed consent, for any AE related to study participation. Adverse events will be collected on an AE eCRF and applicable source documentation. To the extent possible, the event to be recorded and reported is the event diagnosis as opposed to event symptoms (e.g., fever, chills, nausea and vomiting in the presence of a clinically diagnosed infection is to be reported as infection only).

11.3. Reporting of Adverse Events

Please refer to Table 3 for a list of the minimum AE reporting requirements for Investigators. If local regulations or IRB/EC require faster reporting, then the Investigator will adhere to those requirements. Reporting of all safety events to the Sponsor will be completed through Investigator submission of the AE eCRF in the remote data capture (RDC) system. In case of emergency only for SAEs (ex. RDC system is unavailable), the Clinical Safety Specialist may be contacted directly at rs.mstsafetymitg@medtronic.com ; this will not serve as a substitute for proper reporting on the appropriate eCRF.

Table 3: Investigator AE Reporting Requirements

Type	Report to	Reporting Timeframe (from time of learning of event)
Adverse Event (AE)	IRB/EC	Per IRB/EC reporting requirements
	Sponsor	Within 10 working days
Serious Adverse Event (SAE)	Sponsor	Within 24 hours
	IRB/EC	Per IRB/EC reporting requirements
Device Deficiency	Sponsor (technical support)	Within 48 hours
	IRB/EC	If SAE occurs due to the device deficiency, within 24 hours of learning of the event and per IRB/EC reporting requirements
Device Related AE/SAE	Sponsor	Within 24 hours

Events will be reviewed by the Sponsor to determine any reporting obligations to the FDA or National Competent Authorities as well as IRB/EC. Reporting will occur within the timelines per local regulations and requirements.

11.4. Notification to Authorities

The following events are generally considered reportable during the course of this study and should be reported to the Sponsor:

- any SAE
- any Device Deficiency that might have led to an SAE if
  - suitable action had not been taken or
  - intervention had not been made or
  - if circumstances had been less fortunate
- new findings/updates in relation to already reported events.
- deaths

Events will be reviewed by the Sponsor for reporting obligations to National Competent Authorities. Reporting to National Competent Authorities will occur within the timelines described in the study Safety Plan by the Sponsor.

11.5. Device Deficiencies

All device deficiencies will be documented on the appropriate Device malfunction eCRF and the device should be returned to the Sponsor for analysis, if possible. Instructions for returning the device will be provided. Device deficiencies should also be documented in the subject's medical record.

Device deficiencies are NOT to be reported as AEs. However, if there is an AE that results from a device deficiency, that specific event would be recorded on the appropriate eCRF.

A device deficiency must be reported to Medtronic (technical support) within 48 hours after the investigator is made aware of the event.

12. Data Review Committees

A Medical Advisor and Steering Committee will be utilized in this study. This study will not have a Data Monitoring Committee (DMC) or an Adverse Events Advisory Committee (AEAC).

12.1 Medical Advisor

The Sponsor will utilize a Medical Advisor to provide an independent medical review according to the study safety plan. The Medical Advisor will not be affiliated with an investigative center.

12.2 Steering Committee

The Steering Committee will consist of Investigators participating in this study, expert gastroenterologists, as well as appropriate members of Medtronic Clinical and Medical Affairs. The role of the Steering Committee is to make recommendations on the design and conduct of the study, the analysis of data, and the communication of results in alignment with the Medtronic Publication and Authorship Policy. The Steering Committee will also review aggregate adverse event data on an as needed basis, as described in the Steering Committee Charter.

13. Statistical Design and Methods

13.1 Sample Size Determination

The sample size for this study will be comprised of subjects enrolled by April 30, 2019 forming a convenient sample. Therefore, the study is not powered to make statistical inference.

13.2 Effectiveness Analyses

Sensitivity, Specificity, PPV and NPV will be estimated for each treatment group, along with the 95% confidence interval. The difference between treatment groups in Sensitivity and Specificity will be compared.

13.3 Safety Analysis

Individual listings of AEs, including type of device, AEs (reported term) start date, duration, severity, and procedure-relatedness will be provided. Procedure relatedness will be assessed separately relative to the imaging modality and colonoscopy, as described in Section 13.1.9. The recording of AEs for all enrolled subjects will begin with the start of baseline imaging procedures (MRE) and 2 weeks following the final imaging procedure, IC. Adverse events will be summarized using frequency counts and percentages. Descriptive statistics will be provided by treatment group and by severity and relationship, according to the definitions in Section 13.1.9.

13.4 Analysis Populations

The effectiveness and safety analyses will be based on all subjects who go through procedures MRE, CE, and IC modalities and can be evaluated for overall active CDat baseline (i.e., a modified intent-to-treat (mITT) population).

The effectiveness analyses will also be conducted on the per protocol population, which includes all subjects in the mITT population who have no major protocol deviations (defined to be protocol violations that may have a significant impact on subject outcomes) and who do not meet any of the following criteria:

- Subject withdraws
- Capsules remained in the stomach or small bowel during the entire procedure
- System technical failure

Subgroup analyses will be performed on following designated bowel segments: proximal small bowel, terminal ileum, and colon. Additional analyses may also be explored and will be specified in the Statistical Analysis Plan (SAP).

The SAP will include procedures for reporting any deviation(s) from the original statistical plan, specifications for subgroup analysis, and criteria for the termination on statistical grounds. Changes to the planned statistical analysis as defined in the protocol will be documented in the SAP.

13.5 Interim Analyses

No interim analysis is planned for this study.

13.6 Handling of Missing Data

All practical monitoring and follow-up steps will be taken to ensure complete and accurate data collection. No data imputation for missing data will be performed for the primary analysis. As sensitivity analysis, missing data strategies such as multiple imputations may be used to assess the robustness of study results.

14. Ethics

14.1. Statement(s) of Compliance

This clinical investigation will be conducted in accordance with the protocol and ethical principles that have their origin in the Declaration of Helsinki (2013 version). In Austria and Israel, local laws and regulations for the execution of a post-market, non-regulatory clinical trial will be followed. In the US, the study will be conducted in compliance with the abbreviated requirements for a non-significant risk IDE as defined in 21 CFR 812.2(b). All principles of the Declaration of Helsinki have been implemented in this clinical study by means of the patient informed consent process, IRB/EC approval, clinical study training, clinical study registration, publication policy.

The clinical investigation will not begin at a given site until the required approvals/favorable opinions from the IRB/EC and/or notification/approvals from a regulatory authority have been obtained, as appropriate and a Site Activation Letter has been provided by the Sponsor. Should an IRB/EC or regulatory authority impose any additional requirements, they will be followed. PillCam® Crohn's has been approved for use in the US (K170210), Israel and Europe.

Information regarding the study and study data will be made available via publication on clinicaltrials.gov (NCT03241368). Additionally, the results of this study will be submitted for publication in an appropriate journal.

15. Study Administration

15.1. Monitoring

Monitoring will be conducted to ensure the protection and safety of human subjects, the quality and integrity of the clinical data, and compliance with the protocol. The Monitoring Plan will give details on how and when data review will be conducted by clinical monitors. It will be updated and revised as needed due to changes in documents or processes.

Employees of the Sponsor, or its designees, who have received appropriate training, will serve as the Study Monitor(s). Monitoring visits will be conducted based on Medtronic's Standard Operating Procedures and the needs of the study. Quality documents will be followed for the conduct of all activities related to monitoring for this study.

Site Qualification and Initiation Visits will be completed at each site prior to enrollment of the first subject. On Site study monitoring activities will include an inspection of completed study documents, source document verification and reporting, verification of database accuracy and completeness. All subjects enrolled in the study will be monitored and the eCRF data verified against the subjects' original source documents. Following each monitoring visit, a report will be prepared by the Monitor. From initiation of study to close out visit, the Study Monitor(s) and Clinical Research Specialist(s) will share responsibility for communications between the Study Investigators and the Sponsor.

Site visits will be conducted by an authorized Medtronic representative to inspect study data, subjects' medical records, and eCRFs in accordance with appropriate FDA regulations (US only) and the respective local and national government regulations and guidelines (if applicable). The Study Investigator and the investigating site will permit authorized clinical research personnel and clinical monitors from Medtronic and/or designee(s) employed by Medtronic to review completed eCRFs, IRB/EC decisions, and clinical site records, and facilities relevant to this study at regular intervals throughout the study per the monitoring plan. Additionally, subject charts and clinical records will be requested and reviewed so that protocol adherence and source documentation can be verified. In instances where data protection regulations prohibit the direct examination of hospital records by the study Sponsor or designee(s), the Investigator will cooperate in a system of source data verification with the Sponsor. Monitoring may be performed with in person visits or remotely, when applicable.

All monitoring visits to the investigational center will be recorded using the Monitoring Visit Log. The log will be kept in the site regulatory binder and a copy will be collected and submitted to the Sponsor.

To ensure the rights, safety, and welfare of study subjects are being maintained, the monitor will review training records to ensure all study staff are adequately trained on the study protocol and use of the study devices. If the monitor discovers that an Investigator is not complying with the signed Investigator Agreement, the investigational plan, applicable laws, or any conditions of approval imposed by the reviewing IRB/EC, the monitor will report to the Sponsor and take such steps necessary to promptly secure compliance. If compliance cannot be secured, device shipments to the Investigator may be discontinued and the Investigator's participation in the investigation terminated. The monitor shall also require such an Investigator to dispose of or return the device, unless this action would jeopardize the rights, safety, or welfare of a subject.

15.2. Data Management

The Sponsor will oversee and/or perform all data management functions. Data management functions include database development, system maintenance, data queries, and report generation. This study will utilize Oracle to manage data via RDC. The RDC system is a validated technology system, compliant with 21 CFR Part 11, and adheres to all applicable federal regulations.

15.2.1 Data Collection

All data required for analysis will be collected and entered on standardized eCRFs using OC-RDC module.

Required data will be recorded on eCRFs by authorized site personnel as indicated on the Delegation of Authority Log. The Investigator will ensure that all eCRFs are completed promptly, completely, and accurately. Information on case report forms must conform to the information in the source documents.

Investigators must ensure that clinical records clearly indicate that the subject has been enrolled in a clinical investigation. Regulations require that Investigators maintain information in the study subject's medical records to corroborate data collected on the eCRF. In order to comply with these regulatory requirements, the study site will manage the following information, and retain/manage it as required to make it available to monitors, auditors and/or regulatory bodies. Complete hospital and clinical medical records for all study subjects should include all study required procedures, labs and assessments as noted in Study schedule and Site Collection Data.

15.2.2 Data Access

Secure access to the RDC system will be maintained. Users will be given appropriate levels of access for their delegated responsibilities in the study. An audit trail is maintained in OC-RDC to capture any corrections or changes of the eCRFs. If a person is only authorized to complete CRFs or to make changes to an already signed CRF, the Investigator shall re-sign this CRF. Training will be provided to users of the eCRF electronic data capture system. The RDC system maintains an audit trail on entries, changes or corrections in the eCRFs. System backups for data stored in the OC-RDC system will be consistent with Medtronic standard procedures.

15.2.3 Electronic Case Report Form Guidelines

Medtronic will provide detailed instructions to assist with eCRF completion.

15.2.4 Data Queries

During monitoring visits, the Monitor will perform a source verification of required data points that comprise the eCRF for each subject.

Discrepancies will be queried by Medtronic and must be resolved by the investigational site staff and PI in a timely manner, and as requested by Medtronic.

Manual and/or automatic queries will be created in the OC-RDC system and will be issued to the site for appropriate response. The site staff will be responsible for responding to all queries in the database.

- Manual discrepancies will be issued in accordance with the Data Review Guidelines
- Automatic discrepancies will be issued in accordance with the Edit Check Document and the eCRF Database Question Specifications

In the event of data discrepancies, investigational centers will be asked to resolve queries electronically in the RDC system; otherwise, irresolvable data-related issues will be routed to the Sponsor for review and final disposition.

Imaging discrepancies will be issued by the Imaging Core Lab, ICON PLC, in SQUARE. For information on accessing and responding to imaging queries, please refer to the BLINK Imaging Manual.

15.2.5 Audits and Inspections

Medtronic-initiated audits or regulatory authority-initiated inspections at the investigational sites may occur during the course of or after completion of the study. In the event that an audit is initiated by Medtronic or a designee, the investigator shall allow access to the original medical records and provide all requested information. In the event that an inspection is initiated by a regulatory authority, the investigator shall immediately notify Medtronic of the impending inspection and allow the regulatory body access to the medical records and other information as required by applicable laws and regulations.

15.2.6 Close Out

Medtronic will only consider eCRFs to be complete when all discrepancies have been resolved by the site and reviewed and closed by Medtronic. In addition, specific eCRFs must also be reviewed and electronically signed by the Investigator, indicating his/her agreement with the accuracy of all recorded data. It is expected that the Investigator and his/her staff will cooperate with the monitoring team and provide any missing data in a timely manner.

15.3. Direct Access to Source Data/Documents

The investigator(s)/institution(s) will permit study-related monitoring, audits, IRB/EC review, and regulatory inspection(s) and provide direct access to source data/documents as per local policies and regulations.

15.4. Confidentiality

All records identifying the subject will be kept confidential and will not be made publicly available.

Subject names will be kept confidential. Only the subject number will be recorded in the eCRF, and if the subject name appears on any other document, it must be obliterated. In cases where the local law does not allow using the subject initials, for example in Europe, serial number will be appointed (e.g. AAA,

BBB). Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed in writing that representatives of the Sponsor, IRB or Regulatory Authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

Subjects will also be informed that information regarding the study that does not include subject identifiers will be posted on clinicaltrials.gov.

If the results of the study are published, the subject's identity will remain confidential. The Investigator will maintain a list to enable subjects' records to be identified.

15.5. Liability

Given Imaging Ltd, is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a clinical study insurance statement/certificate will be provided to the IRB/EC.

15.6. CIP Amendments

A CIP amendment will be prepared when there are revisions that are significant changes or corrections, or modifications that impact subject safety, ethical conduct, data integrity or study design. CIP amendments must undergo review by IRB/EC and any appropriate regulatory authority and will be logged in the document version history (Section 1). IRB/EC approval, site training and a new Acknowledgement form will be signed and returned before any new procedures take place.

15.7. Record Retention

The Investigator and the Sponsor will maintain the records of the study including all pertinent correspondence, the study protocol with any/all amendments, all correspondence with and approval from the IRB/EC, the clinical study agreement, the Investigator Agreement, device accountability records, individual subject records, and signed ICFs. In addition, the Investigator will retain the source documents from which the information entered on the eCRF was derived. Original source data that supports the eCRF entry must be maintained by the Investigator in compliance with national regulations. Investigator records are subject to inspection and copying by regulatory authorities and Medtronic

Subject files and other source data must be kept for a period of not less than 2 years after the latter of the following two dates: the date on which this investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket application. Records may need to be maintained by the Investigator for a longer duration if national regulations require or if agreed to in writing with Medtronic. The Investigator should not dispose of these records without the approval of the Sponsor. The Investigator should take measures to prevent accidental or early destruction of the clinical study related material. Should the Investigator wish to assign the study records to another party or move them to another location, advance written notice should be given to the Sponsor.

All data and documents should be made available if requested by relevant authorities.

15.8. Publication and Use of Information

The Medtronic Publication and Authorship Policy is aligned with the International Committee of Medical Journal Editors (ICMJE) recommendations (www.icmje.org). Medtronic will seek to publish, in appropriate peer-reviewed journals and scientific conferences, results of clinical studies where human subjects are involved, regardless of outcome. Information regarding the study and study data will be made available via publication on clinicaltrials.gov. Additionally, the results of this study will be submitted for publication in an appropriate journal. While study results are owned by Medtronic, all data on which a publication is based will be made available to all authors as required for their participation in the publication process. Furthermore, data may be published or used by study investigators provided that such publication or use is in accordance with this this protocol, the Medtronic-MITG Publication and Authorship Policy, and the Clinical Investigation Agreement. Investigators must submit a copy of all manuscripts and/or abstracts to Medtronic for review and comment 30 days prior to planned submission. Medtronic acknowledges that its right to review and comment shall relate solely to the proprietary, licensing, and/or confidential rights Medtronic may have in such proposed publication, rather than whether such results and/or opinions are favorable to Medtronic.

The publication of substudies, post-hoc analyses, regional results, or single-center experiences based on multicenter clinical studies should not precede that of the primary multicenter publication, and should cite the primary publication whenever possible, as required by specific journal and scientific meeting guidelines.

Medtronic involvement in a publication (e.g., funding of the study; sponsor of the study; collection, analysis, and interpretation of data; professional writing assistance) must be disclosed according to journal-specific policies, submission requirements, and prevailing editorial standards, in addition to those specified by ICMJE. Authors must ensure that an acknowledgement/disclosure statement is included in the body of the manuscript for Medtronic to review for accuracy. All authors must also disclose financial or personal affiliations that could be considered conflicts of interest as per journal/conference requirements.

To enable health care providers, payers, and patients access to the wealth of Medtronic's research, Medtronic will report its scientific data in accordance with the principles outlined in the Guidance Document on Registration and Reporting Results of Company-Sponsored Clinical Trials Under FDAAA 2007 (Title VIII).

15.9. Suspension or Early Termination

Medtronic reserves the right to discontinue the study at any stage, with suitable written notice to all investigators, all reviewing IRB/ECs, FDA and Competent Authorities. The appropriate ethics committees will be notified of discontinuation of the study for any reason no later than 5 working days after the Sponsor makes this determination. In addition, local ethics committee and/or regulatory authority can decide whether the study is to be terminated and will notify the Sponsor.

Similarly, investigators may withdraw from the study at any time, subject to providing written notification to Medtronic 30 days prior to the date they intend to withdraw. However, Medtronic and investigators will

be bound by their obligation to complete the follow-up of subjects already participating in the study. The subjects must be followed according to the clinical protocol, and information obtained during subject follow-up shall be reported to Medtronic on the appropriate eCRF.

Suspension or termination of a site may include but is not limited to:

- Ethics Board approval expiration
- Consistent non-compliance to the protocol (e.g. failure to follow subjects, etc.)
- Lack of enrollment
- Non-compliance to regulations and the terms of the Agreement with Medtronic
- Ethics Board suspension of the site

If the site terminates or suspends participation without prior agreement of Medtronic:

- The site must promptly inform Medtronic and provide a detailed written explanation of the termination or suspension
- The site must promptly inform the institution (where required per regulatory requirements)
- The site must promptly inform the Ethics Board, if applicable

If the Ethics Board terminates or suspends its approval:

- The site must promptly inform Medtronic and provide a detailed written explanation of the termination or suspension within 5 working days.
- Patient enrollment must stop until the Ethics Board suspension is lifted
- Subjects already enrolled should continue to be followed in accordance with the Ethics
- Board policy or its determination that an overriding safety concern or ethical issue is involved
- The site must inform his/her institution (where required per local requirements)
- The site must promptly inform the patients, if applicable

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17. Appendices

17.1 Appendix A – Montreal Classification

Data for Montreal classification will be captured at screening.

Montreal classification:

i. Age at diagnosis (years)

a. < 16, A1
b. 16-40, A2
c. > 40, A3

ii. Disease behavior

a. Inflammatory, B1
b. Stricturing, B2
c. Penetrating, B3

iii. Disease location

a. Ileum, L1
b. Colon, L2
c. Ileocolon, L3

17.2 Appendix B - Study Schedule for Clinical Laboratory and Pregnancy Tests

1. Stool *Clostridium difficile* (if not done within previous 3 months).
2. Stool ova/parasites OR stool PCR microorganism panel (if not done within previous 3 months).
3. Clinical Chemistry
   - Blood urea nitrogen (BUN)
   - Serum creatinine
   - Serum albumin
   - Fecal calprotectin
   - C-reactive protein (CRP)
4. Complete blood count (CBC):
   - Hemoglobin
   - Hematocrit
   - Erythrocyte count (RBC)
   - Leukocytes (WBC)
   - Absolute Neutrophils
   - Platelets
5. Pregnancy Test - Female subjects will be assessed for childbearing potential, and if they do have childbearing potential, they will undergo a pregnancy blood or urine test. If the test is positive, they will be withdrawn from the study. If the pregnancy test is negative, these subjects should practice contraceptive methods through the course of the study. s.

	Screening (No more than 30 days prior to first Baseline Procedure - MRE)	Baseline Procedure (Day 0)[5]				
Stool *Clostridium difficile*[1]	X					
Stool ova/parasites OR stool PCR microorganism panel[1]	X					
BUN[2]	X					
Serum creatinine[2,3]	X					
Serum albumin		X				

Fecal calprotectin[4]		X				
CRP		X				
CBC w differential		X				
Pregnancy test	X					

1. Prior standard of care C.difficile and stool O&P/PCR microorganism panel results may be leveraged for the screening visit once informed consent has been collected and provided that the date of results is no more than 3 months prior to informed consent date. These lab results, along with pregnancy test, must be evaluated as part of inclusion/exclusion criteria prior to subject enrollment.

2. BUN and serum creatinine data will be collected to evaluate renal function and results must be evaluated prior to MRE.
3. Serum creatinine measurement will be used to estimate the glomerular filtration rate (eGFR) and results must be evaluated prior to MRE.

4. A central laboratory will be used for analysis of fecal calprotectin. Please see Laboratory Manual for additional information.

5. Baseline labs may be collected on the day of the MRE procedure, prior to the procedure.

17.3 Appendix C - MRE Procedure Instructions

The MRE procedure will be in accordance with Coimbra et al., Aliment Pharmacol Ther 2016; 43: 61–72. Instructions for subjects can be found in Appendix C1.

All deviations from prep and procedural requirements should be appropriately documented and reported.

1. Subjects will fast for 4 hours and drink up to 1000-1800 mL of an oral non-absorbable bowel preparation solution (Breeza® [Beekley Medical, Bristol, CT, USA], or VoLumen® [Bracco Diagnostics Inc., Princeton, NJ, USA] or 5% mannitol solution). Non-proprietary oral contrasts containing sugar alcohols (e.g., 3% sorbitol solution) are also permissible, but should be cleared with Medtronic prior to study initiation.
2. An intravenous (IV) catheter will be placed into a peripheral vein.
3. An IV or subcutaneous injection of an anti-peristaltic agent (0.5 mg glucagon [Lilly, Indianapolis, IN, USA] in the US or 10 mg buscopan [Boehringer Ingelheim, Sant Cugat, Spain] in Europe) will be administered prior to scanning. The anti-peristaltic agent can be administered in a split dose (prior to scanning and immediately prior gadolinium administration) or as a single dose prior to administration of gadolinium (step 5 below).
4. Following a fast scout series and a succession of breath holds, T2-weighted true fast imaging with steady-state free precession (FISP) and T2-weighted single-shot fast spin echo (SSFSE) series will be acquired, with and without fat suppression, using coronal and axial images, as described in Table 2 of the BLINK Imaging Manual. The field of view will be adjusted to cover the digestive tract from the fundus of the stomach to the anus. It is appropriate to move the field of view inferiorly to not image the liver dome and stomach so that the anus is within the imaged volume. The number of slices for each series will be adjusted to keep the series duration within approximately 25 seconds and to allow for acceptable breath hold periods. Multiple staggered series will be allowed to fulfil the prescribed coverage. Prone positioning is preferred by not mandatory. Supine positioning is preferred for patients with end ileostomies.

   **Optional* – it is optional for sites to acquire axial images using either types of pre-contrast pulse sequence instead of coronal images. At least one precontrast series should be acquired in the axial plane.
5. A fast breath-hold 3D gradient-recalled echo (GRE) coronal T1-weighted, fat-suppressed series will be acquired prior to and approximately 45 seconds and 180 seconds following the IV administration of an extracellular gadolinium-based contrast agent (such as 0.1 mmol/kg MultiHance [Bracco Diagnostics Inc., Princeton, NJ, USA], 0.1 mmol/kg Omniscan [GE Healthcare Inc., Oslo, Norway] or 0.1 mmol/kg Dotarem [Guerbet LLC., Bloomington, IN, USA]). The small bowel (including duodenum), colon, rectum, and anus need to be imaged. Required and suggested parameters are listed in Table 2 of the BLINK Imaging Manual*. Slice thicknesses can be interpolated.

   * Optional - For large patients, the coronal slice thickness can be increased to 4 mm and the axial slice thickness can be increased to 5 mm to permit for coverage and appropriate signal, if needed.
6. Finally, one final breath-hold series of axial T1-weighted GRE with fat suppression will be acquired.

17.3.1 Appendix C1 - MRE Subject Instructions

See attached document "Appendix C1_BLINK_MRE Subject Instructions"

Subject Instructions
MRE Procedure
BLINK Clinical Trial (COVSBCC0549)

To be completed by research staff:

Subject #: | | | | | | | | | **Site #:** | | | | | | |

Please arrive at the clinic on _____ at _____ for your procedure.
Date Time

Your MRE is scheduled to begin at _____
Time

Contact for questions:

Name: _____ Phone: _____

Thank you for your participation in this study. The preparation for your examination is a very important part of your exam. **Please follow all instructions carefully to ensure a successful procedure.**

- After completion of each step, check box (✓) and specify time in the column on the right, otherwise detail why step was not followed in Comments section.
- Both you and the Research Staff Member should sign and date Page 3 of this form

On the day of the examination:

- Bring these instructions with you to the clinic
- Dress in comfortable 2-piece clothing

Subject #: | | | | | | | | |

Time	Action	✍
The Day of the Examination **Day of the week:_____, Date:____/____/___**		
Start: **4 hours prior to procedure** (see top of Page 1)	• Drink <u>water only</u>. No solid foods or other beverages.	☐
As defined by Radiologist	• Ingest 1000-1800mL of the bowel preparation solution provided to you.	Start Time: ☐-------- Finish Time: ☐--------
As Scheduled	• MRE Procedure	☐

Subject #: | | | | | | | | |

Additional Information and Comments

Time	Comments

Research Staff Signature _____ Date _____

Patient Signature _____ Date _____

17.4 Appendix D – PillCam® Patency Study

In all subjects with evidence of stricture on MRE, or according to investigator's discretion, a PillCam® patency study must be performed prior to the PillCam® procedure.

During the PillCam® patency study, if the patency capsule is excreted structurally whole or located structurally whole in the colon at any time, then this confirms patency of the GI tract of the subject for objects the size of the capsule. The capsule is designed to dissolve starting 30 hours following ingestion, during a period of approximately 12 hours. If any time before 30 hours after capsule ingestion the patency capsule cannot be detected in the subject's body, it indicates the following:

- The PillCam® patency capsule was excreted naturally and structurally whole
- Patency of the GI tract for objects the size of the capsule is confirmed

The PillCam® patency scanner is used to detect the presence of the patency capsule in the subject's body. If desired, fluoroscopy or X-ray may be used. The subject should return to the clinic as close to, but no more than, 30 hours after ingestion of the patency capsule to be evaluated – suggest scheduling subject appointment for 28 hours after initial ingestion.

If the PillCam® patency scanner or x-ray does not detect the patency capsule in the GI tract any time prior to 30 hours post-ingestion, this implies that it has been excreted structurally whole, and patency of the GI tract can be confirmed.

17.5 Appendix E – CE and IC Procedure Instructions

This appendix includes instructions for the capsule endoscopy (CE) and IC procedures in 4 parts:

- Appendix E1 – CE Capsule and IC Bowel Preparation Instructions
- Appendix E2 – CE Capsule and IC Subject Instructions Form
- Appendix E3 – CE Procedure Instructions
- Appendix E4 – CE and IC Bowel Cleansing Scale

17.5.1 Appendix E1 – CE and IC Bowel Preparation Instructions

Subjects will be instructed to follow a detailed dietary and colon preparation regimen prior to and during the CE procedure day. All colon preparation products will be standard colon cleansing products approved by the FDA and/or EMA. Additional bowel prep after capsule endoscopy, prior to ileocolonoscopy is at the discretion of the investigator.

Subjects will keep a timed diary of key preparation steps and bowel activity, including capsule excretion, located in Appendix E2. CE Procedure Instructions can be located in Appendix E3.

Preparation Procedure

The Day Before the Procedure Day	
All Day	Clear liquid diet.
15 hours prior to capsule ingestion	Begin ingestion of 2L PEG (such as ELS; NuLYTELY, Braintree Laboratories, Braintree, MA), one 8-10 oz. cup every 10-15 minutes.
13 hours prior to capsule ingestion	Complete ingestion of 2L PEG
Procedure Day	
3 hours prior to capsule ingestion	Begin ingestion of remaining 2L PEG, one 8-10 oz. cup every 10-15 minutes.
1 hour (±15 minutes) prior to capsule ingestion	Complete ingestion of remaining 2L PEG[1,2]. Subject should remain NPO until capsule ingestion. Strongly suggest requiring subject to finish morning PEG in clinic to assure capsule ingestion occurs within 1 hour (±15 minutes) of completion.
As scheduled	Capsule Ingestion with a sip of water then resume NPO until Alert 1. Capsule MUST be ingested within 1 hour (±15 minutes) after completing ingestion of PEG.
Alert 0 (1 hour after capsule ingestion)	10 mg Metoclopramide or 250mg oral Erythromycin Please note, not all subjects will receive Alert 0
Alert 1 (Upon SB Detection)	3 oz. (half bottle) SUPREP® (US), Eziclen®/Izinova® (EU) diluted per package insert instructions + drink 1L water
Alert 2 (3 hrs later)	3 oz. (half bottle) SUPREP® (US), Eziclen®/Izinova® (EU) diluted per package insert instructions + drink 1L water
Alert 3 (2 hrs later)	10 mg Bisacodyl suppository.

[1] Any subject ingesting <2.5L of PEG (combined between evening and morning dose) should not proceed with CE procedure and should be discontinued from the trial.

[2] Any subject requiring >3 hours to ingest the morning PEG dosage (2L) should not proceed with CE procedure and should be exited from the trial.

Following capsule endoscopy procedure, physician must instruct subject regarding clear liquid diet and/or NPO status until completion of IC procedure. Physician may administer additional prep following completion of the CE procedure, prior to the IC procedure at his/her discretion.

EXAMPLE Subject Schedule for 8am capsule ingestion:

The Day Before the Procedure Day	
All Day	Clear liquid diet.
5pm (15 hrs prior to scheduled ingestion))	Begin ingestion of 2L PEG

7pm (13 hrs prior to scheduled ingestion)	Complete ingestion of 2L PEG
Procedure Day	
5am (3 hrs prior to scheduled capsule ingestion)	Begin ingestion of remaining 2L PEG
7am (±15 minutes) (1 hour prior to scheduled capsule ingestion)	Complete ingestion of remaining 2L PEG. Subject should remain NPO until capsule ingestion.
8am (08:00)	Capsule Ingestion with a sip of water then resume NPO until Alert 1.

17.5.2 Appendix E2 – CE and IC Subject Instructions Form

During the CE procedure, subjects will be asked to use a Subject Instructions Form to document their activities during the bowel preparation and capsule examination. This form will be used to document the subject's adherence to the procedure steps. The Subject Instructions Form will also serve as source data for eCRF entries. Site staff must complete the instructed "start" and "finish" times in the left-hand column of the CE Subject Instruction Form to inform the patient when they should start and finish each step of the bowel prep, based on the timelines set in Appendix E1, CE Bowel Preparation Instructions.

See attached document, "BLINK_CE and IC Subject Instructions Form"

Subject Instructions

Capsule Endoscopy (PillCam® Crohn's) and Ileocolonoscopy Procedure

BLINK Clinical Trial (COVSBCC0549)

To be completed by research staff:

Subject #: | | | | | | | | | Site #: | | | | | | |

Please arrive at the clinic on:

_____ at _____ for your capsule endoscopy procedure AND
Date Time

_____ at _____ for your ileocolonoscopy procedure.
Date Time

Contact for questions:
Name: _____ Phone: _____

Research Staff: Please complete the blank information in the left hand column of Pages 2 and 3 to indicate when the subject should start and finish each step of the procedure based on the requirements in Appendix E1. Remember to sign and date Page 4, along with the patient.

Thank you for your participation in this study. The preparation for your examinations are very important part of your exam. **Please follow all instructions carefully to ensure adequate cleansing of the bowel for your procedure.** The Research Staff will complete the information in the left hand column, to indicate when you should start and finish each step of the procedures. You must complete the column on the right, indicating the exact time you started and finished each step. BOTH the Research Staff and Patient must sign and date Page 4.

- **Important:** After the capsule endoscopy, you **must** follow your physician's instructions on what you can eat or drink until your ileocolonoscopy procedure (IC) is complete; either directly following the PillCam® Crohn's procedure or the next morning.
- After completion of each step, check box (✓) and specify time in the column on the right, otherwise detail deviation in comments
- During the preparation period do not take any iron supplements or vitamin supplements containing iron
- If you take anti-coagulants (*Warfarin, Aspirin)* or antibiotics as a preventive treatment for heart disease, please consult your physician first
- It is recommended to use moist baby wipes instead of toilet paper

On the day of the Capsule Endoscopy procedure:

• Bring these instructions and the remaining 2L of PEG (SF-ELS) with you to the clinic

• Dress in comfortable 2-piece clothing and bring any reading material or electronic personal entertainment you with to use during the capsule endoscopy procedure.

During your capsule endoscopy procedure:

•Try to remain active and take short walks, this can speed up the transit of the capsule through your body. No sleeping.

•Do not lean on or sit in metal chairs during the procedure as this can cause interference.

•Avoid intense sunlight during procedure

Subject #: | | | | | | | | |

	Action	✍
The Day Before the Procedure **Day of the week:_____, Date:____/____/___**		
All day	• Drink clear fluids only, see description below, No solid foods. • It is recommended to drink a lot of sugared clear drink of your choice through the day (e.g. carbonated soda, apple juice, energy drinks etc.)	☐--------
Afternoon	• Prepare PEG *solution* according to the instructions on the package. Shake well until all the powder is dissolved and keep refrigerated	☐--------
To be completed by Study Coordinator: **Expected Start:** _____ **Expected Finish:** _____	• Document the time you actually Start and Finish each step in the column to the right • Drink ½ gallon (2 liters) of PEG (SF-ELS) solution, one 200-250ml cup every 10-15 minutes, for up to **2 hrs**. Do not ingest too quickly in order to avoid stomach discomfort. During this time, you should avoid drinking other fluids. • Document the Start and End times of drinking the solution • Keep the remaining volume (1/2 gallon) of the PEG (SF-ELS) solution refrigerated and bring it with you on the day of the examination • Contact the study coordinator in case you are having trouble completing the entire volume	Actual Start: ☐-------- Actual Finish: ☐-------- Total PEG intake: ☐-------- liters

Clear Liquid Diet

- Water
- Apple, white cranberry, white grape juices
- Tea or black coffee (no milk or cream)
- Clear sports drinks or carbonated soft drinks (no red or purple colored)
- Popsicles or jello (any color except red or purple)
- Bubble gum or hard candy (lemon or mint flavored)

AVOID: Juices with pulp, milk, cream, soup or broth, alcoholic beverages and solid foods

Subject #: | | | | | | | | |

Day of the Examination

(Day of the week:_____, Date:____/____/____)

	Action	✍
All Day	•Only clear fluids are allowed. No solid foods	☐
To be completed by Study Coordinator: **Expected Start:** _____ **Expected Finish:** _____	• May start morning PEG at home depending on scheduled capsule ingestion time (see top of Page 1 for scheduled time) •Drink ½ gallon (2 liters) of PEG (SF-ELS) solution, one 200-250ml cup every 10-15 minutes, for up to **2 hours.** • It is recommended that you bring a small amount of remaining PEG with you to the clinic to finish at the clinic. This will help ensure you ingest the PillCam capsule within 1hr of completing your PEG ingestion • Try to avoid consumption of any other liquid during PEG ingestion • When finished, maintain a complete fast until instructed otherwise by the study staff.	Actual Start: ☐-------- Actual Finish: ☐-------- Total PEG intake: liters ☐--------
1 hour (±15min) after finishing PEG	•Ingest PillCam® Crohn's capsule with a cup of water	☐--------

Action		Alert Number & Time
Prokinetics	10mg Metoclopromide or 250mg Erythromycin *Not all patients will receive Alert 0	0 _____
1st Boost	•Drink SuPrep solution (0.5 bottle (88ml) diluted to 240ml) •Drink at least 1 liter (Four 8 oz cups) of water	1 _____
2nd Boost* (3 hrs after 1st Boost)	•Drink SuPrep solution (0.5 bottle (88ml) diluted to 240ml) •Drink at least 1 liter (Four 8 oz cups) of water	2* _____
Suppository (2 hrs after 2nd Boost)	Insert suppository (10mg *Bisacodyl*) as described in the package insert	3 _____
End of Procedure*	Capsule was naturally excreted -- or -- Recorder (DR3) alert "End of Procedure"	**End of Procedure** _____

*Subjects are allowed to leave the clinic (at the physician's discretion) after Alert 2 is received and all associated actions completed, if the capsule is not yet excreted. If subject leaves before excretion they must insert the suppository when Alert 3 is received and document the time. They must also document the time the capsule is excreted or "End of Procedure" alert is received. They may disconnect the recorder at excretion or battery failure (whichever comes first).

Subject #: | | | | | | | | |

Additional Information and Comments

Time	Comments

Research Staff Signature _____ Date _____

Patient Signature _____ Date _____

17.5.3 Appendix E3 – CE Procedure Instructions

On the day of the examination, the arrival time of the subject at the clinic will be documented on the Subject Instructions Form (see Appendix E2) and the subject will complete the bowel preparation procedure as detailed in Appendix E1. All deviations from bowel prep and procedural requirements should be appropriately documented and reported.

The subject's last bowel movement should be clear to yellow effluent prior to the CE exam. Any subject ingesting <2.5L of PEG should not proceed with CE procedure and should be discontinued from the trial.

After the final PEG ingestion, subjects should remain NPO until capsule ingestion. Within 1 hour (±15 minutes) of the final PEG ingestion, the subject will swallow the PillCam® Crohn's capsule with a cup of water. The subject will then resume their NPO status until they receive an alert. The subject will follow the instructions for any alert they receive until the capsule is excreted. The subject will be instructed to notify the staff upon exit of the capsule from the body and to record the time on the subject instruction form. After the baseline capsule endoscopy procedure, the subject should be instructed to follow the anesthesiologist's instruction in regard to NPO status until the completion of the baseline IC procedure.

Throughout the CE procedure, the subject will be instructed to verify when the capsule has exited the body and to inform the physician or the clinical coordinator of the time of exit. The time of exit should be documented on the Subject Instructions Form and in the eCRF.

Throughout the CE procedure, the subjects will be instructed to notify the study physician if experiencing abdominal pain, headache, vomiting, bloating, and nausea which are anticipated symptoms that could be related to the procedure.

The system may be disconnected upon one of the following: capsule excretion ("End of Procedure" alert) or until battery failure, whichever comes first. The PillCam® Recorder may also be removed in case of procedure failure.

Subjects will be allowed to leave the clinic once the capsule is excreted ("end of procedure" alert) OR once Alert 2 has been received and all associated instruction for Alert 2 is completed by the subject, approximately 8 hours after ingestion. Subjects leaving before excretion must be instructed and agree to the following; the importance of complying with these instructions should be stressed:

- Insert the biscodyl suppository at home upon notification of Alert 3
- Document the time of Alert 3 on the CE Subject Instructions (Appendix E2).
- Evaluate bowel movements for capsule excretion and document the time of excretion on the CE Subject Instructions (Appendix E2). If the capsule is not excreted prior to returning to the clinic, the "End of Procedure" alert time or the time the battery failed should be recorded on the Subject Instructions, whichever occurs first.
- The subject may disconnect the recorder at excretion ("End of Procedure" alert) or battery failure (whichever comes first) and return the equipment to the clinic the next day.

Site staff must continue to follow the subject until the capsule is excreted. If the capsule is not confirmed to have been excreted by 14 days after ingestion, then a plain abdominal film will be performed to verify the capsule exit.

Since the capsule endoscopy and ileocolonoscopy share a single bowel prep, the physician may administer additional bowel prep at his/her discretion if the ileocolonoscopy is to be conducted the day after completion of the capsule endoscopy. The physician must also instruct the subject whether they may have a meal or must maintain clear liquid diet or NPO between the 2 procedures. If the capsule has not been excreted by the time the IC is conducted, and the battery has already failed, the colonoscopist may remove the capsule during IC.

17.5.4 Appendix E4 – CE and IC Bowel Cleansing Scale

Cleansing Level Scale for Capsule Endoscopy

Rating	Description
Poor	Inadequate
	Large amount of fecal residue precludes a complete examination
Fair	Inadequate, but examination completed
	Enough feces or turbid fluid to prevent a reliable examination
Good	Adequate
	Small amount of feces or turbid fluid not interfering with examination
Excellent	Adequate
	No more than small bits of adherent feces

Adapted from Leighton JA et al. Endoscopy 2011;43:123-7.

17.7 Appendix F – Accuracy for Active Crohn's Disease in Overall and Designated Bowel Segments

Accuracy of CE versus IC plus MRE for detection of active CD in the small bowel and colon will be assessed.

Accuracy measures (sensitivity, specificity, negative predictive value, positive predictive value) will be calculated for the overall bowels (small bowel and colon) as well as for the designated bowel segments (proximal small bowel, terminal ileum, and colon).

Accuracy for active CD needs to be first be measured for each designated bowel segment. The gold standard for each segment will vary:

- MRE+CE in the proximal small bowel
- MRE+CE+IC in the terminal ileum
- CE+IC in the colon

Once accuracy is defined for each segment, the data will be aggregated to measure accuracy for the overall bowels. If there is any positive finding of active CD in any of the three designated segments (proximal small bowel, terminal ileum, colon), it will be counted as positive for overall accuracy.

17.8 Appendix G – Scores for Capsule endoscopy, Ileocolonoscopy, and MRE

This appendix includes scores that will be used by central readers for assessment of active CD and mucosal disease activity using CE, IC, and MRE.

- Appendix G1 – Lewis Score
- Appendix G2 – Simple Endoscopic Score for Crohn's Disease Index (SES-CD) Score
- Appendix G3 – Magnetic Resonance Index of Activity (MaRIA) Score

17.8.1 Appendix G1 – Lewis Score

The Lewis Score will be used to evaluate the more proximal small bowel for CE.

	Number	**Extent**	**Descriptors**
Villous appearance (worst-affected tertile)	Normal – 0 Edematous – 1	≤10% – 8 11-50% – 12 >50% – 20	Single – 1 Patchy – 14 Diffuse – 17
Ulcer (worst-affected tertile)	None – 0 Single – 3 2-7 – 5 ≥ 8 – 10	≤10% – 5 11-50% – 10 >50% – 15	<1/4 – 9 1/4-1/2 – 12 >1/2 – 18
Stenosis (whole study)	None – 0 Single – 14 Multiple – 20	Non- ulcerated – 2 Ulcerated – 24	Traversed – 7 Not traversed – 10

Total score will be calculated based on the most severe tertile plus the stenosis score. On central reading, a Lewis score of ≥ 135 will be considered active disease.

17.8.2 Appendix G2 – Simple Endoscopic Score for Crohn's Disease Index (SES-CD) Score

The Simple Endoscopic Score for Crohn's Disease Index (SES-CD) will be used to evaluate the terminal ileum and colon for CE and IC. On central reading, a SES-CD score of ≥ 3 will be considered active disease.

Variable	0	1	2	3
Size of ulcers (cm)	None	Aphthous ulcers (diameter 0.1-0.5)	Large ulcers (diameter 0.5-2)	Very large ulcers (diameter > 2)
Ulcerated surface	None	< 10%	10-30%	> 30%
Affected surface	Unaffected segment	< 50%	50-75%	> 75%
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

17.8.3 Appendix G3 - Magnetic Resonance Index of Activity (MaRIA) Score

The Magnetic Resonance Index of Activity (MaRIA) Score will be used to evaluate the small bowel for MRE in accordance with Coimbra et al., Aliment Pharmacol Ther 2016; 43: 61–72 .

The per segment MaRIA score is defined as:

$$MaRIA_{seg} = 1.5 \times WT + 0.02 \times RCE + 5 \times edema + 10 \times ulcer$$

WT = wall thickness of bowel in mm, measured at thickest point in the segment
RCE = relative contrast enhancement

Edema and ulcer are each assigned a value of 1 if there is evidence of either in the segment; 0 if there is no evidence.

RCE is measured at areas with the largest enhancement in a bowel wall segment after IV contrast administration:

$$RCE = 100 \times \frac{WSI_{post\text{-}Gd} - WSI_{pre\text{-}Gd}}{WSI_{pre\text{-}Gd}} \times \frac{SDnoise_{pre\text{-}Gd}}{SDnoise_{post\text{-}Gd}}$$

Gd = gadolinium
$WSI_{post\text{-}Gd}$ = mean bowel wall signal intensity after Gd
$WSI_{pre\text{-}Gd}$ = mean bowel wall signal intensity before Gd
$SD_{noisepost\text{-}GD}$ = standard deviation of MRE image in air after Gd
$SD_{noisepre\text{-}GD}$ = standard deviation of MRE image in air before Gd

The MaRIA score for the small bowel and TI will be computed separately per the formula above. On central reading, a MaRIA score of ≥ 7 will be considered active disease.

17.9 Appendix H – Patient Satisfaction Questionnaire

The questionnaire will be completed by subjects after the last baseline procedure (IC). If the subject is unable to complete the questionnaire on the same day following completion of imaging procedures due to sedation, the questionnaire may be completed by phone the following day.

BLINK Patient Satisfaction Questionnaire

Subject #:_____

Baseline Visit:

Which procedure would you prefer to have in the future?

- ○ PillCam Crohn's capsule
- ○ MRE + colonoscopy
- ○ Colonoscopy

Why do you prefer this procedure? (choose all that apply)

- ○ less invasive
- ○ less discomfort
- ○ safer
- ○ less embarrassing
- ○ no need to be put to sleep
- ○ no time off of work/school
- ○ no need for someone to drive me
- ○ cutting edge technology
- ○ single procedure to look at all of intestines
- ○ no need to be in a small space
- ○ can collect tissue (biopsy) at same time
- ○ more familiar with it
- ○ standard procedure
- ○ more accurate

- ○ less bowel prep
- ○ finds disease outside of intestines
- ○ no need for an IV
- ○ can move around during procedure
- ○ no need to drink chalky solution
- ○ other: provide comment _____

How likely are you to recommend the procedure you chose to others with your condition?

- ○ not likely
- ○ likely
- ○ very likely

Name of Research Staff Obtaining Responses from Subject:

_____

Research Staff Signature: _____

Date: _____

18. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• N/A	Mamata Thapa, PhD; Medical Writer
2.0	• Transferred to new CIP template (056-F275, Version 2.0) per Medtronic policy. Sections were added and/or revised to meet global Medtronic CIP template and checklist requirements. • Changed "PillCam SBC" to "PillCam Crohn's" due to renaming of product. • Added "diagnosis based on radiological, endoscopic, or histological evidence" in inclusion criteria for subjects with known Crohn's disease. • Excluded pediatric subjects. Removed procedure details and supporting documents (pediatric patient satisfaction and quality of life questionnaires) pertaining to pediatric population. • Excluded vulnerable subjects. • Updated study status for ClinicalTrial.gov: NCT01631435 and NCT02025777. • Added "terminal ileum" to bowel segments that will be evaluated with the Lewis score. • Removed "sub-investigator" designation for radiologist. • Added information as required by Medtronic checklist in following sections: Study Design, Product Description, Study Procedures, Risks and Benefits, Statistical Design and Methods, Study Administration, Data Management, and Study Contact and Information. • Deleted "standard of care" since "IC plus MRE" is not considered standard of care for monitoring CD in the small bowel and colon. Reported comparator group procedure/s at baseline (IC plus MRE) and 6- and 12- month follow-ups (IC with or without MRE). • Modified protocol to reflect that the study will be a post-market, off-label trial in the US (NSR IDE) and post-market, on-label, non-regulatory trial in EMEA. • Added statement that the study will begin in Europe; and the study will begin in the US and Israel only after the product has been approved for use in these countries. • Updated proposed indication for the US, Europe, and Israel. • Minor updates and minor clarifications were made throughout the protocol. These minor changes did not affect the purpose or requirements of the study.	Mamata Thapa, PhD; Medical Writer

3.0	• Updated version number and date • Removed ADE, UADE, USADE definitions from glossary • Updated Section 4 and Section 10.4 to include the exclusion criteria "Subject has any medical condition that would make it unsafe for them to participate, per the Investigator's discretion" • Updated Section 11.2 to include collection of subject's birth year in demographics • Updated Section 11.4 to note an impartial witness must also sign the ICF if the subject is unable to read • Updated Section 11.10 to indicate Medtronic personnel may be present during capsule endoscopy procedure to provide technical support • Updated Sections 11.8, 11.10, 11.11 to include requirement of transfer of imaging to Imaging Core Lab within 48 hours of completion of procedure • Updated Section 13 to remove definitions and reporting timelines for ADEs, UADEs and USADEs as this will be a post-market study. Country-specific requirements will be captured in Safety Plan • Updated Appendix B to allow for stool PCR microorganism panel as an alternative to stool ova/parasite • Updated Appendix C to remove administration of remaining dose of anti-peristaltic agent • Updated Appendix E1 to clarify that subjects are required to remain at the endoscopy clinic until excretion of the capsule or battery failure of the device (whichever comes first) • Updated Appendix E3 to clarify subjects must remain in clinic for duration of the procedure	Jessica Carlson, Principal Clinical Research Specialist
4.0	• Moved to v3.0 of CIP Template • Added definition of stricture to Section 3 Protocol Synopsis, Section 8.4 Exclusion Criteria, and Section 9.5 Baseline • Corrected typo in Section 3 Protocol Synopsis and Section 8.4 Exclusion Criteria #2 to change "and" to "or" • Removed exclusion criteria #7 from Section 3 and Section 8.4 • Added Belgium to Section 3 Study Locations and throughout document • Updated Section 4.1 to indicate PillCam Crohn's capsule has received FDA clearance in the US • Updated Section 5.2.1 Primary Endpoint to "IC with or without MRE" • Updated Section 5.2.3 Safety Endpoints to correct references in Section 11 • Removed Lewis Score as CE scoring mechanism for terminal ileum throughout document • Removed collection of age from Section 9.2 Subject Screening • Updated Section 9.3 Prior and Concomitant Medications to clarify restriction on use of NSAIDs	Jessica Carlson, Clinical Research Specialist

	• Updated Section 9.4 Baseline to allow responses to questionnaires by phone • Updated Section 9.5 Randomization and Treatment Assignments to clarify randomization procedures. • Removed requirement for withdrawal time of IC endoscope to be at least 6 minutes from Section 9.12 • Added definition of subtle lesions to Section 9.13.1 • Removed reference to USADEs from Section 11 as this does not apply to a post-market trial • Reference to "Medical Advisor Charter" removed from Section 12.1 • Updated Section 13.5 to indicate subjects Subject ingesting <2.5L of PEG bowel preparation prior to CE or IC procedure will be excluded from analysis • Added clinicaltrials.gov study identifier to Section 14.1 Statement of Compliance • Updated Appendix C "MRE Procedure Instructions" to clarify choice of Breeza or Volumen as oral non-absorbable bowel preparation solution • Added Appendix C1 "MRE Subject Instructions" • Updated Appendix E3 "CE Procedure Instructions" to align with Appendix E2 "CE Subject Instructions" and to allow subjects to leave the clinic if procedure is not complete at 10 hours • Appendix E2 "CE Subject Instructions" updated to provide more clear instruction • Appendix F1 "IC Bowel Preparation" to indicate clear liquid diet only on day of procedure • Updated Appendix H3 to clarify calculation of MaRIA score. • Updated Appendices I and J to reflect that questionnaires may be completed via phone call with subject • Appendix I "Patient Satisfaction Questionnaire" updated to include information regarding research staff collecting subject responses. • Appendix J attachments "EQ-5D-3L" and "Inflammatory Bowel Disease Questionnaire" updated to include information regarding research staff collecting subject responses.	
5.0	• Updated document version number to version 5 in Header, Footer, Title page and Investigator Statement • Added term NPO and definition to Section 2 – Glossary • Removed Germany as a participating country throughout document • Updated Primary Objective, Secondary Objectives #1 and #2, Primary Endpoint, and Secondary Endpoints #1 and #2 to indicate "CE as compared to IC plus MRE" instead of "IC with or without MRE" as these outcomes are determined by baseline data when all subjects will undergo all imaging procedures.	Jessica Carlson, Principal Clinical Research Specialist

	• Section 5.2.3 – Safety Endpoints: Removed "All AEs will be captured, regardless of severity or relationship to the procedure" as only the adverse events defined in Section 11.1 are being collected. • Updated Section 7.9 – Product Receipt and Tracking to clarify study equipment and device will be sent to site upon execution of Clinical Trial Agreement to allow adequate time for shipment and installation but site is not allowed to use product or begin enrollment until the Sponsor provides notification of Site Activation. • Updated Section 9.1 – Schedule of Events and Appendix B – Study Schedule for Clinical Laboratory and Pregnancy Tests to clarify Screening Procedures should occur no more than 30 days prior to baseline MRE, not 30 days prior to baseline IC as previously stated. Removed requirement for Baseline pregnancy test as deemed not clinically necessary given timing of screening pregnancy test. • Updated Section 9.1, Footnote #3 to indicate all required labs should take place no more than 14 days prior to the first imaging procedure at any given visit timepoint to remain within required visit windows. • Updated Section 9.5 – Baseline and 9.12 - Ileocolonoscopy to indicate physician may instruct subject to be NPO after completion of baseline CE Procedure to prepare for IC procedure and associated sedation. • Updated Section 11 – Adverse Events and Device Deficiencies for clarity. • Updated Section 11.1 – Definitions/Classifications to clarify all AEs related to subject's Crohn's disease, all device deficiencies and all SAEs should be reported • Updated Section 11.1.2 – Serious Adverse Event (SAE) to remove "that is not related to the device comparator or study procedure" from the definition • Changed Emergency Safety contact to Safety Representative email in Section 11.3 – Reporting of Adverse Events • Updated Section 13 "Statistical Design and Methods" to correct analysis population to align with primary endpoint and provide additional clarifications. • Section 15.2.4 – Data Queries - Added clarification that queries related to imaging will be issued by ICON through the SQUARE system. • Appendix C – MRE Procedure Instructions updated to clarify procedural requirements per Lead Radiologist • Appendix C1 – MRE Subject Instructions updated to correct a page numbering error • Appendix E1 – CE Bowel Prep Instructions and Appendix E2 – CE Subject Instructions updated to be easier to understand and follow for research staff and study subjects. Additionally,	

	250mg oral Erythromycin has been added as an acceptable substitute for 10mg Metoclopramide at Alert 0. • Appendix E3- CE Procedure Instructions updated to be easier to understand and follow. • Appendix F1 – Ileocolonoscopy Bowel Preparation and Appendix F2 – Ileocolonoscopy Subject Instructions updated to be easier to understand and follow for research staff and study subjects. Removed Bowel Prep requirements for 2 days prior to the procedure, including removal of requirement for subject to take 4 Senna tablets. Provided clarification, that as required, subjects should be instructed to be NPO prior to any sedation for the ileocolonoscopy per standard care.	
6.0	• Updated entire document to remove 3, 6, 9, and 12 month follow-up visits (and associated procedures) throughout. • Removed Appendices J1 EQ-5D-3L and J2 Short IBD Questionnaire • Combined Appendices E1 CE Bowel Preparation Instructions and F1 Ileocolonoscopy Bowel Preparation Instructions • Combined Appendices E2 CE Subject Instruction Form and F2 IC subject Instruction Form. • Added lines for Subject and Study Coordinator signature and date to Appendix C1 MRE Subject Instructions and Appendix E2 CE and IC Subject Instructions for verification of source documents • Updated document to version 6 in Header, Footer, Title page and Investigator Statement • Added "or other clinical evidence" to Study Design section of Synopsis • Removed other European countries throughout, leaving Austria • Updated Inclusion Criteria #4 to include subjects with known CD and active disease, based on clinical judgment based on symptoms, laboratory data or other clinical information. • Removed "any current condition believed to have an increased risk of capsule retention such as" from Exclusion Criteria #7 for clarity and to reduce redundancy. • Added Exclusion Criteria #17, "Subject with ileostomy or colostomy, history of total or subtotal colectomy (including those with ileosigmoidostomy, and ileorectostomy" • Clarified AE reporting requirements in Sections 5.2.3, 11.1, 11.2, 13.4 to specify that reporting of AEs should start beginning with first baseline imaging procedure (MRE). • Updated language in Section 6 Study Design in alignment with Inclusion Criteria #4 to allow enrollment of subjects with current active disease based on symptoms, laboratory data, or other clinical information • Increased maximum number of enrolled subjects from a single site to 70 (20%) in Section 6.1 Duration	Jessica Carlson, Clinical Research Manager

	• Updated Section 7.10 Product Storage to indicate Temperature Logs are not required for BLINK as storage is expected at ambient temperature • Updated footnotes in Table 1 Schedule of Events to provide additional clarity • Added clarification to Section 9.2 Screening Visit that Medical History should include any history within the last 2 years related to the study inclusion/exclusion criteria; Previous GI Procedures should be captured for the last 5 years; and Surgical History should include only GI-related surgeries • Clarified Section 9.5 Baseline to include: completion of MRE to completion of IC should be no more than 4 weeks, all baseline labs must be completed no more than 14 days prior to baseline MRE, and instruction regarding determination of patency prior to capsule endoscopy • Removed "pregnancy test" from Section 9.5 Baseline in alignment with Baseline Laboratory requirements • Clarified Section 9.10 PillCam Patency Study to designate when subjects should be exited from trial due to stricture and when patency procedure should be completed • Added additional detail to Section 9.13 Central Reader Image/Video Reading to indicate procedures for assessing disease activity in cases where an imaging modality is not available for evaluation • Added detail of specific PillCam Crohn's procedure-related AEs that must be reported • Clarification added to Section 13.5 Analysis Populations for handing of subjects with missing imaging • Removed all interim analyses in Section 13.6 Interim Analyses due to enrollment ending in April 2019 • Added footnote to Appendix B Study Schedule for Clinical Laboratory and Pregnancy Tests to clarify that standard of care C. Difficile and Stool O&P lab results may be used for trial purposes provided the date of results is no more than 90 days prior informed consent date • Appendix C MRE Procedure Instructions updated to include allowance of split does of anti-peristaltic agent and increased imaging thickness for larger patients • Corrected typo in Appendix C1 MRE Subject Instructions • Added additional clarification to Appendix D PillCam Patency Procedure to make instructions easier to follow • Added additional clarification to Appendix E1 CE Bowel Preparation Instructions to make them easier to follow • Added additional clarification to Appendix E2 CE Subject Instructions Form to make it easier to follow • Added additional clarification to Appendix F1 Ileocolonoscopy Bowel Preparation Instructions to make them easier to follow	

	• Added active disease scoring thresholds to Appendix G1 Lewis Score, Appendix G2 SES-CD Score, and Appendix G3 MaRIA Score for transparency	